

Suppression of benign prostate hyperplasia by *Kaempferia parviflora* rhizome

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ABSTRACT

Background: *Kaempferia parviflora* rhizome is used as a folk medicine in Thailand for the treatment of various symptoms. In the present study, the inhibitory activities of extract from *K. parviflora* rhizome against 5 α -reductase (5 α R) were subjected. Furthermore, the effects of the extract from *K. parviflora* rhizome in benign prostate hyperplasia (BPH) were studied using the model mice. **Materials and Methods:** Preparations of extracts from the rhizomes of *K. parviflora*, *Curcuma zedoaria* and *Zingiber officinale*, and methoxyflavones isolated from *K. parviflora* was used for 5 α R inhibition assay. The effects of *K. parviflora* extract on growth suppression for the prostates and seminal vesicles were performed based on the Hershberger's method. The *K. parviflora* extract was administered to castrated mice for 14 days. **Results:** *K. parviflora* extract showed more potent inhibitory activity on 5 α R than *C. zedoaria* and *Z. officinale* extracts. The active principles were identified as 3,5,7,3',4'-pentamethoxyflavone and 5,7,3',4'-tetramethoxyflavone by activity guided fractionation. Furthermore, *K. parviflora* extract suppressed the weights of prostates and seminal vesicles in BPH model rats by daily administration for 14 days. **Conclusion:** These results indicate that *K. parviflora* extract can be a promising agent for the treatment of BPH.

Key words: 5 α -reductase, benign prostate hyperplasia, *Kaempferia parviflora*, methoxyflavone

INTRODUCTION

Plant materials have been used for treatments of diseases in the Eastern countries, especially East Asia, for thousands of years. In the specific tribes in Thailand, *Kaempferia parviflora*, a Zingiberaceae plant, has been used a folk medicine called "Krachai Dum." The rhizome and tincture of *K. parviflora* has been applied as medicine for general pain, colic gastrointestinal disorders, and male impotence. These various pharmacological activities of *K. parviflora* prompted researchers to elucidate its activities scientifically using the *in vivo* and *in vitro* assays. Among them, inhibition of P-glycoprotein function,^[1] anti-plasmodial, anti-fungal and anti-mycobacterial effects,^[2] cytotoxicity against various cancer cell lines,^[3] anti-cholinesterase activity,^[4] anti-allergic activity,^[5] modulation of the function of multidrug resistance associated-proteins,^[6] anti-gastric ulcer effect,^[7] anti-obese activity,^[8] anti-diabetes activity,^[9,10] and

inhibition of fat absorption^[11] have been demonstrated. These multi-functional effects of *K. parviflora* makes it an attractive potential treatment for life-style-related diseases. Thus, continuous research to discover novel effects of *K. parviflora* on life-style-related diseases has been performed in our laboratory.

Among various life-style-related diseases, we first focused on anti-hyperuricemia activity based on inhibition on xanthine oxidase. Xanthine oxidase has been recognized as a key enzyme for producing uric acid and a treatment for gout. *K. parviflora* extract showed potent inhibitory activity compared to other Zingiberaceae plants used as crude drugs and the active principles were determined as 3,5,7,3',4'-pentamethoxyflavone and 5,7,3',4'-tetramethoxyflavone.^[12] In addition, we focused on an improvement effect on blood fluidity. Stagnation of blood causes a loss of metabolism, obesity, and poor circulation. *K. parviflora* has been shown to have fibrinolysis activity and improved the blood fluidity in disseminated intravascular coagulation model rats.^[13] Thus, we have been demonstrated some novel *K. parviflora* function and believe that other novel functions are yet to be revealed.

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Benign prostate hyperplasia (BPH) is life-style-related illnesses caused by inappropriate diet habits and the social stress leading to hormone imbalance. The incidence of BPH is approximately 50-60% in males 40-60 years old and greater than 90% in men over 80 years.^[14] It also causes urinary tract obstruction and infection.^[15] Androgen plays an important role in the growth, and maintenance of normal prostate gland, function as well as in the development of BPH. The androgens testosterone and dihydrotestosterone (DHT) contribute to the onset of BPH.^[16] Testosterone is converted to DHT by 5 α -reductase (5 α R).^[17] DHT is a potent androgen whose action is mediated through binding to the androgen receptor (AR) in the prostate, which induces protein synthesis and abnormal growth of the prostate.^[17,18] Therefore, inhibition of 5 α R could help prevent BPH. Finasteride, a potent 5 α R inhibitor and flutamide, a binding inhibitor to AR are used as effective agents in BPH treatment. These drugs, however, are known to produce side-effects including impaired liver function, diarrhea, and headache. Alternatively, functional foods including natural products that show 5 α R inhibitions may be useful in the prevention of BPH.

Some 5 α R inhibitors from natural products have been discovered by our group, i.e., 12-methoxycarnosic acid in *Rosmarinus officinalis* leaf,^[19] ginsenoside Ro in the rhizome of red ginseng,^[20] kaikasaponin and soyasaponin in flowers of *Pueraria thomsonii*^[21] and fatty acids and ethinylestradiol in spores of *Lygodium japonicum*.^[22]

In the present study, extract from *K. parviflora* rhizome was subjected to the inhibitory assay against 5 α R along with other Zingiberaceae plants. *K. parviflora* showed potent activity and the active principle was revealed. Furthermore, a result on the improvement of BPH by *K. parviflora* using *in vivo* BPH model is described.

MATERIALS AND METHODS

Materials

Rhizomes of *K. parviflora* were purchased from Aoba trading Co. (Tokyo, Japan). Voucher specimens were deposited at the Faculty of Pharmacy, Kinki University. Reagents used in this study were of analytical grade and were purchased from Wako Pure Chemicals Industries (Osaka, Japan) or Nacalai Tesque (Kyoto, Japan) unless otherwise stated.

Preparations of extracts and methoxyflavones

Preparations of extracts from rhizomes of *K. parviflora*, *Curcuma zedoaria* and *Zingiber officinale*, and methoxyflavones were performed according to the methods previously reported.^[12]

Inhibitory assay for 5 α R

The enzyme 5 α R was prepared according to the method reported^[23] with modifications. Rats (Wistar, 9 weeks, 270-290 g) were purchased from Shimizu Laboratory Supplies Co., Ltd. (Kyoto, Japan), and were maintained at a constant temperature and humidity under a 12 h light/dark cycle for 11 days. Water and pellet chow (Labo MR stock, Nosan Corporation, Tokyo, Japan) were freely available. The epididymis was removed from 100 rats and homogenized with a blender in cooled physiological saline containing 0.25 M sucrose and protease inhibitor cocktail. Homogenates were filtered and centrifuged at 300 $\times g$ for 10 min, and the supernatants were centrifuged again under the same conditions to obtain crude enzyme the protein assay method (Bio-Rad Laboratories, Inc., Hercules, CA) and crude enzyme solution was diluted to 10 mg/ml and stored at -85°C until use.

The 5 α R inhibition assay was performed as reported previously^[24,25] with minor modifications. The reaction solution containing 50% ethanol (50 μl) with various concentrations of test compounds, 600 μl of 100 mM McIlvaine buffer (pH 5.0), 20 μl of testosterone (0.4 mM in propylene glycol [PG]-citrate/phosphate buffer, pH 5.0 [1:1 v/v]) and 110 μl of enzyme solution.^[26] Reactions were initiated by the addition of 20 μl of 34 mM nicotinamide adenine dinucleotide phosphate reduced form. The mixture was incubated at 37°C for 30 min. After addition of 1.0 ml of dichloromethane and 20 μl of *p*-hydroxybenzoate *n*-hexylester as an internal standard (IS), the organic layer was obtained by centrifugation (3000 $\times g$ for 3 min), and transferred to another tube and air dried. The residue was dissolved in 0.2 ml of methanol, and an aliquot of 30 μl was injected into an high performance liquid chromatography (HPLC) system under the following conditions: Column, YMC-Park ODS-AM302 (4.6 i.d. \times 150 mm); column temperature, 40°C ; mobile phase, methanol/water (65:35, v/v); flow rate, 1.0 ml/min; detection, UV at 254 nm, t_{R} ; testosterone, 7 min, t_{R} ; IS, 14 min. The control-0-min tube received 1.0 ml of dichloromethane before addition of the enzyme solution, whereas, the control-30-min tube received 50 μl of methanol instead of the test sample. A similar procedure to that described previously was carried out for these control tubes. The 5 α R inhibitory activity was determined from the following equation using the peak-area ratios (r = testosterone/IS). Finasteride (Tokyo Chemical, Tokyo, Japan) was used as a reference drug.

$$\text{Inhibition (\%)} = 100 \times (C_{\text{sample}}/C_{\text{control}})$$

C: Conversion rate (%) of testosterone to DHT

C_{sample} (C for sample groups) = r of the test sample – r of control-30 min

C_{control} (C for control groups) = r of control-0 min – r of control-30 min.

Animals

Male Crj: CD Sprague-Dawley (SD) rats, which castrated at 6 weeks age and normal (not castrated) SD rats (7 weeks age) were purchased from Shimizu Laboratory Supplies (Kyoto, Japan). The rats were acclimatized for 1 week in an animal room, which is maintained by air-conditioning with lighting from 7 a.m. to 7 p.m. The temperature and humidity were controlled automatically. Laboratory pellet chow (Labo MR stock, Nihon Nosan Kogyo, Tokyo, Tokyo, Japan) and water were freely available. All experimental protocols using animals were approved by the Committee for the Care and Use of Laboratory Animals at Kinki University.

Animal treatments

The growth suppression assay of prostates and seminal vesicles in castrated rats was performed based on the Hershberger's method.^[27,28] The castrated rats were randomized to four groups of 6 rats: (1) A negative control group receiving intraperitoneal administration (i.p.) of olive oil and oral administration (p.o.) of 100 μ l of 50% PG, (2) testosterone propionate (TP) (2 mg/kg, i.p.) and 100 μ l of PG (p.o.), (3) TP (2 mg/kg, i.p.) and *K. parviflora* ext in PG (200 mg/kg, p.o.) and (4) TP (2 mg/kg, i.p.) and finasteride in PG (2 mg/kg, p.o.). Non-treatment group (not castrated rats) was also prepared. The administrations were performed once a daily for 14 days.

Sacrifice and evaluation of prostates and seminal vesicles weights

The day after the last treatment (at the day 15 from the starting of administration), rats were sacrificed under anesthesia with pentobarbital (35 mg/kg). Their prostates and seminal vesicles were removed and weighted.

Statistical analysis

Data were evaluated statistically by Bonferroni/Dunn multiple range tests using a Microsoft Excel add-in software Statcel (Ver. 3, OMS publishing, Saitama, Japan). Significant differences were detected at $P < 0.05$ and 0.01 .

RESULTS AND METHODS

Effects of *K. parviflora*, *C. zedoaria* and *Z. officinale* extracts on 5 α R inhibition

Firstly, the inhibitory activity (conversion rate of testosterone to DHT) of the *K. parviflora* extract was studied compared with those of *C. zedoaria* and *Z. officinale* extracts on 5 α R. The results are shown in Table 1. *K. parviflora* extract showed enzyme inhibition of 75.8% at 500 μ g/ml while the values for the *C. zedoaria* and *Z. officinale* extracts

were 28.2% and 21.1%, respectively. This result suggested that *K. parviflora* has the most potent activity and may be effective in the treatment of BPH.

Effects of methoxyflavones from *K. parviflora* on 5 α R

Secondly, the inhibitory activities of methoxyflavones from *K. parviflora* were examined since methoxyflavones are known to be multi-potential active compounds. The results are shown in Table 2. Among the compounds tested, 3, 5, 7, 3', 4'-pentamethoxyflavone and 5, 7, 3', 4'-tetramethoxyflavone showed the most potent inhibitory activities of 55.9% at 50 μ M (Figure 1). Their IC₅₀ values were 46.6 and 48.7 μ M for 3, 5, 7, 3', 4'-pentamethoxyflavone and 5, 7, 3', 4'-tetramethoxyflavone, respectively. These results indicated that these two methoxyflavones were the most potent among the nine methoxyflavones.

Effects of *K. parviflora* extract on rat prostate and seminal vesicle weights

The effects of *K. parviflora* extract on the growth of rat prostates and seminal vesicles were studied. The results are shown in Figure 2. The mean prostate weight/body weight of the group, which received PG (control group) was 145.0 ± 30.7 mg/kg [Figure 2a]. The mean prostate weight/body weight of the group with BPH induced by TP injection was 1898.0 ± 325.2 mg/kg, which was significantly higher than that of the control group ($P < 0.01$). The mean prostate weight/body weight of the rats that received the *K. parviflora* extract (200 mg/kg) was 986.1 ± 124.6 mg/kg. Compared with the BPH group, *K. parviflora* showed a significant reduction in prostate weight ($P < 0.05$). The mean prostate weight/body weight of the finasteride-administered (2 mg/kg) rats was 742.3 ± 84.0 mg/kg, which was significantly lower than the BPH group ($P < 0.01$). The mean prostate weight/body weight of the non-castrated and treated rats was 397.0 ± 61.9 mg/kg [Figure 2a].

Table 1: Inhibitory effects of crude Zingiberaceae extracts on 5 α R

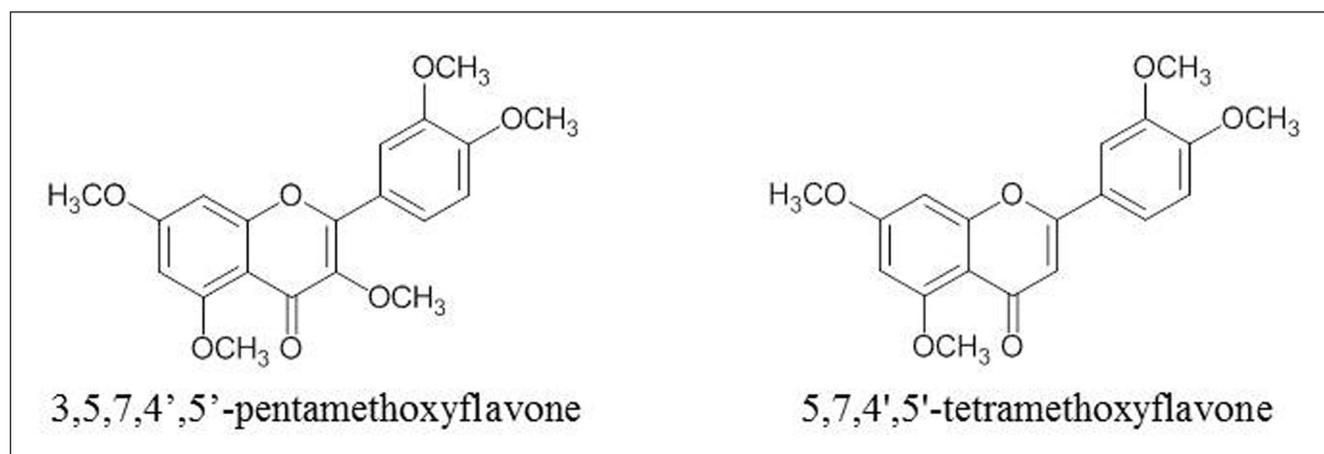
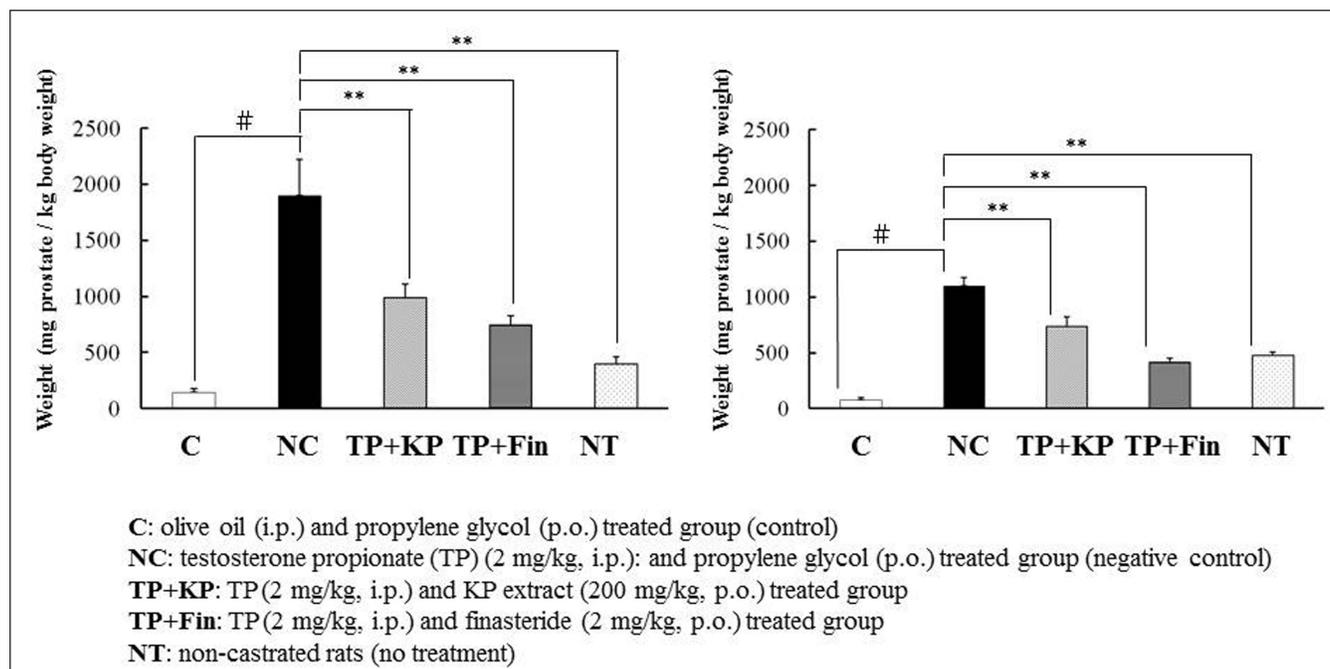
Extracts	Concentration (μ g/ml)	Conversion rate (%)	Inhibition (%)
Control	–	41.2 \pm 0.8	–
<i>K. parviflora</i>	100	23.0 \pm 0.6**	44.1
	200	15.4 \pm 0.6**	62.5
	500	10.0 \pm 0.6**	75.8
<i>C. zedoaria</i>	100	30.8 \pm 0.2**	25.1
	200	35.9 \pm 0.4**	12.9
	500	29.6 \pm 0.6**	28.2
<i>Z. officinale</i>	100	35.6 \pm 0.4**	13.4
	200	34.2 \pm 0.3**	16.9
	500	32.5 \pm 0.1**	21.1
Finasteride	250 (nM)	21.4 \pm 1.4**	48.0

Each value represents the mean \pm S.E. of triplicates. Significantly different from the control group at; ** $P < 0.01$.

Table 2: Inhibitory effects of methoxyflavones on 5 α R

Compounds	Concentration (μ M)	Conversion rate (%)	Inhibition (%)
Control	–	35.3 \pm 0.9	–
3,5,7,3',4'-pentamethoxyflavone	50	15.6 \pm 0.2**	55.9
5,7,3',4'-tetramethoxyflavone	50	15.4 \pm 0.4**	55.9
3,5,7-trimethoxyflavone	50	23.0 \pm 0.6**	34.9
5,7-dimethoxyflavone	50	24.3 \pm 0.2**	31.3
5-hydroxy-3,7-dimethoxyflavone	50	26.1 \pm 0.0**	26.1
3,5,7,4'-tetramethoxyflavone	50	27.0 \pm 0.1**	23.5
5-hydroxy-3,7,3',4'-tetramethoxyflavone	50	28.7 \pm 0.2**	18.7
5,7,4'-trimehoxyflavone	50	30.6 \pm 0.4**	13.3
5-hydroxy-3,7,4'-trimethoxyflavone	50	31.3 \pm 0.9*	11.2
Finasteride	250 (nM)	16.3 \pm 0.6**	53.7

Each value represents the mean \pm S.E. of triplicates. Significantly different from the control group at; ** P <0.01; * P <0.05

**Figure 1:** Chemical structures of 3,5,7,3',4'-pentamethoxyflavone and 5,7,3',4'-tetramethoxyflavone**Figure 2:** Suppression of testosterone propionate-induced hyperplasia of prostates (a) and seminal vesicles (b) in castrated rats by *Kaempferia parviflora* extract. Values represent mean \pm SE of $n = 6$. Significantly different from control group at # P < 0.01. Significantly different from negative control group at ** P < 0.01

The mean seminal vesicles weight/body weight of the group, which received PG (control group) was 78.7 ± 16.7 mg/kg [Figure 2b]. The mean seminal vesicles weight/body weight of the group with BPH induced by TP injection was 1099.1 ± 73.9 mg/kg, which was significantly higher than that of the control group ($P < 0.01$). The mean seminal vesicles weight/body weight of the rats that received *K. parviflora* extract (200 mg/kg) was 737.2 ± 85.4 mg/kg. Compared with the BPH group, *K. parviflora* showed a significant reduction in seminal vesicle weight ($P < 0.05$). The mean seminal vesicles weight/body weight of the finasteride (2 mg/kg)-administered rats was 415.2 ± 36.0 mg/kg, which was significantly lower than that of the BPH group ($P < 0.01$). The mean seminal vesicles weight/body weight of the non-castrated and treated rats was 477.7 ± 28.3 mg/kg [Figure 2b].

In the present study, *K. parviflora* extract treatment resulted in a significant decrease in the weights of prostates and seminal vesicles in TP injected-castrated rats. These effects can be attributed to the inhibitory activity against 5α R exhibited by *K. parviflora* extract as shown in this manuscript.

Search for effective plant resources for the improvement of BPH has been performed extensively. Among them, *Serenoa repens*,^[29,30] *Ganoderma lucidum*,^[31] *Lepidium meyenii* (Red Maca),^[32] banana peel,^[33] and *Echinacea purpurea*^[34] showed significant improvements of BPH. The results obtained in this study could have successfully presented that *K. parviflora* is a novel entry from Zingiberaceae plant and *K. parviflora* would be a promising candidate. Further, studies on the mode of action of *K. parviflora* extract are now underway.

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