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# Compounds inhibitory to rat liver 5α-reductase from tropical commercial wood species: resveratrol trimers from melapi (*Shorea* sp.) heartwood

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**Abstract** 5α-Reductase inhibitory activity of methanol extracts of the heartwood of 13 tropical wood species were examined. Strong 5α-reductase inhibitory activity was observed with *Shorea* species. From melapi (*Shorea* sp.), two known resveratrol trimers, vaticanol A and ampelopsin C, and two novel trimers were isolated as active compounds. The structures of the two novel resveratrol trimers were elucidated by one- and two-dimensional nuclear magnetic resonance spectroscopic analyses, including $^{1}$H-$^{1}$HCOSY, HMQC, and HMBC. The compounds were named melapinol A and melapinol B. There were no significant differences among the 5α-reductase inhibitory activities of the four resveratrol trimers, which were significantly stronger than those of α-linolenic acid and epigallocatechin gallate, known 5α-reductase inhibitors.

**Key words** Melapi · *Shorea* species · Dipterocarpaceae · 5α-Reductase inhibitor · Resveratrol trimer

## Introduction

Androgen regulates the function and growth of some types of cells in androgen target tissues. In the skin and prostate, typical androgen target tissues, testosterone is converted to a potent androgen, 5α-dihydrotestosterone (DHT), by the steroid 5α-reductase.[1] Excessive production of DHT is responsible for male-pattern baldness, the pathogenesis of benign prostatic hyperplasia, acne, and female hirsutism.[2] Therefore, 5α-reductase inhibitors may provide a remedy or prevention of these androgen-dependent diseases. Many steroid derivatives, including azasteroids, have been investigated as 5α-reductase inhibitors.[3] Recently, 4-azasteroid (finasteride) was commercialized for therapy of symptomatic benign prostatic hyperplasia and male-pattern baldness. Finasteride decreases the serum concentration of DHT and increases that of testosterone.[4] However, loss of libido, loss of erection, ejaculatory dysfunction, hypersensitivity reactions, gynecomastia, and severe myopathy have been reported after 5 mg finasteride in older men.[5] It is preferable to develop therapeutic agents without such serious adverse effects.

In the present study we evaluate bioactive components from typical tropical commercial woods for the development of new therapeutic agents. About 50% of the forest area in the world is in tropical regions, where there is a great diversity of plants. In the plant kingdom, tropical woods also have a great diversity of extractives, which are obtained in much larger quantities than are the extractives of temperate woods. Tropical woods are useful as industrial raw materials (e.g., in the furniture and construction industries in Japan). Processing of wood results in large amounts of wastewood, which may become a source of chemicals for medical or cosmetic agents. Thus, tropical woods offer the possibility of providing new bioactive components.

We report here an examination of 5α-reductase inhibitory compounds in heartwood extracts of 13 typical tropical commercial woods. Of them, three *Shorea* species exhibited strong inhibitory activities. It is suggested that *Shorea* species contain specific 5α-reductase inhibitory components. Therefore, further purification was carried out for heartwood extractives of melapi, one of the three *Shorea* species, and four inhibitory compounds were isolated.

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## Materials and methods

### Sample woods

Blocks of seven tropical wood species – *Dalbergia latifolia* (Leguminosae), *Diospyros* sp. "ebony" (Ebenaceae),

*Eusideroxylon zwageri* (Lauraceae), *Intsia* sp. "merbau" (Leguminosae), *Shorea laevifolia* (Dipterocarpaceae) and *Shorea* sp. "selangan batu merah" (Dipterocarpaceae), *Tectona grandis* (Verbenaceae) – were collected in Indonesia by Dr. Wasrin Syafii (Bogor Agricultural University, Indonesia). The planks of six tropical wood species – *Aucoumea klaineana* (Burseraceae), *Dactylocladus stenostachys* (Melastomataceae), *Hevea brasiliensis* (Euphorbiaceae), *Palaquium* sp. "nyatoh" (Sapotaceae), *Scaphium* sp. "kembang sumangkok" (Sterculiaceae), and *Shorea* sp. "melapi" (Dipterocarpaceae) – were purchased from a timber company. All blocks were ground in a Wiley mill. The former seven tropical wood specimens are preserved at the herbarium of the Department of Forest Products, Kyushu University, Japan; and the latter six tropical wood specimens are at the Interior Design Research Institute, Fukuoka Industrial Technology Center, Japan.

## Extraction of heartwood meals of 13 tropical species

The heartwood portion of each species was milled. The meal was extracted with methanol for 24 h at room temperature.

## Extraction and separation of extractives of melapi

Air-dried heartwood meal of melapi (0.8 kg) was extracted with methanol for 6 days at room temperature, and the extract was concentrated to about 50 ml. After addition of the same volume of water, the mixture was partitioned with 100 ml of $Et_2O$ in a 500-ml separatory funnel to give aqueous- and $Et_2O$-soluble fractions. The $Et_2O$-soluble fraction was concentrated to dryness. The residue (24 g) was separated repeatedly by silica gel column chromatography (42 mm i.d. × 105 cm) using EtOAc-*n*-hexane gradient as eluent. Separate activity-guided fractionation was repeated on a smaller scale using EtOAc-*n*-hexane (2:1) as eluent. A 5$\alpha$-reductase inhibitory fraction (350 mg) was obtained. Further isolation was performed by preparative high performance liquid chromatography (HPLC) (GL Sciences, C-18 column Inertsil PREP-ODS: 20 mm i.d. × 250 mm), eluting with $H_2O$-$CH_3CN$ (75:25, 10 ml/min), to give compound **1** [58 mg, room temperature (RT), 33 min), compound **2** (113 mg, RT, 44 min), and a mixture of compounds **3** and **4** (38 mg, RT, 48–49 min). Compounds **3** and **4** were made separable only using analytical scale HPLC (Phenomenex PRODIGY 5$\mu$m ODS-3V: 4.6 mm i.d. × 150 mm) eluting with $H_2O$-$CH_3CN$ (77:23, 1 ml/min), RT, 38 and 41 min, respectively, which were indivisible by preparative HPLC and by thin-layer chromatography (TLC).

## Isolated compounds from melapi

The $^1H$ and $^{13}C$ spectra, $^1H$-$^1H$ COSY, HMQC, and HMBC experiments were performed in acetone-$d_6$ with trimethylsilane (TMS) as an internal standard, using a 400-MHz spectrometer. Complete assignment of all protons and carbons in $^1H$ and $^{13}C$ spectra of melapinol A and B were confirmed by the HMQC spectra.

Vaticanol A (compound **1**). $^1H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra matched well with the published data.[6]

Ampelopsin C (compound **4**). $^1H$ and $^{13}C$ NMR spectra matched well with the published data.[7]

Melapinol A (compound **2**). Yellow solid: $[\alpha]_D$ + 186°, (MeOH). $\delta_H$3.59 (*d*, *J* = 10.5, H-8), 4.07 (*m*, H-7), 4.30 (*dd*, *J* = 9.2, *J* = 2.2, H-7″), 4.83 (*d*, *J* = 2.2, H-8″), 5.36 (*d*, *J* = 9.5, H-8′), 5.67 (*d*, *J* = 9.3, H-7′), 6.05 (*d*, *J* = 8.8, 2H, H-2″, H-6″), 6.08 (*s*, H-12), 6.12 (*d*, *J* = 2.4, H-14′), 6.12 (*t*, *J* = 2.2, H-12″), 6.15 (*d*, *J* = 2.4, H-12′), 6.30 (*d*, *J* = 2.0, 2H, H-10″, H-14″), 6.31 (*d*, *J* = 8.3, 2H, H-3″, H-5″), 6.85 (*d*, *J* = 8.5, 2H, H-3, H-5), 7.00 (*d*, *J* = 8.7, 2H, H-3′, H-5′), 7.21 (*d*, *J* = 8.3, 2H, H-2, H-6), 7.56 (*d*, *J* = 8.5, 2H, H-2′, H-6′); $\delta_C$42.4 (C-8″), 51.1 (C-7″), 51.1 (C-8), 52.3 (C-8′), 58.1 (C-7), 95.4 (C-7′), 96.1 (C-12), 101.5 (C-12′), 101.9 (C-12″), 107.4 (C-10″, 14″), 107.8 (C-14′), 113.5 (C-3″, 5″), 115.2 (C-3, 5), 115.8 (C-14), 116.3 (C-3′, 5′), 123.3 (C-10), 123.5 (C-10′), 130.1 (C-1′), 130.4 (C-2, 6), 131.1 (C-2′, 6′), 132.6 (C-1″), 132.7 (C-2″, 6″), 133.4 (C-1), 140.2 (C-9″), 143.8 (C-9), 147.9 (C-9′), 155.3 (C-4′), 155.6 (C-4″), 156.1 (C-4), 156.1 (C-13′), 157.6 (C-13), 158.3 (C-11′), 159.1 (C-11″, 13″), 160.1 (C-11).

Melapinol B (compound **3**). Brown solid: $[\alpha]_D$-108°, (MeOH). $\delta_H$3.87 (*dd*, *J* = 105, *J* = 2.4, H-7″), 4.41 (*dd*, *J* = 8.5, *J* = 3.1, H-8), 4.69 (*d*, *J* = 2.2, H-8″), 5.37 (*d*, *J* = 3.4, H-7), 6.06 (*d*, *J* = 8.5, 2H, H-3″, 5″), 6.11 (*brs*, 2H, H-10″, 14″), 6.14 (*brs*, H-12″), 6.27 (*d*, *J* = 8.3, 2H, H-2″, 6″), 6.34 (*d*, *J* = 2.2, H-12′), 6.34 (*d*, *J* = 8.5, 2H, H-3, 5), 6.66 (*d*, *J* = 2.5, H-14′), 6.77 (*d*, *J* = 8.8, 2H, H-2, 6), 6.85 (*d*, *J* = 8.8, 2H, H-3′, 5′), 6.90 (*s*, H-12), 7.46 (*d*, *J* = 8.1, 2H, H-2′, 6′); $\delta_C$41.6 (C-7), 51.5 (C-8), 57.4 (C-8″), 61.0 (C-7″), 96.2 (C-12), 101.1 (C-12″), 102.4 (C-12′), 106.1 (C-10″, 14″), 109.6 (C-14′), 114.2 (C-3″, 5″), 114.5 (C-3, 5), 116.1 (C-3′, 5′), 116.2 (C-8′), 119.7 (C-10), 124.1 (C-1′), 125.4 (C-10′), 127.3 (C-14), 130.2 (C-2, 6), 130.4 (C-2″, 6″), 130.6 (C-2′, 6′), 134.1 (C-1″), 134.4 (C-9′), 135.2 (C-1), 140.8 (C-9), 149.0 (C-9″), 151.6 (C-7′), 152.6 (C-13), 154.6 (C-4″), 154.9 (C-11), 155.8 (C-11′, 13′), 156.2 (C-4), 158.4 (C-4′), 159.1 (C-11″, 13″).

## Preparation of rat liver microsomes

Sprague-Dawley female rat livers were removed and homogenized in medium A (0.32 M sucrose, 1 mM dithiothreitol, and 20 mM sodium phosphate, pH 6.5) as described by Shimizu et al.[8] The homogenate was centrifuged at 10000*g* for 10 min at 0°C. The resulting pellets were suspended in medium A, and centrifugation was performed again. The microsomes were obtained as a precipitate after further ultracentrifugation (105000*g* for 1 h at 0°C) of the preceding supernatants. The washed microsomes were suspended in 10 ml medium A, and the microsomes were dispersed using a syringe with 18-, 23-, and 26-gauge needles in succession. The microsome suspension

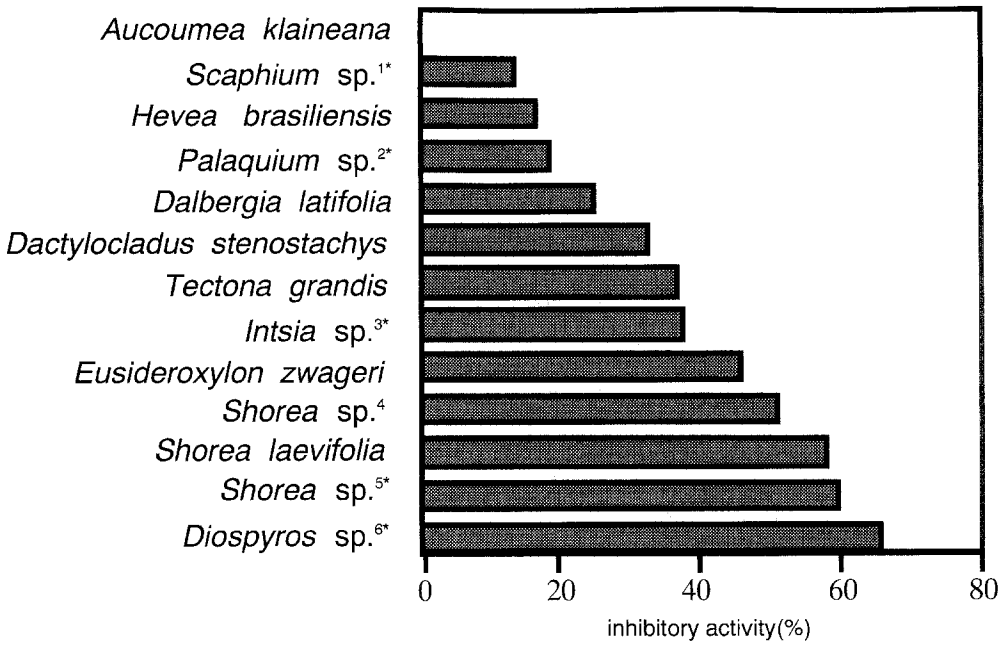


**Fig. 1.** Inhibitory activity of 13 tropical woods: methanol extracts against rat liver 5$\alpha$-reductase. Extracts concentration was 50ppm. Standard names selected by the ATIBT committee on tropical timber nomenclature[9] are as follows: [1]*Kembang sumankok. [2]*Nyatoh. [3]*Merbau. [4]*Melapi. [5]*Selangan-batu-merah. [6]*Ebony

was divided into small aliquots and stored at −80°C. The microsomes were diluted with medium A just before use.

Protein determination

The protein content of microsomes was determined by a Bio-rad protein assay kit (catalog no. 500-0006) using bovine serum albumin (BSA) as a standard.

Determination of 5$\alpha$-reductase inhibitory activity

The standard reaction mixture, in a final volume of 3.0ml, contained microsomes (1mg of protein), 150$\mu$M testosterone in 100$\mu$l of ethanol, 167$\mu$M NADPH, and medium A, with or without the indicated amount of a sample in 100$\mu$l of dimethylsulfoxide (DMSO). The reaction was started by the addition of microsomes to the preheated reaction solution in a tube. After 10min the incubation was terminated by adding 100$\mu$l of 3M NaOH; 100$\mu$l of 1.0mM cholesterol acetate in *n*-hexane was then added as an internal standard for gas chromatography-mass spectrometry (GC-MS). To extract metabolites, 40ml of diethyl ether 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$\mu$l ethyl acetate for GC-MS. Inhibitory activity was evaluated by the dihydrotestosterone (DHT)/internal standard ratio derived from the GC-MS analysis [selected ion monitoring (SIM)] according to the methods of Shimizu et al.[8]

## Results and discussion

The heartwood meals of 13 tropical wood species were extracted with methanol for about 24h at room temperature. Rat liver 5$\alpha$-reductase inhibitory activity was assayed in each of the methanol extracts at a concentration of 50ppm. Among all of the heartwood extractives investigated, three *Shorea* species showed inhibitory activities over 50%, together with *Diospyros* sp. (Fig. 1). This suggested that *Shorea* species heartwood contain specifically the extractives that inhibit 5$\alpha$-reductase activity. In this study, for the first time, melapi extractives were further investigated among the three *Shorea* species.

To isolate 5$\alpha$-reductase inhibitory components, extraction was done on a larger scale. 5$\alpha$-Reductase inhibitory activity-guided fractionation led to isolation of compounds **1**, **2**, **3**, and **4** as inhibitory components. Compound **1** was identified as vaticanol A, recently isolated from *Vatica rassak*,[6] and compound **4** was identified as ampelopsin C, previously isolated from *Ampelopsis brevipedunculata* var. *hancei*.[10] Compounds **2** and **3** were novel compounds and were called melapinol A and B, respectively. Their structures are shown in Fig. 2.

Melapinol A was identified as follows. The FAB mass spectral data ($[M + H]^+ = 681$) together with the $^{13}$C-NMR data (42 carbons) indicated the molecular formula to be $C_{42}H_{32}O_9$. The $^1$H-NMR spectrum also exhibited six sets of AX-type hydrogen, $\delta = 6.05$ (2H, *d*, $J = 8.8$), $\delta = 6.31$ (2H, *d*, $J = 8.3$), $\delta = 6.85$ (2H, *d*, $J = 8.5$), $\delta = 7.00$ (2H, *d*, $J = 8.7$), $\delta = 7.21$ (2H, *d*, $J = 8.3$), $\delta = 7.56$ (2H, *d*, $J = 8.5$); one set of $AX_2$-type hydrogen $\delta = 6.30$ (2H, *d*, $J = 2.0$), $\delta = 6.12$ (1H, *t*, $J = 2.2$); *meta*-coupled aromatic hydrogen $\delta = 6.12$ (1H, *d*, $J = 2.4$), $\delta = 6.15$ (1H, *d*, $J = 2.4$), singlet aromatic hydrogen $\delta = 6.08$ (1H, *s*); and six aliphatic signals at $\delta = 5.67$ (1H, *d*, $J = 9.3$), $\delta = 5.36$ (1H, *d*, $J = 9.5$), $\delta = 4.83$ (1H, *d*, $J = 2.2$), $\delta = 4.30$ (1H, *dd*, $J = 9.2$, $J = 2.2$), $\delta = 4.07$ (1H, *m*), and $\delta = 3.59$ (1H, *d*, $J = 10.5$). Complete assignment of all protons and carbons were also confirmed by HMQC. The $^1$H-$^1$H-COSY spectrum on the mutually coupled methine hydrogens showed that at $\delta = 5.66$, $\delta = 4.83$, and $\delta = 4.07$ correlated with at $\delta = 5.36$, $\delta = 4.31$, and $\delta = 3.60$.

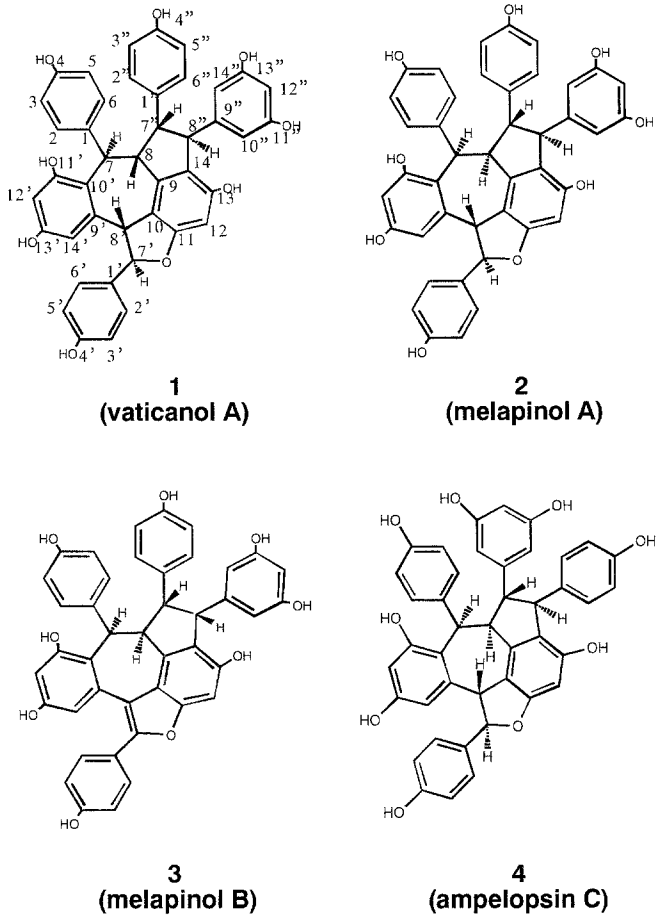


**Fig. 2.** Structures of compounds **1**, **2**, **3**, and **4**

HMBC correlation of H-8″ with C-7″ C-10″, C-14″, and C-14, H-7 with C-1, C-8, and C-10′, H-8 with C-9 and C7″, H8′ with C-9′, C-10, and C-1′ established that the planar structure can be drawn as melapinol A in Fig. 2. Melapinol A showed NOE interactions between H-8′ and H-7″; H-7 and H-2″ (6″); H-8 and H-2″ (6″); H-7″ and H-14″; and between H-8″ and H-2″ (6″), which is proof of the *trans*-configuration between H-7″ and H-8″ of melapinol A. Unusual chemical shifts of *ortho*-coupled hydrogens was observed at $\delta$ = 6.05 (H-2″, H-6″) and $\delta$ = 6.31 (H-3″, H-5″) in melapinol A. Similar shielding effects were recognized in the resveratrol trimers, suffruticosols A, B,[11] and vaticanol A, which are the stereoisomers of melapinol A.

Melapinol B was identified as follows. The FAB mass spectral data ($[M + H]^+$ = 679) together with the $^{13}$C-NMR data (42 carbons) revealed its molecular formula to be $C_{42}H_{30}O_9$. The $^1$H-NMR spectrum also exhibited six sets of AX-type hydrogen, $\delta$ = 6.06 (2H, *d*, *J* = 8.5), $\delta$ = 6.27 (2H, *d*, *J* = 8.3), $\delta$ = 6.34 (2H, *d*, *J* = 8.5), $\delta$ = 6.77 (2H, *d*, *J* = 8.8), $\delta$ = 6.85 (2H, *d*, *J* = 8.8), $\delta$ = 7.46 (2H, *d*, *J* = 8.1); two sets of *meta*-coupled aromatic hydrogen $\delta$ = 6.11 (2H, *brs*), $\delta$ = 6.14 (1H, *brs*), $\delta$ = 6.34 (1H, *d*, *J* = 2.2), $\delta$ = 6.66 (1H, *d*, *J* = 2.5); singlet aromatic hydrogen $\delta$ = 6.90 (1H, *s*); and four aliphatic signals at $\delta$ = 5.37 (1H, *d*, *J* = 3.4), $\delta$ = 4.69 (1H, *d*, *J* = 2.2), $\delta$ = 4.41 (1H, *dd*, *J* = 8.5, *J* = 3.1), and $\delta$ = 3.87 (1H, *dd*, *J* = 9.5, *J* = 2.4), whereas vaticanol A and melapinol A exhibited six aliphatic hydrogens. Complete assignment of all protons and carbons were also confirmed by HMQC spectra.

**Table 1.** $IC_{50}$ of resveratrol trimers and known inhibitors against rat liver 5$\alpha$-reductase

| Compound | $IC_{50}$ ($\mu$M) |
|---|---|
| Melapinol A | 49.4 |
| Melapinol B | 44.5 |
| Vaticanol A | 59.1 |
| Ampelopsin C | 52.2 |
| $\alpha$-Linolenic acid | 116.0 |
| Epigallocatechin-3-gallate | $\gg$218.0 |
| Finasteride | 0.73 |

$IC_{50}$, 50% inhibitory concentration

The $^1$H-$^1$H-COSY spectrum on the mutually coupled methine hydrogens showed a correlation between values at $\delta$ = 4.42 and $\delta$ = 3.87. All one- and two-dimensional NMR spectroscopic analyses data indicate that melapinol B is a dehydro derivative of vaticanol A and melapinol A. In comparison with vaticanol A and melapinol A, a similar HMBC correlation pattern was revealed in melapinol B, although some differences arose from the unsaturated benzofuran structure. In melapinol B, H-7″ was *cis* oriented to H-8″ based on its NOE results. The unusual chemical shift of *ortho*-coupled hydrogens was also observed at $\delta$ = 6.27 (H-2″, 6″) in melapinol B.

Compounds **1** and **4** were identified as vaticanol A and ampelopsin C, respectively, by a comparison of their NMR data with those in the literature.[6,7]

The 50% inhibition concentrations ($IC_{50}$) for each sample in regard to 5$\alpha$-reductase inhibitory activity are shown in Table 1. No inhibition was observed in the case of resveratrol monomer (data not shown), whereas high $IC_{50}$ values, 44–59$\mu$M, were observed with resveratrol trimers. In comparison with $\alpha$-linolenic acid[12] and finasteride,[4] which were reported to be potent 5$\alpha$-reductase inhibitory compounds, the inhibitory activity trimers was about 2.0- to 2.5-fold that of $\alpha$-linolenic acid; however, these values were considerably higher than that of finasteride. On the other hand, in the case of epigallocatechin-3-gallate, which has also been reported as a potent inhibitory compound,[13] no inhibitory activity was detected in our assay system. Thus, resveratrol trimers derived from melapi heartwood, which exhibited strong inhibitory activity, agreed well with the possibility of their use as therapeutic agents for androgen-dependent diseases.

The resveratrol trimers strongly inhibited 5$\alpha$-reductase, but these activities were indistinguishable from each other. These compounds have a resveratrol dimer portion as a common structure, as shown in Fig. 3. Therefore, a certain part of this portion could play an important role as a 5$\alpha$-reductase inhibitor. Ishibashi et al. reported 5$\alpha$-reductase inhibition by synthetic components including unsaturated 2-phenylbenzofuran derivatives, which have strong inhibitory activity against rat and human 5$\alpha$-reductase.[14] A portion common to both unsaturated 2-phenylbenzofuran deriva-

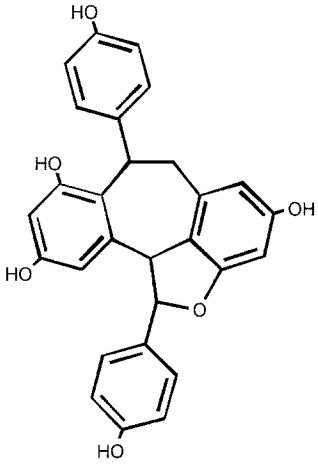


**Fig. 3.** Resveratrol dimer moiety as a common structural unit in resveratrol trimers isolated from melapi heartwood

tives and resveratrol trimers might be involved in 5α-reductase inhibition. According to our results, however, it is evident that no importance was attached to 5α-reductase inhibition, whether the compound has an unsaturated benzofuran moiety or a saturated one.

This is the first report of 5α-reductase inhibitory effects of melapi heartwood extractives and of resveratrol oligomers. Some previous papers revealed the bioactivity of resveratrol trimers on antifungal activity,[15,16] DNA topoisomerase II inhibitory activity,[17] ecdysteroid antagonist activity,[11] and antiinflammatory activity.[18]

*Shorea* species belong to the Dipterocarpaceae family. Isolation of resveratrol trimer has been reported from some species in this family.[19] One, distichol,[20] was from *Shorea* species, but until now it had not been found in melapi heartwood. In addition, ampelopsin C was isolated from two Vitaceae species[6,10] and one Cyperaceae species,[17] but it has never been reported from *Shorea* species.

In the plant kingdom, resveratrol oligomers have been isolated from the following eight families: Dipterocarpaceae, Vitaceae, Cyperaceae, Gnetaceae, Leguminosae, Haemodoraceae, Musaceae, and Paeoniaceae. These compounds were of dimer, trimer, and tetramer formation. Recently a pentamer compound, davidiol D, was found in Leguminosae species.[21]

5α-Reductase inhibitory activity of the resveratrol trimers was appreciably weaker than the inhibitory activity of finasteride. For designing a more potent inhibitor, the structure–activity correlation between stilbenoids and 5α-reductase inhibitory activity is interesting, and further investigation is needed.

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