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

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Submission date: 25-Oct-2021 09:02AM (UTC+0700)
Submission ID: 1682992715
File name: Enos_Tangke_Arung-Nat_Prod_Comm_2020.pdf (419.65K)
Word count: 3630
Character count: 19850

Original Article

Natural Product Communications
Volume 15(3): 1–6

DOI: 10.1177/1934578X20911272
journals.sagepub.com/home/npx

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 fractioned to isolate the compounds with biological activities. Two prenylated flavonoids were obtained, named broussoflavonol 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

Received: December 11th, 2019; Accepted: February 13th, 2020.

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. x 250 mm) and elution with MeOH/water (H_2O) (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, ^{13}C, 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 broussoflavonol F[13] 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 μM 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 467 μL 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 μL of 140 mM potassium persulfate were used as working solutions. The results were determined and expressed in terms of Trolox equivalent antioxidant capacity (TEAC, μg/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 μL of a 2.5 mM solution) and 600

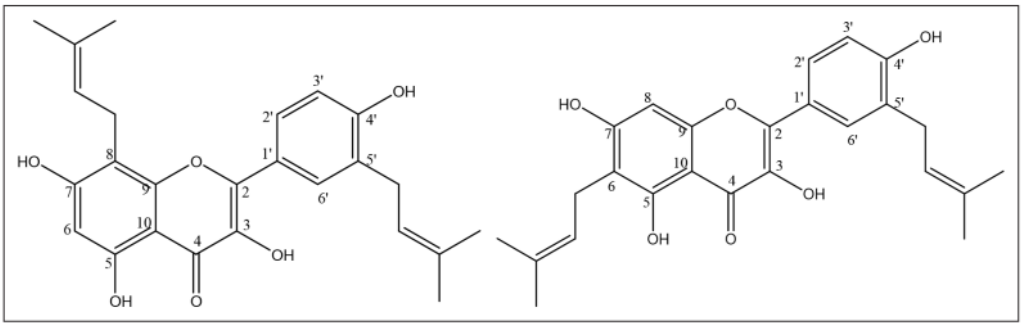

Figure 1. Isolated compounds (broussoflavonol F[13] [left]; glyasperin A[14,15] [right]).

Table 1. Antioxidants of Some Propolis Samples.

	DPPH		ABTS	
Propolis extracts	IC_{50} (mg/mL)	TEAC (µg/mg)	IC_{50} (mg/mL)	TEAC (µg/mg)
Homotrigona apicalis	0.72 ± 0.01	78.0 ± 1.1	0.26 ± 0.00	116.1 ± 2.5
Tetragonula fuscibasis	31.1[a] ± 0.01	34.5 ± 0.15	0.72 ± 0.01	74.8 ± 1.7
Tetragonula fuscobalteata	38.7[a] ± 0.02	44.6 ± 0.4	0.26 ± 0.00	115.9 ± 0.01
Wallacetrigona incisa	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.
[a]At 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 (IC_{50}) = 0.72 mg/mL). In the DPPH and ABTS assays, the extracts of *H. apicalis, T. fuscobalteata,* and *W. incisa* showed the same activity (IC_{50} = 0.26 mg/mL) but were higher than for *T. fuscibasis* (IC_{50} = 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 *Saptotrigona 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 (IC_{50} <100 µg/mL), while those of *T. fuscibasis*, *W. incisa,* and *T. fuscobalteata* were 36% (IC_{50} >100 µg/mL), 26% (IC_{50} >100 µg/mL), and 14% (IC_{50} >100 µg/mL), respectively. In this experiment, kojic acid, a well-known tyrosinase

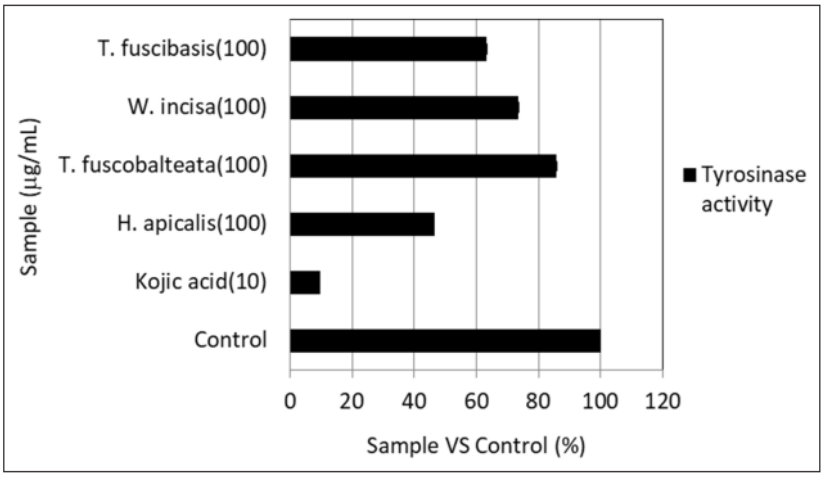

Figure 2. Effect of 4 stingless bees' propolis extracts on tyrosinase activity (all values: mean ± standard deviation).

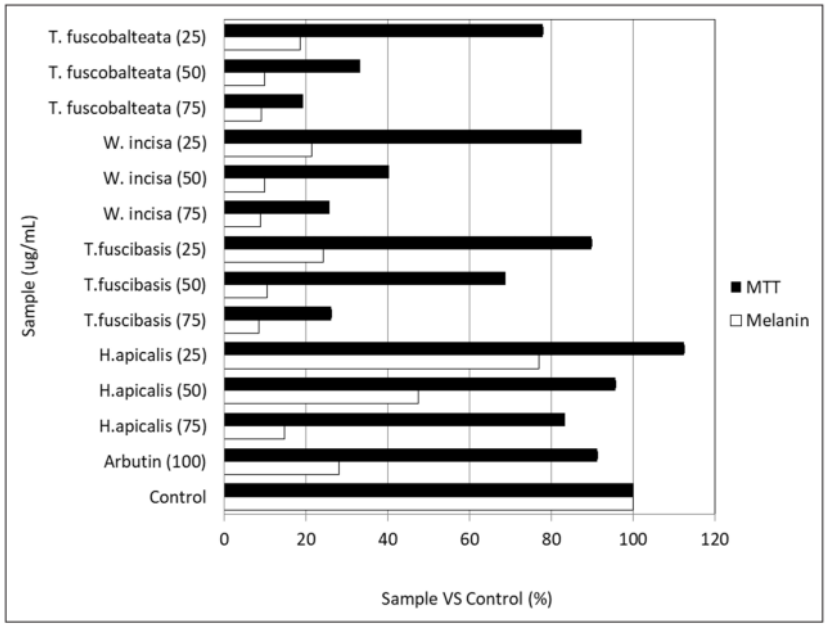

Figure 3. Effect of 4 stingless bees' propolis extracts on melanin inhibition of B16 melanoma cells (all values: mean ± standard deviation). MTT was representative of cell viability. Melanin was representative of melanin content in cells.

inhibitor,[21] used as the positive control, produced 90% inhibition at 10 μg/mL (IC_{50} <10 μg/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 μg/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 μg/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 μg/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 μg/mL. The propolis extract of *W. incisa* inhibited 79% melanin growth in B16 melanoma cells and 87% of viable cells at the concentration 25 μg/mL. Arbutin, a well-known melanin inhibitor and less cytotoxic[22] used as the positive control inhibited 72% melanin growth in B16 melanoma cells and 90% of viable cells at the concentration 100 μg/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 (^{1}H, ^{13}C, DEPT, HSQC, and HMBC), broussoflavonol F[13] 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 (IC_{50} = 443.0 ± 8.0 μM) is more active in the DPPH assay as an antioxidant than broussoflavonol F (IC_{50} = 623.3 ± 0.2 μM), but kaempferol, which is well known as an antioxidant, was

Table 2. Antioxidant Activites of Broussoflavonol F and Glyasperin A.

	DPPH	ABTS
Compound	IC_{50}(μM)	IC_{50}(μM)
Broussoflavonol F	623.3 ± 0.2	226.9 ± 0.0
Glyasperin A	443.0 ± 8.0[a]	210.0 ± 2.7[a]
Kaempferol	23.8 ± 3.3[a]	111.0 ± 1.6[a]

ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); DPPH, 2,2-diphenyl-1-picrylhydrazyl; IC50, half-maximal inhibitory concentration.
[a]Data from Arung et al.[22]

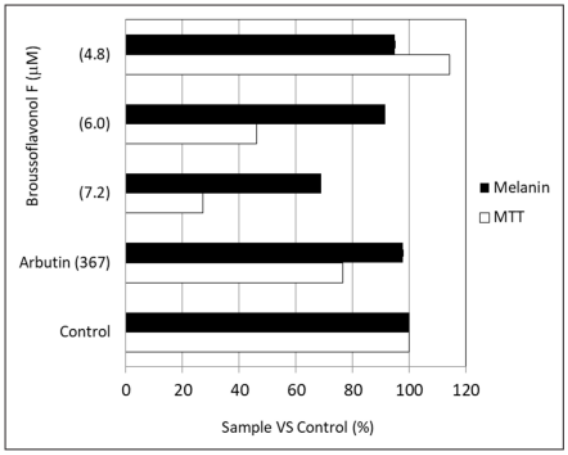

Figure 4. Effect of broussoflavonol F on melanin inhibition of B16 melanoma cells (all values: mean ± standard deviation). MTT was representative of cell viability and melanin was representative of melanin content in cells.

superior with an IC_{50} of 23.8 ± 3.3 μM. In the ABTS assay, glyasperin A (IC_{50} = 210.0 ± 2.7 μM) was also more active as an antioxidant than broussoflavonol F (IC_{50} = 226.9 ± 0.0 μM); the IC_{50} of kaempferol was 111.0 ± 1.6 μM. 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 broussoflavonol F inhibited melanin growth in B16 melanoma cells (54%) but showed less cytotoxicity at a concentration of 6 μM, which was better than arbutin, the positive control. Broussoflavonol F was then tested in the tyrosinase enzyme assay but did not show any inhibition (data not shown). Broussoflavonol 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 broussoflavonol F as an antioxidant and melanin inhibitor in B16 melanoma cells.

In summary, broussoflavonol 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.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article. Part of this work was funded by the Ministry of Research, Technology and Higher Education, Republic of Indonesia in the scheme of the Excellence Basic Research/Kemenristekdikti (Grant no. 080/UN17.41/KL/2018 for Syafrizal); JST SICORP Japan (Grant no. JPMJSC15H1 for Enos Tangke Arung), and Basic Research 2019 (Grant no. 198/UN17.41/KL/2019 for Enos Tangke Arung).

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