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Diversity of medicinal plants used for skincare by Bulungan tribe in North Kalimantan, Indonesia and its melanin biosynthesis inhibition

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Abstract. *Kartina, Batubara I, Kuspradini H, Kusuma IW, Wahyuni WT, Egra S, Matsunaga T. 2022. Diversity of medicinal plants used for skincare by Bulungan tribe in North Kalimantan, Indonesia and its melanin biosynthesis inhibition. Biodiversitas 23: 1246-1253.* Indigenous people of the Bulungan tribe in North Kalimantan, Indonesia have been utilizing plants for health purposes, including for skincare such as preventing skin from being dark due to melanin production. This study aimed to evaluate the diversity of medicinal plants utilized by the Bulungan tribe for skincare and determine the melanin biosynthesis inhibition activity. Plants having medicinal uses were investigated through literature studies and interviews with the members of Bulungan tribe in Tanjung Palas Tengah Village. Melanin biosynthesis inhibition was determined by identifying the tyrosinase inhibition potential using commercial tyrosinase enzyme, while intracellular and extracellular melanin biosynthesis production activity was determined using B16 melanoma cells. The results showed at least 19 plant species that have medicinal uses, including for skincare, with some of them having the potential for melanogenesis, both in suppressing and producing melanin. We found a plant sample with melanin suppression potential on B16 melanoma cell, namely *Jatropha curcas,* at 6.2 µg/ml concentration, which could decrease extracellular melanin content by 18%. Tyrosinase activity with L-tyrosine showed that *Cinnamomum burmannii* (root) (IC_{50}: 3.4 µg/mL) showed an insignificant difference with kojic acid, which served as positive control by showing an inhibitory level of (IC_{50}: 0.14 µg/mL). Based on the data obtained, a pharmacological study is recommended to investigate melanin biosynthesis as a skin whitening agent. We believe that this study can become basic data to discover several active compounds in future studies.

Keywords: Antimelanogenesis, antityrosinase, *Bulungan* tribe, medicinal plant biodiversity, North Kalimantan

INTRODUCTION

Indonesia has various local wisdom originated from indigenous people. Among many local wisdoms owned by traditional tribes in Indonesia, indigenous knowledge and practice related to natural resource management are the most prominent wisdom, including those related to the utilization of plants for medicinal purposes. In 2015, the Indonesian Ministry of Health explored knowledge of tribes in Indonesia regarding medicinal plant utilization, including in Kalimantan Island. In the province of North Kalimantan alone, at least 18 tribes have specific traditional knowledge on medicinal uses of plants. For example, the *Dayak Lundayeh* tribe in Malinau utilizes approximately 90 medicinal plant species for traditional medication (Diana 2017). *Tidung* tribe utilizes 39 medicinal plants for curing ailments, spices, and traditional ceremonies (Listiani 2019). *Bulungan* tribe utilizes around 164 plants for food, spices, traditional ceremonies, building, clothes, decorations, hunting tools, and 65 plants are used for healthcare, including skin (Puri 2001).

Indonesia is a tropical country where the sun shines throughout the year. In particular regions, such as Kalimantan, sun exposure is even more prevalent since this region is located around the equatorial line. Therefore, it is important for the people in Indonesia to protect their skin from ultraviolet (UV) light radiated from the sun shines. Naturally, to overcome the negative effect of UV light exposure, the human body produces melanin by skin (Chan et al. 2011). Melanin is formed by pigment-producing cells (melanocytes) which give colors for skin, hair, and eyes (Ines et al. 2012). The process of melanin synthesis and distribution is known as melanogenesis, a process that is based on melanocytes present among the basal cells of the epidermis. Melanogenesis is triggered by the melanocytic stimulant hormone, adrenocorticotropin hormone, estrogens and progesterone. Pigments formed in melanocyte melanosomes are then stored in the basal layer of epidermal cells, and dermal macrophages, which become melanophores (Maranduca et al. 2019. Melanin biosynthesis is initially started from L-tyrosine oxidation catalized by tyrosinase (Mitsunaga and Yamauchi, 2015) to become 3,4-dihydroxyphenylalanine (L-DOPA), followed by L-DOPA oxidation into dopaquinone, before polymerized oxidation process occurs into several dopaquinonen derivatives which form melanin (Parvez et al. 2016). The result of melanin biosynthesis is a darker and uneven skin color, which is unfavorable by people in some cases.

Therefore, melanin inhibition is used to prevent the darkening of the skin, or in many cases, the inhibition is used to whiten the skin. While there are enormous methods and products for melanin inhibition nowadays, traditional communities have actually been utilized plants for skincare, including for skin whitening or preventing the skin from becoming darker. This study aimed to evaluate the medicinal plant biodiversity utilized for skincare by the Bulungan tribe in North Kalimantan Province, Indonesia, by investigating potential plants regarding their melanin biosynthesis inhibitory activity and discovering their tyrosinase enzyme inhibitory activity. The local wisdom of the Bulungan tribe for skin care can become a basic reference to discover a new skin-whitening agent that adds value to plant biodiversity, especially those with medicinal values.

MATERIALS AND METHODS

Plant materials

This study focused on plant species with the initial information to have potential uses for medication, particularly skincare. Information on plant species used in this study was obtained from a Research for Medicinal Plants and Herbs, Indonesian Ministry of Health (MoH 2015), performed in Kalimantan. These plant species were explored from knowledge about ethnomedicine and community-based medicinal plants in Bulungan District, North Kalimantan (Figure 1). Additional information was also obtained from direct interviews with several Bulungan tribe members living in Tanjung Palas, Bulungan District, who understood medicinal plants.

Leaves, fruits and roots of the medicinal plants were collected following the preparation method commonly practiced by the Bulungan tribe. Selected plants listed in daily use included *Uncaria gambir*, *Tamarindus indica*, *Garcinia parvifolia*, *Selaginella intermedia*, *Cinnamomum iners*, *Cinnamomum parthenoxylon*, *Eurycoma longifolia*, and *Pometia pinnata*. Collected specimens were identified as their scientific names by a taxonomist from Universitas Mulawarman and crosschecked with relevant references.

Sample preparations

The dried parts of selected plants (40-70 g) were extracted with methanol (Wako Chemicals HPLC grade, Richmond, VA) at room temperature through the maceration method using a shaker (7400 Tubingen; Edmun Buchler, Germany) for 48 hours. The extraction process was repeated three times. The extract produced was vaporized using an evaporator at 40°C.

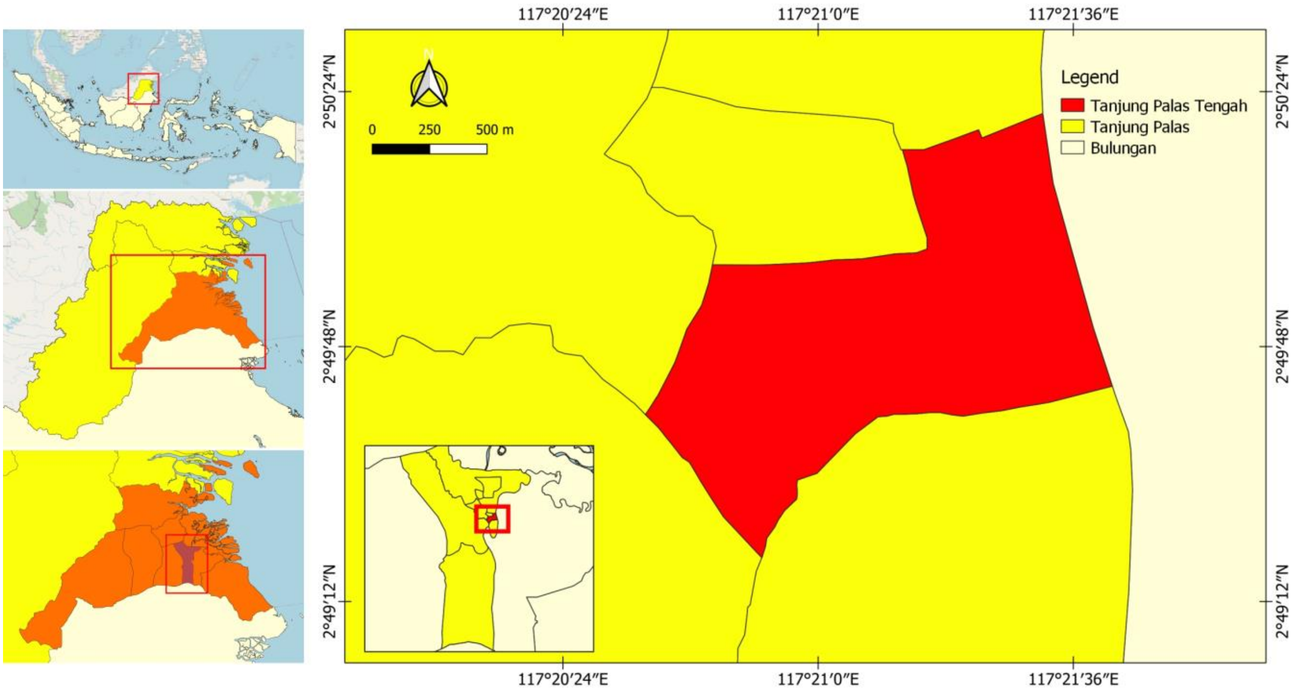

Figure 1. Map showing Tanjung Palas Tengah Village, Tanjung Palas Sub-district, Bulungan District, North Kalimantan, Indonesia. The study site of Bulungan Tribe was at geographical coordinates of 2.8391656° N, 117.3506372° E

Melanin level and cell viability measurements

Cells were turned on in DMEM added with 324.5 mg L-glutamine, 38.9 mg penicillin, 55.6 mg streptomycin, and fetal bovine serum (FBS). Cells were incubated at 37°C with 5% CO_2 for 72 hours. Melanin biosynthesis inhibitory effect was measured using the cultured B16 melanoma cells that were rinsed in phosphate-buffered saline (PBS) and removed with 0.25% trypsin/EDTA. The B16 melanoma cells (5×10^4 cells/well) at 998 µL culture medium were added in two culture plates with 24 wells, incubated for 24 hours, and added with 2 µL DMSO. Cells were incubated in 5% CO_2 at 37°C for 72 hours. Melanin level was determined in the B16 melanoma cells based on the extracellular and intracellular melanin detected from the medium absorbance using a microplate reader at 510 nm wavelength. The B16 melanoma cells were washed with PBS and dissolved in 600 µL 1 N NaOH, before incubating at 100°C for 30 minutes. Cell absorbance level was measured using a microplate reader at 510 nm wavelength. Arbutin was used as a positive control. Cell viability was determined with the MTT test. After incubation, 50 µL MTT reagent in 5 mg/ml PBS was added to each well. The dish was incubated in 5% CO_2 at 37°C for 72 hours. After exposure from the media, cells were dissolved in 1.0 ml PBS and the cell absorbance value was measured at 590 nm wavelength.

Tyrosinase activity

The tyrosinase activity was measured following Yamauchi (2015). The tyrosinase activity was determined using L-DOPA dan L-Tyrosine (Nacalai Tesque, Inc., Kyoto, Japan) as substrates. The 60 µL sample was added to 96 wells added with 30 µL of 333 U/mL tyrosinase (Sigma, St. Louis, MO, USA) in 50 mM phosphate buffer at pH 6.5 in different concentrations (500 µg/mL, 250 µg/mL, and 3.9 µg / mL). The 110 µL substrate (2 mM L-Tyrosine and 2 mM L-DOPA) in 50 mM phosphate buffer at pH 6.5 was prepared, before being mixed in 96 wells (Corning Incorporation, USA). The mixture was incubated at 37°C for 5 minutes. The amount of melanin produced in the mixture reaction was determined against the blank at 510 nm in a microplate reader (ImmunoMini NJ-2300, Japan). Kojic acid (Nacalai Tesque, Inc., Kyoto, Japan) at 100 µg/mL concentration was used as a standard tyrosinase inhibitor (Shimizu et al. 2001).

RESULTS AND DISCUSSION

Medicinal plants used by Bulungan tribe

There were 19 medicinal plant species used by Bulungan tribe based on literature studies (i.e., MOH 2015) and direct interviews with five traditional physicians of Bulungan tribe. Information regarding the scientific name, local name, family, habitus, medicinal plant parts used for skincare, and another traditional usage by Bulungan tribe both from MOH 2015 and direct interview can be seen in Table 1. Therefore, the total plant samples observed in this study became 12 plant species that have potential as cosmetics, especially for skincare. Plant habitus utilized by Bulungan tribe varied, namely herbs, liana, and trees. Plant parts also varied, namely leaves, rhizomes, barks, and fruits, which were mostly obtained from the forest.

Among the 19 species listed to have medicinal uses as listed in Table 1 above, several plant species were then selected to determine their capability to inhibit melanin biosynthesis and tyrosinase enzyme activity. Plant species selection was based on the information gained from the community who often used the plants and survey results of MOH 2015, then the plant parts used frequently by the tribe community were tested. Based on this condition, there were ten selected plant species for skincare uses, as summarized in Table 2.

Melanin biosynthesis inhibitory activity and cell viability

The capability of 10 selected plant extracts in inhibiting melanin formation in cells (intracellular melanogenesis) and outer cells (extracellular melanogenesis), and cell viability level are summarized in Table 3. Several extracts were literally toxic for B16 melanoma cells, such as the extracts of *G. parvifolia*, *E. longifolia*, and *P. pinnata* (leaves and fruits). Most non-toxic extracts improved intracellular melanin production. These non-toxic extracts also improved the extracellular melanin production, namely *U. gambir*, *T. indica*, and *C. iners* extracts. Other non-toxic plant extracts inhibited extracellular melanin biosynthesis in high concentration at 300 µg/mL. However only *J. curcas* extract inhibited the extracellular melanin production in low concentration (75 µg/mL). To identify the capability of *J. curcas* extract in inhibiting melanin biosynthesis, further analysis in a lower concentration at 0.2 µg/mL was performed. The analysis result showed that although at 0.2 µg/mL concentration, the extracellular melanogenesis could still be inhibited (Figure 2).

Tyrosinase enzyme inhibitory activity

The tyrosinase enzyme inhibitory activity was assessed using L-tyrosine and L-DOPA substrates from 10 medicinal plant extracts and the result is summarized in Table 4. Most extracts were incapable of inhibiting 50% tyrosinase enzyme activity on both substrates up to 500 µg/mL concentrations, namely *U. gambir*, *S. intermedia*, *C iners*, *C. parthenoxylon*, and *J. curcas* extracts. Several extracts could inhibit the tyrosinase enzyme activity on both L-tyrosine and L-DOPA substrates. However *T. indica*, *G. parvifolia*, and *C. burmanii* extracts could only inhibit tyrosinase on L-tyrosine substrate. Meanwhile, *E. longifolia* and *P. pinnata* (fruit) extracts could only inhibit tyrosinase on L-DOPA substrate. Kojic acid as positive control showed the highest inhibition level among all tested extracts.

Table 1. Medicinal plants species, the part used and traditional uses by Bulungan tribe, North Kalimantan, Indonesia

Scientific name	Local name	Family	Habitus	Part use	Traditional use	Source
Alpinia galanga	Laos	Zingiberaceae	Herb	Rhizome	postpartum care, beauty care/ cosmetics (*timung*)	MoH 2015
Aristolochia papillopia	Kedayan	Aristolochiaceae	Liana	Root	poison antidote	MoH 2015
Cinnamomum burmannii	Kayu manis	Lauraceae	Tree	Bark, leaf	skin care, hearth, arthistis, diabetic, hernia, oral care	MoH 2015, interview
Cinnamomum iners	Kayu manis	Lauraceae	Tree	Bark, leaf	skin care, hearth, arthistis, diabetic, oral care	Interview
Cinnamomum parthenoxylon	Kayu manis	Lauraceae	Tree	Bark, leaf	skin care, hearth, arthistis, diabetic, oral care	Interview
Curcuma longa	Kunyit	Zingiberaceae	Herb	Rhizome	postpartum care, skin ache, beauty care/cosmetics (cold *pupur*), (*timung*/sauna), hemorrhoids, cancer	MoH 2015
Cymbopogon nordus	Serai	Poaceae	Herb	Herb	postpartum care, bone pain, high blood pressure, beauty care/cosmetics (*timung*)	MoH 2015
Eurycoma longifolia	Pasak bumi	Simaroubaceae	Tree	Root	stomach ache, fever, aphrodisiac, antimalaria	Interview
Jatropha curcas	Tangan-tangan	Euphorbiaceae	Tree	Leaf	fever, skincare, oral care	MoH 2015, interview
Garcinia parvifolia	Asam kandis	Clusiaceae	Tree	Leaf	spice, oral care, sore throat, diare	Interview
Piper betle	Sirih	Piperaceae	Liana	Leaf	postpartum care, baby care (umbilical cord), beauty/cosmetic care (cold *pupur*), cancer	MoH 2015
Pometia pinnata	Kelengkeng papua	Sapindaceae	Tree	Leaf	oral care, skin care, hemorrhoid	Interview
Premna corymbosa	Singkil	Lamiaceae	Tree	Leaf	beauty care/cosmetics (black spots on the face)	MoH 2015
Quercus infectoria	Minyakkani	Fagaceae	Tree	Fruit	postpartum care, beauty care/cosmetics (*cold pupur*)	MoH 2015
Sellagenila intermedia	Cakar ayam	Selaginellaceae	Herb	Leaf	tonsilitis, fever, hemostatis, blood flow	Interview
Syzygium polyanthum	Salam	Myrtaceae	Tree	Leaf	high cholesterol, beauty care/cosmetics (diet)	MoH 2015
Tamarindus indica	Ansom	Fabaceae	Tree	Leaf	oral care, stomach ache, flu, cough	Interview
Uncaria gambir	Gambir	Rubiaceae	Liana	Leaf	skin care, oral care, stomach ache	Interview
Zingiber montanum	Padaran	Zingiberaceae	Herb	Rhizome	postpartum care	MoH 2015

Table 2. Several medicinal plants used for skincare by Bulungan Tribe in Tanjung Palas, Bulungan District, North Kalimantan

Scientific name	Leaf	Bark
Cinnamomum iners		
Cinnamomum parthenoxylon		
Jatropha curcas		
Eurycoma longifolia		
Pometia pinnata		
Tamarindus indica		
Garcinia parvifolia		
Sellagenila intermedia		
Cinnamomum burmanni		
Uncaria gambir		

Table 3. Cell viability and melanogenesis inhibition of selected plant extracts in B16 melanoma cells

Scientific name	**Part**	**Cell viability (%)**			**Intracellular melanogenesis (%)**			**Extracellular melanogenesis (%)**		
		Concentration (ug/mL)			**Concentration (ug/mL)**			**Concentration (ug/mL)**		
		75	**150**	**300**	**75**	**150**	**300**	**75**	**150**	**300**
Uncaria gambir	Leaf	112.7	110.6	97.5	130	180.9	833.6	33.6	428.9	497.1
Tamarindus indica	Leaf	110.5	113.2	129.2	169.1	257.3	648.1	383.6	414.7	404.2
Garcinia parvifolia	Leaf	8.5	3.6	3.4	36.4	88.2	552.7	84.5	157.5	148.3
Selagenilla intermedia	Leaf	100.2	106.8	11 0	52.3	113.8	159.6	128.1	100.9	65.5
Cinnamomum burmanii	Leaf	95	93.1	79.4	171.5	242.2	528.4	205.3	172.6	41.5
Cinnamomum iners	Leaf	94.8	99.2	104.3	160.5	175.2	266.1	175.9	171	179.9
Cinnamomum parthenoxylon	Leaf	90.4	82.9	85.7	142.3	161.3	493.7	127.7	136.2	67.9
Jatropha curcas	Leaf	97.8	100.6	101.3	108.1	166.7	316.2	26.5	34.2	49.7
Eurycoma longifolia	Root	36.8	17.9	2.3	42.3	23.4	26.1	11.7	14.4	21.9
Cinnamomum burmannii	Root	107.4	113.6	104.9	97.5	154.6	208.6	130.4	141.9	50.7
Pometia pinnata	Leaf	85.8	76.3	39	101.2	168.9	544.1	13.9	216.8	66.4
Pometia pinnata	Fruit	79.3	69.4	51.8	73.9	81.9	99.4	183.2	196	206.9
Arbutin (730 uM)				102.1			77.5			12.9
DMSO (control cells)		100	100	100	100	100	100	100	100	100

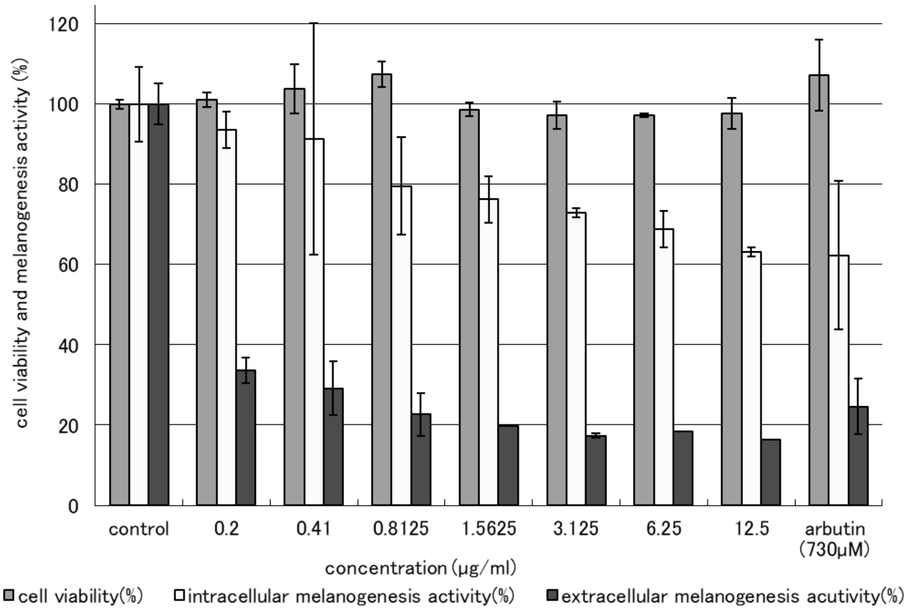

Figure 2. Melanogenesis activity and cell viability of B16 melanoma cells by *J. curcas* at 12.5-0.2 µg/ml concentration

Table 4. Tyrosinase inhibitory activity of selected plant extracts

Scientific name	**Part**	**IC_{50} Tyrosinase activity (µg/mL)**	
		L-Tyrosine	**L-DOPA**
Uncaria gambir	Leaf	>500	>500
Tamarindus indica	Leaf	87.1	>500
Garcinia parvifolia	Leaf	148.3	>500
Sellagenila intermedia	Leaf	>500	>500
Cinnamomum burmanii	Leaf	51.3	168.3
Cinnamomum iners	Leaf	>500	>500
Cinnamomum parthenoxylon	Leaf	>500	>500
Jatropha curcas	Leaf	>500	>500
Eurycoma longifolia	Root	>500	278.6
Cinnamomum burmannii	Root	3.4	>500
Pometia pinnata	Leaf	82.8	283.1
Pometia pinnata	Fruit	>500	456.0
Kojic acid		0.14	3.9

Discussions

This study focused on one of the tribes in North Kalimantan Province, namely Bulungan tribe. The indigenous people who reside in Bulungan are from Dayak Apo Kayan tribe community who live in Kayan River upstream (Arbain 2018). Information about medicinal plants in Bulungan tribe is inherited from their ancestors. These plants are commonly used to cure minor illnesses, such as cough, flu, fever, inflammation, headache, toothache, stomachache, and major diseases like cancer, heart attack, kidney problem, and hypertension. In addition, these plants are also utilized for skincare with several applications, namely scrub, internal medicine for skin, and steam-bath.

Similar to the Bulungan tribe, other tribes in Kalimantan also utilize plants for skincare. Dayak tribes in East and North Kalimantan are accustomed to using *'bedak* *dingin*' (cold powder) and utilize about 38 plants for cosmetics/skincare (Arung et al. 2017), which are more than the plants utilized by Bulungan tribe (19 plants, Table 1). The Dayak Krayan tribe in Kayan Mentarang National Park, Malinau, North Kalimantan, uses less plant species, namely 12 plants for skincare (Susanti 2019).

The plant habitus used by the Bulungan community varied, depending on where the plants were collected. Several plants were obtained from the community field or plantations since they are easy to cultivate, for example herb. In contrast, medicinal plants in the form of liana and trees were generally obtained from the forest.

The nineteen plant species commonly used by Bulungan tribe in Table 1 belong to 15 families. Families that contributed the largest were Zingiberaceae and Lauraceae with three species in each family. The plant parts used by Bulungan tribe also varied, namely rhizomes, leaves, barks, roots, and fruits. For Zingiberaceae family, almost all parts of the plant are utilized as a mixture ingredient of steam-bath for the bride before marriage. Plants from Zingiberaceae family are utilized by almost all tribes in Indonesia. For example, the Tidung tribe in North Kalimantan uses 6 plant species from Zingiberaceae family as traditional medicines and cooking spices (Puri 2001). North Gorontalo residents were also reported to use rhizome *Zingiber purpureum* to treat itching on the skin (Kandowangko et al. 2018). In addition to Zingiberaceae family, Dayak tribe in Malinau, North Kalimantan, also uses three plant species from Lauraceae family. These plants are mostly used as medicines for stomachache, wound infection, asthma, disrupted blood circulation, and skin disease by utilizing barks, roots, and leaves (Susanti 2019).

Several plant samples tested showed non-toxic properties, indicated from the low cell viability level. The highest cell viability level was 100% obtained from 4 plant species, namely *U. gambir, T. indica, S. intermedia, C. burmannii*. There were also 2 plants with toxic properties, namely *G. parvifolia* and *E. longifolia*, which may have cell-killing capability potential. The Lauraceae, Sapindaceae, and Simaorubaceae families are reported to have toxic properties that showed low viability cell levels. The Lauraceae family and *Cinnamomum* genus are known to have coumarin compound, as this compound is originated from the bark with toxic properties (Mariam et al. 2013). Sapindaceae family also has a possible compound with toxic properties. Ketha et al. (2020) reported that *C. canescens* could be a promising natural source of biological medicines. Methanolic extract from the whole plant of *C. canescens* displayed antioxidant activity by inhibiting DPPH and superoxide free radicals and showing anticancer activity. In Simaroubaceae family, specifically in *E. longifolia* or mostly known as *tongkat ali*, there are 65 compounds isolated from the root. Among these isolates, eight compounds had strong toxic properties against cancer cells (Kuo et al. 2003). These compounds may possibly affect the B16 melanoma cell viability level.

Extracellular melanogenic activity was tested with arbutin as a positive control. Intracellular and extracellular activities closely influence in determining the skin-whitening agent using the B16 melanoma cells. Intracellular activity indicates the melanosis cell's capability to maintain melanosome in the cell, which causes melanosome to remain unremoved and hair color becomes white. On the other hand, extracellular activity indicates excessive melanosome production, resulting in spots. A good result was obtained from *J. curcas* plant from Euphorbiaceae family. *J. curcas* has been widely used as medicine in various countries (Abdelgadir et al. 2013). Both the leaf extract and the sap are known to contain a large number of secondary metabolites (Wei et al. 2015; Soares et al. 2013). Warra (2018) reported that *J. curcas* seed oil plays a role in cosmetic production. The results of another study showed that *J. curcas* sap cream acts as an anti-inflammatory in the wound healing process in rat skin (Salim et al. 2018).

Yamauchi et al. (2015), reported that flavonoids such as quercetin compound could control melanogenesis through tyrosinase and melanogenesis inhibitions on B16 melanoma cells. There are also other compounds that may be responsible for inhibiting melanin formation, which requires further experiment to isolate the active compounds to develop skin-whitening material. *U. gambir* and *C. iners* extracts serve as intracellular melanogenesis stimulators in B16 melanin cells. Excessive accumulation of melanin is caused by the increased p38 Mitogen-activated protein kinase (MAPK) and microphthalmic related transcription factor (MITF) phosphorilations or inducing tyrosinase expressions, namely TRP-1 and TRP-2 (Mitsunaga and Yamauchi 2015). In addition, *U. Gambir* as the highest intracellular melanogenesis activity stimulator has phytochemical compounds, namely flavonoids, alkaloids, sterols, phenolics, resins, proteins, and amino acids (Kassim et al. 2011). Several of these compounds may be responsible for increasing melanin biosynthesis. However, *U. gambir* active compounds still require further study. Therefore, a further investigation should be performed to assess the clinical benefits of these active compounds which show biological activity. This study has proven the medicinal plant potentials as skin-whitening agents or melanin agent inducers.

In conclusion, several medicinal plants commonly used by Bulungan tribe were tested in this study regarding their melanogenesis activity through tyrosinase enzyme and B16 melanoma cell tests. The results showed that leaf, fruit, and root extracts from several plants used by the local tribe of North Kalimantan, Indonesia had melanogenesis activity. *S. intermedia* and *J. curcas* have inhibitory potential in melanin formation on B16 melanoma cells. This study provides a scientific database for medicinal plants from North Kalimantan which may have skin-whitening properties.

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