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Prenylated Flavonoids as Antioxidant and Melanin Inhibitors From Stingless Bee (*Wallacetrigona incisa*) Propolis

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Abstract

Propolis from 4 stingless bees (*Homotrigona apicalis*, *Wallacetrigona incisa*, *Tetragonula fuscobalteata*, and *Tetragonula fuscibasis*) was investigated in the search for medicinal and cosmetic materials from tropical rainforest resources. Methanol extracts of the propolis were screened using antioxidant and antimelanogenesis assays (tyrosinase enzyme activity and melanin inhibitor in B16 melanoma). The extract of *H. apicalis* showed the strongest antioxidant activity, both in the 2,2-diphenyl-1-picrylhydrazyl and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) assays, with half-maximal inhibitory concentration values of 0.72 ± 0.01 (mg/mL) and 0.26 ± 0.00 (mg/mL), respectively. The *H. apicalis* extract also displayed the strongest inhibition of tyrosinase (53% at 100 µg/mL). In the B16 melanoma cell assay, the *W. incisa* extract showed the strongest inhibition of melanin (21%) and was less cytotoxic. The *W. incisa* extract was fractionated to isolate the compounds with biological activities. Two prenylated flavonoids were obtained, named brousoflavonol F and glyasperin A. Both showed potent antioxidant activities, as well as inhibiting melanin in B16 melanoma, but not tyrosinase activity. These results indicated the potential of methanol extract of *W. incisa* to be developed for cosmetic material, but further experiments are needed to verify the function.

Keywords

stingless bee, *Wallacetrigona incisa*, prenylated flavonoid, antioxidant, melanin inhibitor

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Melanin, the major pigment of human skin, is located in the basal layer of the epidermis and is secreted by melanocytes. Melanin is very important in the protection of human skin from harmful ultraviolet (UV) and sun rays.¹ Melanogenesis produces a reactive oxygen species (ROS) and reactive oxidants, including hydrogen peroxide, which creates oxidative stress in the melanocytes. Some ROS scavengers and inhibitors inhibit UV-induced melanogenesis and antioxidants, like reduced glutathione, and ascorbic derivatives are applied for treating several skin problems such as depigmentation of hyperpigmented spots. Therefore, many compounds have been reported as free radical scavengers, antioxidants, and melanin inhibitors, such as vitamin C, arbutin, kojic acid, ellagic acid, tranexamic acid, potassium methoxysalicylate, and 5,5-dipropyl-biphenyl-2,2-diol, which are important to protect human skin from the damaging effects of UV radiation, such as hyperpigmentation.^{2,3}

Stingless bees are a group of insects belonging to 5 genera (*Dectylurina*, *Melipona*, *Meliponula*, *Lestrimelitta*, and *Trigona*), which play an important role in plant pollination.⁴ These

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genera also produce propolis; a mixture of beeswax, plant resins, and pollens which is used to seal their beehives. Stingless bees' propolis is used as a traditional medicine to heal some diseases related to digestive and respiratory systems, female fertility, skin, visual disorders, and various other ailments.^{5,6} Scientifically, propolis from stingless bees has some biological functions such as α -glucosidase inhibition,⁷ antiproliferative activity in human cancer cells,⁸ cytotoxicity to head and neck cancer cell lines,⁹ and antimicrobial, anti-inflammatory, cytotoxic,¹⁰ and antioxidant activities.^{10,11} Evaluation of propolis from stingless bees as a melanin inhibitor has not been reported previously. In this study, our screening data results for the propolis extracts from 4 stingless bees, namely, *Homotrigona apicalis*, *Wallacetrigona incisa*, *Tetragonula fuscobalteata*, and *Tetragonula fuscibasis*, lead us to focus on the isolation of the active antioxidant and melanin inhibitors.

Materials and Methods

Materials

Propolis from *H. apicalis*, *W. incisa*, *T. fuscobalteata*, and *T. fuscibasis* was collected in February 2013 at Mulawarman University Forest Education, Samarinda, East Kalimantan, Indonesia.¹² The stingless bees were identified by Dr Syafrizal and deposited in the Biology Laboratory, Biology Department, Faculty of Mathematics and Sciences, Mulawarman University.

Extraction, Fractionation, and Isolation of the Active Compounds

The propolis was sliced into pieces and extracted with methanol (MeOH). The propolis of *H. apicalis* (21.18 g) was extracted with 100 mL MeOH, the propolis of *W. incisa* (50.04 g) with 200 mL MeOH, the propolis of *T. fuscobalteata* (50.65 g) with 200 mL MeOH, and the propolis of *T. fuscibasis* (50.42 g) with 200 mL MeOH at room temperature for 48 hours. From *H. apicalis* propolis, 2.82 g dry extract was obtained, from *W. incisa* 10.79 g, from *T. fuscobalteata* 13.82 g, and from *T. fuscibasis* 11.63 g. About 10.02 g of *W. incisa* propolis extract was fractionated

by silica gel column chromatography (114.4 g Wakogel C-200, 4.0 × 40 cm) and eluted with *n*-hexane/ethyl acetate (EtOAc) in ratios of 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10 (v/v) and EtOAc/MeOH in ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10 (v/v) to yield 33 fractions (F1–F33). F10 (160 mg) was used for isolating active compounds by preparative high-performance liquid chromatography (HPLC) (Inertsil Prep-ODS:20 mm i.d. × 250 mm) and elution with MeOH/water (H₂O) (0.1% trifluoroacetic acid), 85:15 (v/v), 5 mL/min. Five fractions were obtained, including F10-5-5 (9.4 mg) and F10-5-6 (12.9 mg). Based on nuclear magnetic resonance (NMR) (¹H, ¹³C, distortionless enhancement by polarization transfer [DEPT], heteronuclear multiple-quantum correlation spectroscopy [HSQC], and heteronuclear multiple-bond correlation spectroscopy [HMBC]) spectroscopic data, fractions F10-5-5 and F10-5-6 contained brousoflavonol F¹³ and glyasperin A,^{14,15} respectively (Figure 1).

Radical Scavenging (DPPH) Assay

This assay was performed as described by Arung et al.¹⁶ Five hundred microliters of 60 μ M 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 467 μ L of ethanol were used as working solutions. The positive control in this assay was kaempferol.

ABTS Radical Cation Decolorization Assay

The 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assay used was as described by Tanaka et al.¹⁷ Five milliliters of 7 mM ABTS solution and 88 μ L of 140 mM potassium persulfate were used as working solutions. The results were determined and expressed in terms of Trolox equivalent antioxidant capacity (TEAC, μ g/mg). Kaempferol was used as a positive control.

Tyrosinase Enzyme Assay

The assay was performed as described by Arung et al.¹⁶ L-3,4-dihydroxyphenylalanine (333 μ L of a 2.5 mM solution) and 600

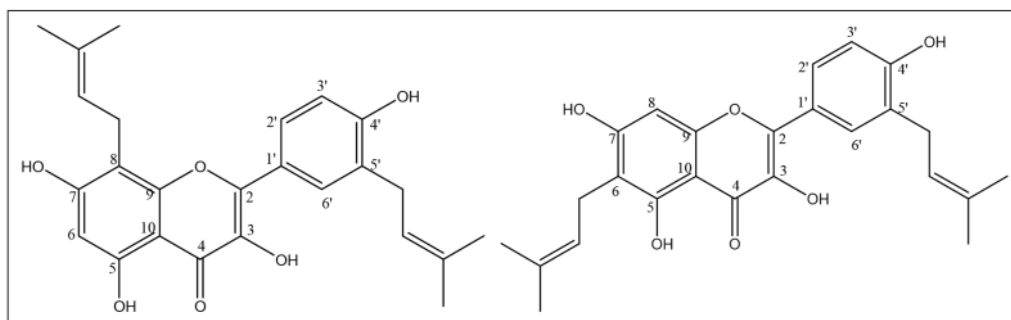


Figure 1. Isolated compounds (brousoflavonol F¹³ [left]; glyasperin A^{14,15} [right]).

Table 1. Antioxidants of Some Propolis Samples.

Propolis extracts	DPPH		ABTS	
	IC ₅₀ (mg/mL)	TEAC (μg/mg)	IC ₅₀ (mg/mL)	TEAC (μg/mg)
<i>Homotrigona apicalis</i>	0.72 ± 0.01	78.0 ± 1.1	0.26 ± 0.00	116.1 ± 2.5
<i>Tetragonula fuscibasis</i>	31.1 ^a ± 0.01	34.5 ± 0.15	0.72 ± 0.01	74.8 ± 1.7
<i>Tetragonula fuscobalteata</i>	38.7 ^a ± 0.02	44.6 ± 0.4	0.26 ± 0.00	115.9 ± 0.01
<i>Wallacetrigona incisa</i>	42.4 ^a ± 0.00	49.5 ± 0.6	0.26 ± 0.00	102.6 ± 3.2

ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); DPPH, 2,2-diphenyl-1-picrylhydrazyl; TEAC, tocoferol equivalent antioxidant capacity.

^aAt 1000 μg/mL.

μL of 0.1 M phosphate buffer (pH 6.8) were used as working solutions in this assay. The positive control was kojic acid.

Determination of Melanin Content and Cell Viability on B16 Melanoma Cells

The B16 melanoma cells were purchased from RIKEN Cell Bank. Eagle's Minimum Essential Medium, 10% (v/v) fetal bovine serum, and 0.09 mg/mL theophylline were used to maintain the cells in the incubator at 37°C with a humidified atmosphere of 5% carbon dioxide. This assay was for determining melanin content and cell viability as previously described by Arung et al.¹⁶ The positive control in this assay was arbutin.

Results and Discussion

We screened propolis extracts from 4 stingless bee species using antioxidant and melanogenesis assays in order to evaluate the potential use of these products as a cosmetic agent. Table 1 shows that the extract of *H. apicalis* propolis produced the highest DPPH scavenging activity (half-maximal inhibitory

concentration (IC₅₀) = 0.72 mg/mL). In the DPPH and ABTS assays, the extracts of *H. apicalis*, *T. fuscobalteata*, and *W. incisa* showed the same activity (IC₅₀ = 0.26 mg/mL) but were higher than for *T. fuscibasis* (IC₅₀ = 0.72 mg/mL). In this experiment, we used Trolox as a positive control for the comparison of these extracts as an antioxidant. Biological activities of propolis as antioxidants using DPPH and ABTS assays have been seldom reported. However, there are reports of the antioxidant properties of propolis extracts of the stingless bees *Scaptotrigona depilis*, *Melipona quadrifasciata*,¹⁸ *Melipona orbignyi*,¹⁹ *Tetragonisca fiebrigi*,¹⁰ and *Melipona fasciculata*.²⁰ Many compounds have been recorded as antioxidants, including flavonoids,¹⁹ phytosterols, terpenes, tocopherol,¹⁸ tannins,²⁰ and phenolics.^{10,18-20}

Next, we screened the propolis samples in melanogenesis assays for tyrosinase enzyme activity and melanin inhibition in B16 melanoma cells. Figure 2 shows the results of the tyrosinase activity of the 4 propolis samples at 100 μg/mL. The propolis of *H. apicalis* showed 53% inhibition of tyrosinase enzyme activity (IC₅₀ < 100 μg/mL), while those of *T. fuscibasis*, *W. incisa*, and *T. fuscobalteata* were 36% (IC₅₀ > 100 μg/mL), 26% (IC₅₀ > 100 μg/mL), and 14% (IC₅₀ > 100 μg/mL), respectively. In this experiment, kojic acid, a well-known tyrosinase

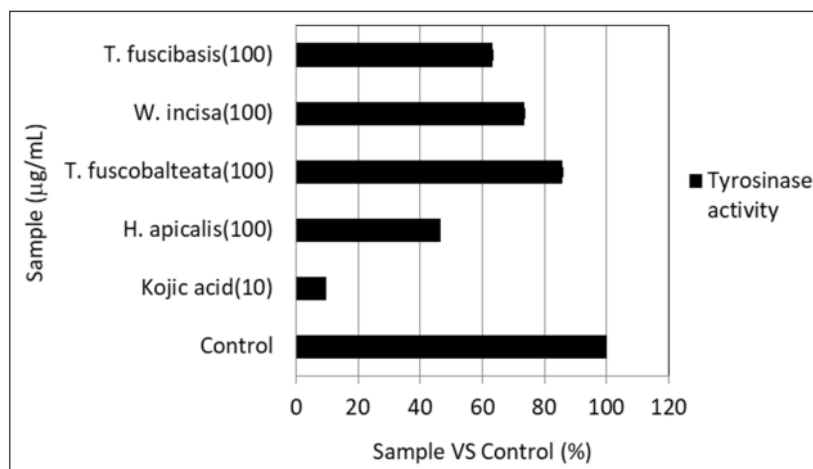


Figure 2. Effect of 4 stingless bees' propolis extracts on tyrosinase activity (all values: mean ± standard deviation).

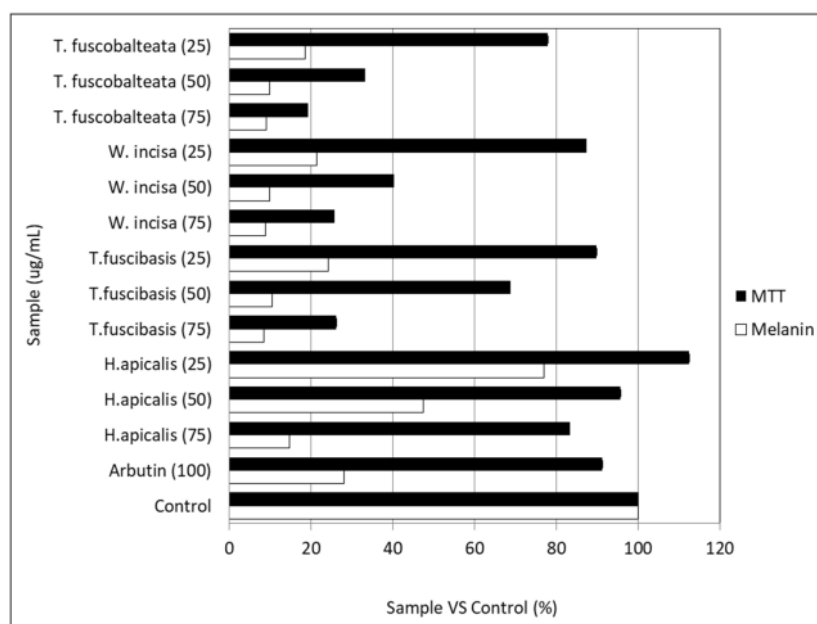


Figure 3. Effect of 4 stingless bees' propolis extracts on melanin inhibition of B16 melanoma cells (all values: mean \pm standard deviation). MTT was representative of cell viability. Melanin was representative of melanin content in cells.

inhibitor,²¹ used as the positive control, produced 90% inhibition at 10 $\mu\text{g/mL}$ ($\text{IC}_{50} < 10 \mu\text{g/mL}$). As far as we know, there has not been a report on the antityrosinase activity of stingless bee propolis extracts. Figure 3 shows the melanin inhibition in B16 melanoma cells of the 4 propolis at various concentrations (25, 50 and 75 $\mu\text{g/mL}$). In this assay, the high melanin inhibition and high viability of cells (represented by MTT) are preferred and potent for a cosmetic agent. The propolis extract of *H. apicalis* at the concentration of 50 $\mu\text{g/mL}$ inhibited 53% of the melanin growth in B16 melanoma cells and 96% of viable cells, whereas that of *T. fuscibasis* inhibited 76% melanin growth in B16 melanoma cells and 90% of viable cells at the concentration of 25 $\mu\text{g/mL}$, and the propolis of *T. fuscobalteata* inhibited 81% of the melanin growth in B16 melanoma cells and 78% of viable cells at the concentration of 25 $\mu\text{g/mL}$. The propolis extract of *W. incisa* inhibited 79% melanin growth in B16 melanoma cells and 87% of viable cells at the concentration 25 $\mu\text{g/mL}$. Arbutin, a well-known melanin inhibitor and less cytotoxic²² used as the positive control inhibited 72% melanin growth in B16 melanoma cells and 90% of viable cells at the concentration 100 $\mu\text{g/mL}$. To our knowledge, it has not been reported that stingless bee propolis extracts inhibit melanin growth in B16 melanoma cells with less cytotoxicity (high viability cells).

Based on the results (Table 1, Figures 2 and 3), thin-layer chromatography (TLC) data (not shown), and high propolis production of stingless bees,²³ we selected *W. incisa* propolis for further fractionation to isolate the active compounds. The

33 fractions collected were screened using DPPH and tyrosinase assays (data not shown). Based on the TLC and HPLC data, and the DPPH and tyrosinase assay results, attention was focused on fraction 10 for isolating the active compounds. Using chromatographic methods and NMR assignments (^1H , ^{13}C , DEPT, HSQC, and HMBC), brousoflavonol F¹³ and glyasperin A^{14,15} were identified. We then evaluated these compounds for their antioxidant and melanogenesis inhibition activities (Table 2 and Figure 4). In previous research, we reported the antioxidant (DPPH and ABTS assays) and melanogenesis activities of glyasperin A from the leaves of *Macaranga pruinosa*.²⁴ In Table 2, glyasperin A ($\text{IC}_{50} = 443.0 \pm 8.0 \mu\text{M}$) is more active in the DPPH assay as an antioxidant than brousoflavonol F ($\text{IC}_{50} = 623.3 \pm 0.2 \mu\text{M}$), but kaempferol, which is well known as an antioxidant, was

Table 2. Antioxidant Activities of Brousoflavonol F and Glyasperin A.

Compound	DPPH	ABTS
	$\text{IC}_{50}(\mu\text{M})$	$\text{IC}_{50}(\mu\text{M})$
Brousoflavonol F	623.3 \pm 0.2	226.9 \pm 0.0
Glyasperin A	443.0 \pm 8.0 ^a	210.0 \pm 2.7 ^a
Kaempferol	23.8 \pm 3.3 ^a	111.0 \pm 1.6 ^a

ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); DPPH, 2,2-diphenyl-1-picrylhydrazyl; IC_{50} , half-maximal inhibitory concentration.

^aData from Arung et al.²²

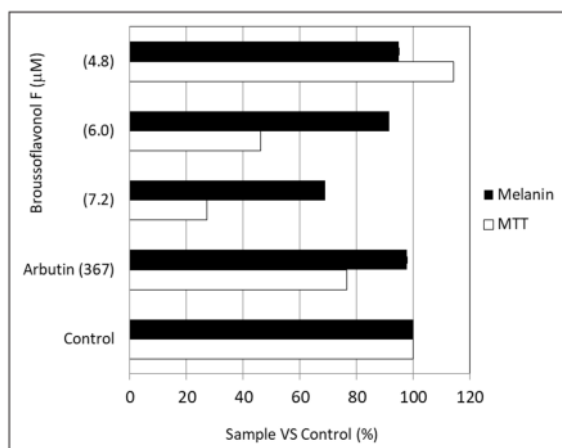


Figure 4. Effect of brousoflavonol F on melanin inhibition of B16 melanoma cells (all values: mean \pm standard deviation). MTT was representative of cell viability and melanin was representative of melanin content in cells.

superior with an IC_{50} of $23.8 \pm 3.3 \mu\text{M}$. In the ABTS assay, glyasperin A ($IC_{50} = 210.0 \pm 2.7 \mu\text{M}$) was also more active as an antioxidant than brousoflavonol F ($IC_{50} = 226.9 \pm 0.0 \mu\text{M}$); the IC_{50} of kaempferol was $111.0 \pm 1.6 \mu\text{M}$. It seems that the positions (positions 6 and 8) of the prenylated moiety have an effect on the antioxidant activities, but this hypothesis needs to be verified. Kim et al.³ reported that antioxidants play an important role in regulating hyperpigmentation and melanogenesis.

Figure 4 shows that brousoflavonol F inhibited melanin growth in B16 melanoma cells (54%) but showed less cytotoxicity at a concentration of $6 \mu\text{M}$, which was better than arbutin, the positive control. Brousoflavonol F was then tested in the tyrosinase enzyme assay but did not show any inhibition (data not shown). Brousoflavonol F and glyasperin A showed antioxidant (DPPH and ABTS assays) activity and inhibited melanin growth in B16 melanoma cells. Some researchers reported the biological function of these compounds as antiplatelet,²⁵ cytotoxic against P-388 cells,²⁶ cytotoxic in some cancer cells,^{27,28} and xanthine oxidase inhibitors.²⁹ To our knowledge, this is the first report about brousoflavonol F as an antioxidant and melanin inhibitor in B16 melanoma cells.

In summary, brousoflavonol F and glyasperin A could be used as cosmetic materials, especially as a skin whitening agent by inhibiting melanin growth and with antioxidant capacity. It still needs other experiments to be addressed for efficacy and safety in human use.



Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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