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5 α -Reductase inhibitory component from leaves of *Artocarpus altilis*

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Abstract The inhibitory effects of 17 samples prepared from Thailand plants on 5 α -reductase activity were examined. The acetone extract of leaves of *Artocarpus altilis* showed potent 5 α -reductase inhibitory activity. Fractionation guided by 5 α -reductase inhibition led to the isolation of 2-geranyl-2',3,4,4'-tetrahydroxydihydrochalcone from the acetone extract of leaves of *A. altilis*. This compound showed more potent inhibitory effect (IC₅₀ = 38 μ M) than α -linolenic acid known as a naturally occurring potent inhibitor.

Key words *Artocarpus altilis* (Parkins) Fosberg · Moraceae · Leaves · 5 α -Reductase inhibitor · 2-Geranyl-2',3,4,4'-tetrahydroxydihydrochalcone

Introduction

Tropical forest comprises 40%–50% of the all forest areas of the world. Thailand possesses an extraordinarily rich flora and great diversity of vegetation types. The great diversity of tropical plants appears in the qualitative and quantitative diversity of extractives from a chemical point of view. Recently, we have reported an antifungal component¹ and melanin biosynthesis inhibitory compounds² from Papua, New Guinea wood species *Pterocarpus indicus* and *Artocarpus incisus* (= *A. altilis*). These tropical plants give us a chance to find bioactive components.

Δ^4 -3-Oxo-steroid 5 α -oxidoreductase (EC 1.3.99.5; 5 α -reductase) is present in many androgen-sensitive tissues such as the prostate and seminal vesicles; it converts

testosterone to a more potent androgen, 5 α -dihydrotestosterone,^{3,4} which then binds to androgen receptor to exert its biological function.⁵ Inhibition of 5 α -reductase would limit the availability of 5 α -dihydrotestosterone; therefore, 5 α -reductase inhibitors would be useful for the selective treatment of androgen-dependent abnormalities, such as benign prostate hyperplasia, prostate cancer, hirsutism, male pattern alopecia, and acne, without affecting testosterone-dependent testicular function, sexual behavior, or muscle growth.⁶ Most 5 α -reductase inhibitors are steroid derivatives or compounds with steroid-like structures. Of these, the 4-azasteroids, such as 17 β -(*N,N*-diethyl)carbonyl-4-methyl-4-aza-5 α -androstan-3-one (4-MA) and finasteride, have been the most extensively studied.^{7,8} The steroidal inhibitors have the possibility of an affinity for the androgen receptor and are expected to produce undesirable antiandrogen effects, such as impotence, impairment of muscle growth, and gynecomastia. Several nonsteroidal inhibitors have also been synthesized, such as ONO-3805⁶ and LY191704.⁹ On the other hand, few naturally occurring inhibitors have been reported, for example unsaturated fatty acids¹⁰ and (–)-epigallocatechin-3-gallate.¹¹ Therefore, we searched for naturally occurring new 5 α -reductase inhibitors, especially from Thailand plants. We report here an inhibitory component of *A. altilis*, which showed potent inhibitory activity in 17 Thailand plant samples.

Materials and methods

Sample plants

The 16 Thailand plant species [*Leucaena leucocephala* (lam.) De Wit, *Mitragyna hirsuta* Hav., *Alpinia galanga* Willd., *Ixora maerthyra* Teyssm & Binn., *Annona squamosa* L., *Passiflora foetida* L., *Alstonia scholaria* (L.) R. BR., *Piper betle* L., *Tamarindus indica* L., *Eucalyptus* sp., *Artocarpus altilis* (Parkins) Fosberg, *Flagellaria indica* L., *Clitoria ternatea* L., *Albizia myriophylla* Benth., *Citrus hystrix* DC., *Acacia concinna* DC.] were obtained from

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Kasetsart Agriculture and Agro Industrial Product Improvement Institute, Kasetsart University, Bangkok, Thailand. All voucher specimens are preserved at the herbarium there.

Extraction of samples

The leaves (*L. leucocephala*, *M. hirsuta*, *A. galanga*, *I. maerthyra*, *A. squamosa*, *P. foetida*, *A. scholaria*, *P. betle*, *T. indica*, *Eucalyptus* sp., *A. altilis*, *F. indica*, *A. myriophylla*), flowers (*C. ternatea*), vines (*P. foetida*), fruits (*A. concinna*), and skin of fruits (*C. hystrix*) were dried and milled. The 100 g of milled samples were extracted with acetone at room temperature for 24 h and then filtered through filter paper quality No. 4. The extractions were performed 3 times, and acetone extracts were pooled together, then concentrated in vacuo at 40°C.

The juice of *C. hystrix* fruits was obtained by squeezing the peeled fruits. The juice was concentrated in vacuo at 50°C and then freeze-dried.

Preparation of liver microsomes

The liver microsomes from female rats were prepared by a method previously reported¹⁰ with modification. Two mature Sprague-Dawley female rats (300 g) were killed. The livers were removed and minced in a beaker with a pair of scissors. The minced tissue was then homogenized in three-tissue volume medium A (0.32 M sucrose, 1 mM dithiothreitol, and 20 mM sodium phosphate, pH 6.5). The homogenate was then centrifuged at 10 000 g for 10 min. The resulting pellet was washed with two-pellet volume medium A. The combined supernatant from the two centrifugations was further centrifuged at 105 000 g for 1 h. The washed microsomes were suspended in 4 ml medium A and the dispersion of microsomes was achieved using a syringe with 18-, 23-, and 25-gauge needles in succession. The microsome suspension was divided into small aliquots and stored at -80°C. The microsomes were diluted with medium A just before use. Protein content in the suspension was determined by the coomassie brilliant blue dye reagent.

5 α -Reductase assay

The standard reaction mixture, in a final volume of 3.0 ml, contained microsomes (1 mg protein), 150 μ M testosterone in 100 μ l ethanol, 167 μ M NADPH, medium A, with or without the indicated amount of a sample in 100 μ l of dimethylsulfoxide (DMSO). The reaction was started by adding microsomes to the preheated reaction solution in a tube. After 10 min the incubation was terminated by adding 100 μ l of 3 M NaOH followed by 100 μ l of 1.0 mM cholesterol acetate in *n*-hexane as the internal standard for gas chromatography-mass spectrometry (GC-MS). To extract metabolites, 40 ml of diethylether was added, and the tubes were capped and shaken. The water phase was frozen in a -20°C freezer; and the organic phase was decanted and

evaporated under reduced pressure. Residue was dissolved in 100 μ l of ethyl acetate for GC-MS. The GC-MS analyses were conducted on a Shimadzu (Kyoto, Japan) GC-17A gas chromatograph equipped with a Neutra Bond-5 (30 m \times 0.25 mm, film thickness 0.4 μ m; GL Sciences, Tokyo, Japan) and coupled to a QP-5000 quadrupole mass spectrometer injector. The mass spectrometer was operated in the electron impact mode at 70 eV. Helium was used as carrier gas with a flow rate of 0.8 ml/min. The first oven temperature was at 240°C, which was then increased to 300°C at a rate of 10°C/min. Sample (1 μ l) was injected into the gas chromatograph at an injector temperature of 310°C. The 5 α -reductase activity was measured by analyzing the extent of the conversion of testosterone to 5 α -dihydrotestosterone. The 5 α -reductase inhibitory activity of each sample was calculated as follows:

$$\begin{aligned} 5\alpha\text{-Reductase inhibitory activity (\%)} \\ = (A_0 - A_s)/A_0 \times 100 \end{aligned}$$

A_0 and A_s represent peak areas of 5 α -dihydrotestosterone in the absence and presence of sample, respectively. Here, the peak areas of 5 α -dihydrotestosterone were normalized to those of the internal standard, cholesterol acetate. The peak areas of other products represented less than 5% of the peak area of 5 α -dihydrotestosterone formation, within the experimental error. Each experiment was carried out in duplicate or triplicate, and replicate values were usually within 5% of each other. α -Linolenic acid (Sigma, St. Louis, MO, USA) was used as a positive control.

Extraction and separation of extractives of *A. altilis*

The acetone extract (2 g) of the leaves of *A. altilis* were suspended in water and partitioned with *n*-hexane, diethyl ether, and ethyl acetate successively to give *n*-hexane-soluble (0.438 g, 22% of the acetone extract), diethylether-soluble (1.452 g, 72.6%), ethyl acetate-soluble (0.026 g, 1.3%), and an aqueous portion (0.086 g, 4.3%), respectively. The diethylether-soluble portion (1 g) was fractionated into eight fractions (A-H) by column chromatography (CC) on silica gel (Wakogel C-200; Wako, Osaka, Japan) (200 g) eluting with ethyl acetate-*n*-hexane gradient [ethyl acetate:*n*-hexane = 1:3, 0.5 ℓ (A 0.081 g, B 0.019 g) \rightarrow 1:2, 0.5 ℓ (C 0.011 g, D 0.400 g) \rightarrow 1:1, 0.5 ℓ (E 0.134 g) \rightarrow 1.0:0.5, 0.5 ℓ (F 0.081 g) \rightarrow ethyl acetate, 0.5 ℓ (G 0.197 g) \rightarrow MeOH, 0.5 ℓ (H 0.003 g)]. Of these, fraction D (thin-layer chromatography, silica gel, EtOAc/*n*-hexane 1:3, R_f 0.2-0.5) was obtained as the 5 α -reductase inhibitory fraction. Compound **1** (95 mg, 0.53% in dried leaves) was isolated as the main active constituent from a portion of fraction D (320 mg) by preparative high-performance liquid chromatography (HPLC) (Inertsil PREP-ODS: 20 mm i.d. \times 250 mm) using H₂O/CH₃CN (40:60), 12 ml/min.

Isolated compound from *A. altilis*

All nuclear magnetic resonance (NMR) experiments were performed at 400 MHz. The sample was dissolved in

acetone- d_6 , and chemical shifts were referred to internal trimethylsilane (TMS) for ^1H -NMR and to deuterated solvents for ^{13}C -NMR.

Compound **1**, 2-geranyl-2',3,4,4'-tetrahydroxydihydrochalcone: yellow powder, FAB-MS (glycerol): $m/z = 409$ ($[\text{M}-\text{H}]^-$). ^1H -NMR (acetone- d_6): $\delta = 1.54$ (3H, d, $J = 0.73$ Hz, 9''-H), 1.60 (3H, d, $J = 0.98$ Hz, 8''-H), 1.75 (3H, d, $J = 0.98$ Hz, 10''-H), 1.97 (2H, m, 4''-H), 2.04 (2H, m, 5''-H), 2.93 (2H, m, β -H), 3.17 (2H, m, α -H), 3.45 (2H, dd, $J = 0.73$, 6.6 Hz, 1''-H), 5.07 (1H, m, 6''-H), 5.19 (1H, m, 2''-H), 6.33 (1H, d, $J = 2.4$ Hz, 3'-H), 6.41 (1H, dd, $J = 2.4$, 8.9 Hz, 5'-H), 6.59 (1H, d, $J = 8.1$ Hz, 5-H), 6.65 (1H, d, $J = 8.1$ Hz, 6-H), 7.77 (1H, d, $J = 8.9$ Hz, 6'-H), 12.82 (1H, s, 2'-OH). ^{13}C -NMR (acetone- d_6): $\delta = 16.5$ (10''-C), 17.7 (9''-C), 25.8 (8''-C), 25.9 (1''-C), 27.5 (5''-C), 28.1 (β -C), 40.2 (α -C), 40.4 (4''-C), 103.1 (3'-C), 108.6 (5'-C), 113.3 (5-C), 113.8 (1'-C), 120.5 (6-C), 124.4 (2''-C), 124.9 (6''-C), 127.3 (2-C), 131.5 (7''-C), 132.1 (1-C), 133.3 (6'-C), 134.9 (3''-C), 143.4 (3-C), 144.1 (4-C), 165.2 (4'-C), 166.1 (2'-C), 204.9 (C=O).

Results and discussion

The 17 samples prepared from 16 Thailand plant species were examined for 5α -reductase inhibitory activity at a concentration of 200 $\mu\text{g}/\text{ml}$. The acetone extracts of *A. altilis* and *I. maerothyra* showed potent inhibitory activity at 75% and 79% on 5α -reductase, respectively (Table 1). In our preliminary activity-guided fractionation of the acetone extract of *I. maerothyra*, α -linolenic acid, which is known to be a potent inhibitor,¹⁰ was identified as a main active component by GC-MS. Therefore, *A. altilis* was selected for further investigation. The acetone extract of leaves of *A. altilis*

Table 1. Effect of 17 samples prepared from Thailand plants on 5α -reductase activity

Sample ^a	5α -Reductase inhibitory activity (%)
Acetone extract	
<i>Alstonia scholaria</i> (leaves)	0
<i>Annona squamosa</i> (leaves)	0
<i>Alpinia galanga</i> (leaves)	1
<i>Tamarindus indica</i> (leaves)	1
<i>Albizia myriophylla</i> (leaves)	5
<i>Acacia concinna</i> (fruits)	21
<i>Flagellaria indica</i> (leaves)	23
<i>Leucaena leucocephala</i> (leaves)	25
<i>Citrus hystrix</i> (skin of fruits)	25
<i>Clitoria ternatea</i> (flowers)	29
<i>Eucalyptus</i> sp. (leaves)	47
<i>Passiflora foetida</i> (vines)	47
<i>Piper betle</i> (leaves)	51
<i>Mitragyna hirsuta</i> (leaves)	53
<i>Artocarpus altilis</i> (leaves)	75
<i>Ixora maerothyra</i> (leaves)	79
Juice: <i>Citrus hystrix</i> (fruits)	14

5α -Reductase inhibitory activity (%) = $(A_0 - A_s)/A_0 \times 100$

A_0 and A_s represent peak areas of 5α -dihydrotestosterone in the absence and presence of sample, respectively

^a Sample concentration was 200 $\mu\text{g}/\text{ml}$

was partitioned by *n*-hexane, diethylether, and ethyl acetate. The 5α -reductase inhibitory activities of *n*-hexane-soluble, diethylether-soluble, ethyl acetate-soluble, and aqueous portions were 20%, 67%, 33%, and 0%, respectively, at a concentration of 100 $\mu\text{g}/\text{ml}$. The diethylether-soluble portion showing the strongest 5α -reductase inhibitory activity was submitted to further separation by silica gel CC giving eight fractions (5α -reductase inhibitory activity at 100 $\mu\text{g}/\text{ml}$: A, 24%; B, 21%; C, 42%; D, 90%; E, 46%; F, 13%; G, 4%; and H, 13%). Fraction D showed the strongest inhibitory activity. Further separation of fraction D by preparative HPLC gave an active constituent, compound **1**.

Compound **1** was identified as follows. The ^{13}C -NMR spectrum revealed 25 carbon atoms (DEPT: $10 \times \text{C}$, $7 \times \text{CH}$, $5 \times \text{CH}_2$, $3 \times \text{CH}_3$). The FAB mass spectral data ($[\text{M}-\text{H}]^- = 409$) together with the ^{13}C -NMR data suggested the molecular formula to be $\text{C}_{25}\text{H}_{30}\text{O}_5$. Compound **1** showed characteristic signals for a dihydrochalcone at δ 2.93 (2H, *m*, CH_2 - β) and 3.17 (2H, *m*, CH_2 - α) in its ^1H NMR spectrum and at δ 28.1 (C- β), 40.2 (C- α), and 204.9 (C=O) in its ^{13}C NMR spectrum.^{12,13} The ^1H -NMR spectrum showed the presence of a geranyl [δ 1.54 (3H, *d*, $J = 0.73$, CH_3 -9''), δ 1.60 (3H, *d*, $J = 0.98$, CH_3 -8''), δ 1.75 (3H, *d*, $J = 0.98$, CH_3 -10''), 1.97 (2H, *m*, CH_2 -4''), 2.04 (2H, *m*, CH_2 -5''), 3.45 (2H, *dd*, $J = 0.73$, 6.6, CH_2 -1''), 5.07 (1H, *m*, CH -6''), 5.19 (1H, *m*, CH -2'')] and a chelated hydroxyl group [δ 12.82 (1H, *s*, OH)], in addition to a set of *ortho*-coupled one proton doublets [δ 6.59 and 6.65 (each $J = 8.1$ Hz, CH-5, 6)] assignable to that of ring A and three protons in an ABX spin system [δ 6.33 (*d*, $J = 2.4$ Hz, CH-3'), 6.41 (*dd*, $J = 2.4$, 8.9 Hz, CH-5') and 7.77 (*d*, $J = 8.9$ Hz, CH-6)] due to ring B.

The substituted positions of rings A and B were determined as follows. In the heteronuclear multiple bond connectivity (HMBC) spectrum (Fig. 1), the methylene protons of the geranyl group at δ 3.45 were coupled with three quaternary carbons at δ 127.3 (C-2), 132.1 (C-1), and 143.4 (C-3). Moreover, the benzyl methylene protons at δ 2.93, assigned to H- β of dihydrochalcone moiety, caused a cross-

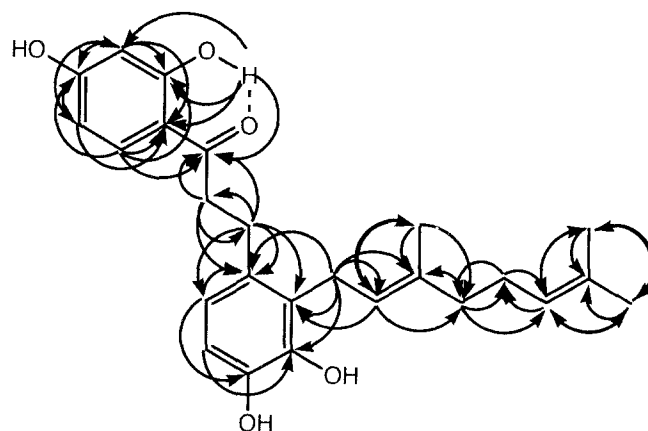


Fig. 1. Heteronuclear multiple bond connectivity (HMBC) correlations of compound **1**

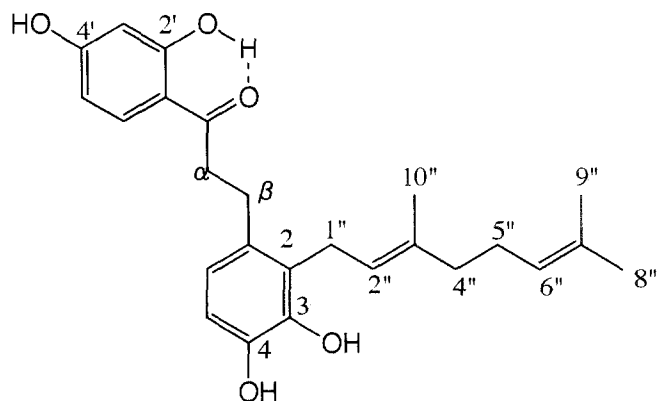


Fig. 2. Chemical structure of compound 1

peak with three quaternary carbons at δ 120.5 (C-6), 127.3 (C-2), and 132.1 (C-1). Consequently, the geranyl group was at C-2. Thus, we concluded that compound 1 was 2-geranyl-2',3,4,4'-tetrahydroxydihydrochalcone (Fig. 2). In this connection, ^{13}C NMR data of compound 1 were not completely identical to the published data¹⁴ for 2-geranyl-2',3,4,4'-tetrahydroxydihydrochalcone. Their ^{13}C NMR data showed δ 58.6 (*t*), but there was no similar value in our data. However, it was confirmed that the previous data¹⁴ had been erroneously published (Y. Fujimoto, College of Pharmacy, Nihon University, personal communication). Our mass spectrometry and ^1H NMR data of compound 1 were almost identical to those for 2-geranyl-2',3,4,4'-tetrahydroxydihydrochalcone.¹⁴ The complete assignment of hydrogen and carbon atoms in the ^1H and ^{13}C -NMR spectra of the compound was accomplished for the first time by HMBC and heteronuclear single quantum coherence (HSQC) (see Materials and methods).

Compound 1, 2-geranyl-2',3,4,4'-tetrahydroxydihydrochalcone, showed more potent 5α -reductase inhibitory activity ($\text{IC}_{50} = 38 \mu\text{M}$) than α -linolenic acid, known as a naturally occurring potent inhibitor ($\text{IC}_{50} = 116 \mu\text{M}$). 2-Geranyl-2',3,4,4'-tetrahydroxydihydrochalcone, one of a few natural occurring C-geranylated dihydrochalcones in nature with highly potent and selective 5-lipoxygenase inhibitory activity, has been isolated from the flower part of the Indonesian plant *Artocarpus communis*^{14,15} (= *A. altilis*). Total synthesis of this compound has been accomplished.^{16,17} In this study we found a new aspect of biological activity: 5α -reductase inhibitory activity.

Several naturally occurring, nonsteroidal compounds had been reported to be 5α -reductase inhibitor. The inhibitory effects of the green tea flavonoids, such as epicatechin-3-gallate and epigallocatechin-3-gallate, against 5α -reductase were examined. Liao and Hiipakka proposed that the gallyl or galloyl group of these tea gallates may interact with a specific site on 5α -reductase; and other parts of the catechin molecule may also important for inhibition, as simple gallates were not active.¹¹ Also, the inhibitory effects of some polyunsaturated fatty acids, such as γ -linolenic acid and α -linolenic acid, against 5α -reductase were examined.¹⁰ Polyunsaturated fatty acids, but not their

monounsaturated or saturated counterparts, are also moderately potent inhibitors of 5α -reductase enzyme activity. 5α -Reductase is a membrane-bound enzyme that appears to require the unique environment of the lipid bilayer for activity.⁶ The addition of phospholipids to solubilized enzyme preparations frequently stimulates activity,¹⁸ suggesting a role for lipids in modulating enzyme activity. The inhibition of 5α -reductase enzyme activity by polyunsaturated fatty acids may therefore reflect another form of this modulation, such as perturbation of the lipid matrix of microsomal membranes.⁶

Some of the isoprenylated compounds from the moraceous plants showed interesting biological activity.¹⁹ It has been reported that isoprenoid-substituted flavonoids and stilbenes isolated from heartwood of *Artocarpus* species have inhibitory effects on melanin biosynthesis,² arachidonate 5-lipoxygenase, and mouse tumor necrosis factor- α (TNF α) release, cytotoxicity, antiplatelet activity and antibacterial activity against carcinogenic bacteria.¹⁹ Thus the *Artocarpus* plants are important medicinal resources.

This is the first report of 5α -reductase inhibitory effects of *A. altilis* leaf extracts. 2-Geranyl-2',3,4,4'-tetrahydroxydihydrochalcone was isolated from the leaf extracts of *A. altilis* as a potent 5α -reductase inhibitor. Additional studies of the inhibitory mechanism and structure-activity relationship are in progress.

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