Potential of Medicinal Plants Extractives as Anti-Melanogenesis Ingredients
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ABSTRACT
Melanin is the pigment in the human and animal skin that is synthesized by tyrosinase from L-tyrosine to L-DOPA, following the oxidation of L-DOPA to L-DOPA quinone. Skin whitening agents have been desired as treatment of skin diseases caused by the excess accumulation of melanin on the human skin, because skin darkening is one of the serious aesthetic problems in human beings. Inhibiting the tyrosinase activity and the protein expression are the target to develop the skin whitening agent. A large number of active compounds have been isolated and identified from natural product to develop whitening agents so far. This review reports the potential of traditional medicinal plant extractives and the effective novel ingredients as anti-melanogenesis.

Keywords: Anti-melanogenesis, potential medicinal plants, whitening agents

1. Introduction
Skin darkening is one of the serious aesthetic problems in the human being. Melasma, post inflammatory melanoderma, solar lentigo, and freckles are skin diseases caused by the accumulation of melanin (Ahn et al., 2006; Unver et al., 2006; Altaei, 2012). The factors triggering these disorders are ultraviolet light, chronic inflammation, and rubbing of the skin as well as the abnormal α-melanocyte stimulating hormone (α-MSH) release (Im et al., 2002 and Kang et al., 2002). Depigmentation is occurred by the loss of melanogenic enzymes in melanocytes (Mishima et al., 1972). The skin pigmentation relies on the melanin biosynthesis in melanocytes which is controlled by the melanogenic enzymes such as tyrosinase, tyrosinase related protein (TRP)-1, and 2 (Hearing, 1999).

Skin whitening agents are usually used to treat the skin pigmentation. It should be noted that safety is a priority consideration for its practical use in human. It has standard concentration which is set in each country for the addable concentration of active ingredients contained in the whitening agent, since it has different problems such as ochronosis, irritation and allergy. The adverse effect of whitening agent is dependent on the dose concentrations (Mahe et al., 2003) or frequent in use that it may induce skin tumorigenicity (Cheng et al., 2006; Burdock et al., 2001; Higa et al., 2002). Hydroquinone (HQ) allowed up to 2% as a cosmetic ingredient in European Union at 1984 by the Commission Directive 84/415/EEC (Fifth Commission Directive, 1984). Resorcinol (RS), an isomer of HQ is not permitted in either the European Union and United States (Sakuma et al., 1999). Finding effectives and safe skin-whitening substances have been encouraged to prevent human hyperpigmentation. Moreover, the potential safety has been taken into consideration.

The utilization of medicinal herbs as cosmetic materials is based on the ancestor experience which is usually called traditional cosmetics or traditional herbal formulation. Recently, the potential use of traditional medicines for the development of new skin care cosmetics has been emphasized (Kiken and Cohen, 2002). Several researchers have searched various plants for finding the novel compounds which utilized for curing skin diseases including over melanin production in the human being. Various active compounds have been found from the medicinal plants for hyperpigmentation as a skin whitening agent. This review reports the potential of traditional medicinal plant extractives and the effective novel ingredients as anti-melanogenesis. Through this review, the author provides the list of potential medicinal plant which is possessing future potential of whitening agents.

2. Melanin
Skin and hair coloration is caused by melanin pigment. Melanin production is regulated by the melanocytes distributed in the skin, hair follicles, and pigment epithelium in the retina (Costin and Hearing, 2007). It plays important role in photo-protection (Riley, 2003). Melanin in the human skin is important as a defense of human skin against the damage of...
UV irradiation due to the ability to absorb (Archambault et al., 1995; Chakraborty et al., 1996; Todd et al., 1993; Lukiewicz, 1972; Hengshan, 2006). Overproduction of melanin contents in human body causes hyperpigmentation in the epidermis that induce several kinds of skin problems (Ahn, 2006; Unver, 2006). In contrast, the deficiency of the melanin production caused skin aging or induces gray hair. The skin or hair pigmentation process are initiated after being stimulated keratinocytes in the skin surface by UV irradiation (Yoshida et al., 2000). Then the keratinocytes releasing messengers (histamine, α-melanocytes-stimulating hormone (α-MSH) and prostaglandin) and bind with the receptors on the melanocyte. Melanin is biosynthesized in the melanosome then transported and accumulated in the keratinocytes, then cornification causes the skin pigmentation (Fig. 1). Correspondingly, hair pigmentation arises due to melanin released to the outside of the melanocyte and accumulated in the hair matrix. Melanocyte locates on the hair bulb to produce pigment of the hair shaft (Slominski et al., 2005; Slominski et al., 1993) (Fig. 2) (Yamauchi and Mitsunaga, 2016). In the late anagen, melanocytes begin to shut down melanogenesis and proceed to regression phase called catagen. Deficiency of melanin biosynthesis in the hair bulb on anagen is induced by a stress or an aging caused in gray hair (Tobin et al., 1998; Slominski et al., 1994; Tobin et al., 1999; Guo et al., 2012). Melanogenesis is a well-known physiological response of human skin induced by ultraviolet light and other sources. Melanin biosynthesis is formed by the melanogenic enzymes in melanocytes.

3. Melanogenic enzymes

Tyrosinase, a major enzyme, catalyzes rate limiting reaction to synthesize melanin through the oxidation of L-tyrosine to L-DOPA (3,4-dihydroxyphenylalanine), following the oxidation of L-DOPA to L-DOPA quinone. The oxidation of L-DOPA quinone results in the formation of melanin (Olivares et al., 2009). Melanin is distinguished into two types that are blackish brown eumelanin and reddish yellow pheomelanin formed by the conjugation of cysteine or glutathione (Tsatmali et al., 2002; Slominski et al., 2004). The human tyrosine related proteins (TRP)-1 and TRP-2 are the key enzymes to biosynthesize eumelanin. Furthermore, cysteine or glutamine is involved in the formation of pheomelanin. The pathways are illustrated in Fig. 3 (Yamauchi and Mitsunaga, 2016).

The expression of melanogenic enzymes is stimulated through the intracellular signaling. When the human epidermis is exposed by UV radiation, a potent cyclic adenosine monophosphate (cAMP) activator and the cytokines bind to the MC1 receptor that activates cAMP-dependent protein kinase A (PKA) and other regulatory proteins (Busca and Ballotti, 2000). The cAMP response element-binding protein (CREB) is phosphorylated by PKA. Activated

CREB induces Microphthalmia-associated transcription factor (MITF) transcription. MITF stimulates tyrosinase expression (Yasumoto et al., 1997). Also, it reported that MITF is regulator of melanocyte proliferation, differentiation and pigmentation (Tachibana, 2000; Costin and Hearing, 2007). MITF up-regulates the expressions of tyrosinase, tyrosinase-related protein (TRP)-1, and dopachrome tautomerase (Dct) that result in promoting melanin synthesis and skin pigmentation (Bertolotto et al., 1998a, b, c). Then MITF and the enzymes regarding to the expression of tyrosinase are known as the target to regulate melanogenesis using ingredients in natural products (Fig. 4) (Mitsunaga, 2015).

Several studies reported that melanogenesis-modulating agents regulate the expression of tyrosinase, TRP-1, TRP-2, by regulating the expression of p38 MAPK, ERK, JNK, and MITF. Yamauchi et al. (2014) (Fig. 5) demonstrated that some quercetin deratives have effectivity on the expression of protein involved in melanin biosynthesis. Compound 3′, 4′, 7-O-trimethylquercetin is able to enhance the expression of tyrosinase, TRP-1, TRP-2, MITF, and p-p38 MAPK against B16 melanoma cell in dose dependent manner. It significantly stimulated the expression of MITF and p-p38 MAPK by increase the expression of tyrosinase, TRP-1, and TRP-2. Besides that, compound 3-O-methylquercetin indicated its effectivity to enhance the expression of tyrosinase, TRP-1, and TRP-2 by stimulating transcriptional factors that are yet to be indicated.

4. Natural resource for whitening agent

Traditional medicinal plants are a rich source of bioactive compounds. The skin-whitening agents derived from natural resources particularly plants have been known so far in cosmetic products (Table 1) (Fig. 6). A large number of skin-whitening agents such as kojic acid, arbutin, azelaic acid and aelosin originally from natural resources have been used in cosmetic products. 5-Hydroxy-2-(hydroxymethyl)-4H-pyran-4-one, known as kojic acid is a potent tyrosinase inhibitor that is produced by Aspergillus spp. and Penicillum spp. Lim (1999) revealed that kojic acid cures the melasma’s patient more than half. Arbutin, hydroquinone-O-β-D-glucopyranoside, is one of the most whitening agent used for cosmetic product. The arbutin analogs were isolated and identified from buds of Vaccinium dunalianum (Zhao et al., 2008). Azelaic acid (AZA) is obtained from Malassezia spp. AZA has been used to cure post-inflammatory hyperpigmentation and melasma (Bernal et al., 2000). Low et al., (1998) found that AZA exhibited decreasing hyperpigmentation in darker-skinned. Aleosin as skin-lightening agent is isolated from Aloe vera plant. Choi et al., (2002) revealed that aloeosin shows tyrosinase inhibitory activity in human skin after UV radiation.

Several studies of bioactive compound which is possessing future possibility as cosmetic agents have found (Fig. 7). Wang (2013) has demonstrated that linderanolide B and subamolide A isolated from Cinnamomum subavenium shows inhibitory activity on mushroom

![Fig.4 Transcriptional regulation of expression of melanogenic enzymes. Source: Mitsunaga and Yamaguchi, J.Wood Sci. (2015). Used with permission.](image-url)
tyrosinase with low doses without cytotoxicity in normal human skin cells. (-)-N-formylanonaine isolated from the leaves of *Michelia alba* D.C. (Magnoliaceae) is capable of inhibiting tyrosinase and reducing melanin activity in human epidermal melanocytes (HEMn) without cytotoxicity. The compound is also reported to inhibit tyrosinase activity due to chelation with two Cu$^{2+}$ ions that are the active site of tyrosinase (Wang et al., 2010).

*Sasa quelpaertensis* containing *p*-coumaric acid inhibits melanin synthesis in human melanocytes stimulated by α-MSH (An et al., 2008). 8-Gingerol from *Zingiber* have identified to suppress

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**Fig. 5** Effect of some quercetin derivatives on the expression of Tyrosinase, TRP-1, TRP-2, MITF, p-p38MAPK, and p38MAPK in B16 melanoma cells. (A) Representative blot of 3-O-methylquercetin. (B) Quantification of the ratio of protein expression in melanoma cells by 3-O-methylquercetin. (C) Representative blot of 3', 4', 7-O-trimethylquercetin. (D) Quantification of the ratio of protein expression in melanoma cells by 3', 4', 7-O-trimethylquercetin. The data show the means ± S.D. from three independent experiments. *p*≤0.05 and **p**≤0.01 compared with control values. Source: Yamauchi et al., *Bioorganic Med Chemistry* (2014). Used with permission.
intracellular tyrosinase activity and decrease the melanin contents. Besides, 8-Gingerol is reported to decrease intracellular reactive species (RS) and reactive oxygen species (ROS) level (Huang et al., 2013). Matsuda et al., (2009) exhibited that the constituents of Alpinia officinarum rhizome such as 5-hydroxy-1,7-diphenyl-3-heptanone, 7-(4’-hydroxy-3’-methoxyphenyl)-1-phenylhept-4-en-3-one, 5-hydroxy-7-(4’-hydroxy-3’-methoxyphenyl)-1-phenyl-3-heptanone, 3,5-dihydroxy-1,7-diphenylheptane, kaempferide, and galangin inhibit melanogenesis. Moreover, 7-(4’-hydroxy-3’-methoxy-phenyl)-1-phenylhept-4-en-3-one, kaempferide, and galangin inhibit mRNA expression of tyrosinase, tyrosinase-related proteins-1, and -2, and reduces the protein level of MITF which is related to the expression of tyrosinase.

5. Potential of Indonesian natural medicinal plant for whitening agent

Natural medicinal treatments are used because it provides several beneficial effects such as anticancer, anti-inflammatory, and protection against UV. Indonesia is one of the world’s major country that possess the sources of useful plant materials and high number of indigenous medical plants. Most of the Indonesian people, particularly in outland areas use traditional herbal medicines known as jamu. Jamu is tribal language from Javanese expressing the traditional medicine from plants. Corresponding to the utilization as a medicine, it is distinguished into four categories: health care, beauty care (cosmetics), tonics, and bodily protection (Riswan and Roemantyo, 2002). The use of herbal ingredients is abundant in the practice of beauty care such as Indonesian traditional spa which is use of ground herbs in the form of powders and scrubs for body treatments. It has been involved into modern businesses which is distributed in the capital city of Indonesia, especially along Jawa and Bali Islands (Ministry of Trade Republic of Indonesia, 2009).

According to the abundance source medical plants, it is very encouraging to explore the potential of Indonesian natural source to maintain the health and to cure the disease. Zingiberaceae family such as Curcuma aeruginosa, C. aurantiaca, C. mangga, C. petiolate, C. purpurascens, C. soloescens, C. xanthorizae, C. domestica and C. zedora are the most frequently used as jamu. They are used for curing some illnesses such as appendicitis,
asthma, itch, rheumatism, abdominalgia, anemia, hypertension, diarrhea, dysentery (Hatcher et al., 2008). Elfahmi et al., (2014) reported that Paenomia alba, Polygalae tenuifolia, Rehmanniae pela, Carthami tinctorius, Leonuri heterophyclus, Angelicae sinensis, Concha ostrea gigas, Albizziae julibrissin have been used for regulating endocrine gland secretion and menstruation, promotes ovulation, and reduces menstrual clots.

Traditional herbal medicine gives an interesting and huge unexplored source for development of potential as new drugs and cosmetics. Several natural remedies have been used since centuries for caring skin conditions and dermatological disorders, including inflammation, phytotoxicity, psoriasis, atopic dermatitis, and alopecia are  

Several Indonesian plants that inhibit melanogenesis have been searched for effectivity as whitening agents Table 2 and Fig. 8. Bengkoang (Pachyrhizus erosus) has been use as a folk medicine for skin-lightening agents and commercially used in the cosmetic product in Indonesia. Lukitaningsih and Holzgrabe (2014) reported that constituent compounds in Bengkoang such as daidzein, daidzein-7-O- β-glucopyranose, 5-hydroxy-daidzein-7-O- β-glucopyranose, and 8,9-furanyl-pterocarpan-3-ol as shown in Fig. 9 suppress tyrosinase activities. Alamanda cathartica is an ornamental plant in Indonesia containing glabridin as an active constituent to inhibit tyrosinase activity with high percentage inhibition (93 %) (Yamauchi et al., 2011). Yokota et al. (1998) revealed that glabridin from Licorice extracts is the main ingredient which affecting on skins by inhibit tyrosinase activity in the B16 melanoma cells and guinea pig skins. It was also detected that glabridin inhibited UVB-induced pigmentation and erythema in the skin guinea pigs. Allium cepa has constituents such as quercetin, quercetin-4-O-glucoside, quercetin 4'-O-β-D-glucopyranoside, and quercetin-3'-O-β-D-glucoside which suppress melanin formation (Arung et al., 2011b, c, d). Batubara et al. (2010) reported that Intia palembanica containing Robinetin as the active compound, it has activity as monophenolase and diphenolase inhibitor of tyrosinase and antioxidant activity.

Salam (Syzygium polyanthum) is original plant from Indonesia, it has been found the bioactive compounds against decreasing melanin production and its capability for inhibiting tyrosinase activity. Setyawati et al. (2018) revealed that three novel compounds are 1-(2,3,5-trihydroxy-4-methylphenyl)hexane-1-one, 1-(2,3,5-trihydroxy methylphenyl)octane-1-one, and (4E)-1-(2,3,5-trihydroxy-4-methylphenyl)decane-1-one and one known compound 1-(2,3,5-trihydroxy-4-methylphenyl)decane-1-one have activity
for decreasing extracellular melanin. Moreover, (4E)-1-(2,3,5-trihydroxy-4-methylphenyl)decan-1-one is possessing activity for tyrosinase inhibition.

6. Bioactivity of folk medicine for whitening agent

*Artocarpus communis* is folk medicine to prevent skin disease as acne and dermatitis. Fu *et al.*, (2014) demonstrated that the extract of *Artocarpus communis* decreases melanin contents and tyrosinase activity by inhibiting the expression of MITF and phosphorylated cAMP response element-binding protein (p-CREB). Oh *et al.*, (2010) revealed that 1-O-Methyl-fructofuranose from *Schisandra chinensis* fruit inhibits both melanin synthesis and tyrosinase activity. It also reported to reduce the expression of melanogenic proteins including MITF and TRP-1. Moreover, it activates melanogenesis inhibitory proteins such as mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) and Akt. An extract of brown seaweed (*Sargassum polycystum*) inhibits melanogenesis by inhibiting cellular tyrosinase activity and is known to treat skin related disorder (Chan *et al.*, 2011).

*Cuscuta japonica* seed have found to inhibit α-MSH-induced melanin synthesis, decrease α-MSH-induced expression of MITF, TRPs, and reduce the level of phosphorylated p38 mitogen-activated protein kinase (MAPK) signaling through the down-regulation of α-MSH-induced cAMP (Jang *et al.*, 2012).

*Nardostachys chinensis* has been used in melasma and lentigines disorder in Korea. Jang *et al.*, (2011) found that *Nardostachys chinensis* inhibits melanogenesis due to decreasing MITF, tyrosinase, TRP-1, dopachrome tautomerase (Dct), MITF, tyrosinase mRNA levels, and intracellular cAMP levels. It is also reported that it activates mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) and phosphatidylinositol 3-kinase (PI3K)/Akt expression that result in suppressing MITF expression.

7. Conclusion

A number of the effects and ingredients in the medicinal plant which is distributed in the world still unknown. Therefore, further investigation such as the toxicity assay, allergy assay, and other biological assay must be conducted to clarify their safety and clinical advantage to the human skin.

REFERENCES


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### Table 2. Review of published literature relating to selected medical plants use in Melanogenesis

<table>
<thead>
<tr>
<th>No</th>
<th>Plant Name</th>
<th>Part</th>
<th>extract</th>
<th>compound</th>
<th>Comment</th>
<th>toxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Phyllanthus emblica (malaka)</td>
<td>Fruit</td>
<td>etil acetate</td>
<td>tanin (galad acid and elegat)</td>
<td>It inhibits melanogenesis and decreases tyrosinase activity with IC₅₀ 95.63 and 16.90 µg/mL. (Hindritiani et al., 2013)</td>
<td>less</td>
</tr>
<tr>
<td>2.</td>
<td>Helminthostachys zeylanica</td>
<td>Roots</td>
<td>50% ethanol and water mixture</td>
<td>Uginon J and Uginon K</td>
<td>Uginon J and K depresses extracellular melanin production to 75 and 19 % at 12.5 µM). (Yamauchi et al., 2015)</td>
<td>no</td>
</tr>
<tr>
<td>3.</td>
<td>Durio katejensis [Bombacaceae (Hassk) Becc]</td>
<td>Fruit</td>
<td>n-hexane, ethyl acetate, ethanol</td>
<td>-</td>
<td>The EtoAc extract inhibits melanin formation by 47% at 200 µg/mL in B16 melanoma cells without cytotoxicity while did not inhibit tyrosinase activity. (Arung et al., 2015a)</td>
<td>no</td>
</tr>
<tr>
<td>4.</td>
<td>Intia palembanica</td>
<td>Wood</td>
<td>methanol</td>
<td>Robinetin</td>
<td>Intsia palembanica (Merbau) has activities as monophenolase and diphenolase inhibitor of tyrosinase on 10.4 µg/mL of IC₅₀ and antioxidant activity. (Batubara et al., 2010)</td>
<td>no</td>
</tr>
<tr>
<td>5.</td>
<td>Allamanda cathartica</td>
<td>Roots</td>
<td>methanol</td>
<td>Glabridin</td>
<td>Glabridin is the center active compound of tyrosinase inhibitory activity by 93% at the concentration 19.3 µM and 2.93 µM of IC₅₀. The results showed that glabridin has activity 10 times stronger than kojic acid. (Yamauchi et al., 2011).</td>
<td>no</td>
</tr>
<tr>
<td>6.</td>
<td>Syzygium aromaticum</td>
<td>Methanol and oil</td>
<td>Eugenol and Eugenol acetate</td>
<td>-</td>
<td>Eugenol and eugenol acetate exhibited melanin inhibition in B16 melanoma cells by 50 and 80% at 100 and 200 µg/mL respectively. (Arung et al., 2011b)</td>
<td>less</td>
</tr>
<tr>
<td>7.</td>
<td>Eupatorium triplinerve Vahl</td>
<td>Leaf</td>
<td>methanol</td>
<td>7-methoxycoumarin</td>
<td>Methanol extract of E.triplinerve Vahl was demonstrated for inhibitory activities on melanin formation in B16 melanoma cells with IC₅₀ 1780 µM and both tyrosinase enzyme activity L-tyrosine (IC₅₀=2360 µM) and L-DOPA (IC₅₀=2840 µM). (Arung et al., 2011a)</td>
<td>no</td>
</tr>
<tr>
<td>8.</td>
<td>Allium cepa</td>
<td>Dried skin</td>
<td>methanol</td>
<td>Quercetin and Quercetin 4′-O-glucoside</td>
<td>The methanol extract suppressed melanin formation in B16 melanoma cells by 40-50% at the concentration 50 and 100 µg/mL. Quercetin and Quercetin-4′-O-glucoside decreased tyrosinase activity with IC₅₀ 26.5 and 131 µM, respectively. (Arung et al., 2012)</td>
<td>no</td>
</tr>
<tr>
<td>9.</td>
<td>Sonneratia caseolaris (Rambai Sungai)</td>
<td>Leaf</td>
<td>Ethanol (EtOH)</td>
<td>luteolin-7-O-β-glucoside</td>
<td>Luteolin-7-O-β-glucoside was inhibitory activity of melanin formation in B16 melanoma with IC₅₀ 223.2 µM. (Arung et al., 2015b)</td>
<td>less</td>
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<tr>
<td>10.</td>
<td>Artocarpus heterophyllus</td>
<td>Wood</td>
<td>methanol</td>
<td>Brosimone I and 3-prenyl luteolin</td>
<td>Brosimone I and 3-prenyl luteolin were potent as melanin inhibitory activity with IC₅₀ 0.8 and 56.7 µM. (Arung et al., 2005; Arung et al., 2006; Arung et al., 2007; Arung et al., 2010a, b, c, d)</td>
<td>less</td>
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<tr>
<td>11.</td>
<td>Allium cepa</td>
<td>Dried skin</td>
<td>methanol</td>
<td>quercetin 4′-O-β-D-glucopyranoside</td>
<td>The quercetin 4′-O-β-D-glucopyranoside was inhibitory of both tyrosinase activity L-tyrosine and L-DOPA with IC₅₀ 4.3 and 52.7 µM. (Arung et al., 2011c)</td>
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</tr>
<tr>
<td>12.</td>
<td>Willughbeia coriacea</td>
<td>Bark part of aerial root</td>
<td>methanol</td>
<td>-</td>
<td>The methanol extracts were potent inhibitory melanin formation in B16 melanoma cells by 92.5 % at 100 µg/mL and scavenging DPPH radicals. (Arung et al., 2009)</td>
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</tr>
<tr>
<td>No.</td>
<td>Species</td>
<td>Part</td>
<td>Extract</td>
<td>IC50</td>
<td>Effects</td>
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<tr>
<td>13</td>
<td>Dendrophthoe petandra</td>
<td>aerial root</td>
<td>methanol</td>
<td>-</td>
<td>The methanol extracts were potent inhibitors of tyrosinase activity and melanin formation in B16 melanoma cells by 95.9% at 100 µg/mL, also to scavenge DPPH radicals. (Arung et al., 2009)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Glochidion philippicum</td>
<td>aerial root</td>
<td>methanol</td>
<td>-</td>
<td>The methanol extracts were potential inhibitory melanin formation by 71% at 100 µg/mL in B16 melanoma cells (Arung et al., 2009)</td>
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<tr>
<td>15</td>
<td>Eleutherine palmifolia</td>
<td>bulb</td>
<td>methanol</td>
<td>-</td>
<td>The methanol extracts were inhibited melanin formation by 37.9% at 100 µg/mL in B16 melanoma cells, exhibited DPPH radical-scavenging activity. (Arung et al., 2009)</td>
<td></td>
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<tr>
<td>16</td>
<td>Eusideroxylon zwageri</td>
<td>seed</td>
<td>methanol</td>
<td>-</td>
<td>The methanol extracts were inhibited melanin formation at 32.4 µg/mL in B16 melanoma cells and DPPH radical-scavenging activity. (Arung et al., 2009)</td>
<td></td>
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<tr>
<td>17</td>
<td>Lansium domesticum</td>
<td>bark</td>
<td>methanol</td>
<td>-</td>
<td>It inhibits melanin formation by 13% at 100 µg/mL in B16 melanoma cells. (Arung et al., 2009)</td>
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</tr>
<tr>
<td>18</td>
<td>Passiflora foetida</td>
<td>stem, fruit</td>
<td>methanol</td>
<td>-</td>
<td>It inhibits melanin formation by 104.1% at 100 µg/mL in B16 melanoma cells. (Arung et al., 2009)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Solanum torvum</td>
<td>roots</td>
<td>methanol</td>
<td>-</td>
<td>It inhibits melanin formation by 98.6% at 100 µg/mL in B16 melanoma cells. (Arung et al., 2009)</td>
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<tr>
<td>20</td>
<td>Gnetum gnemon</td>
<td>seed</td>
<td>Ethanol (EtOH)</td>
<td>Gnetin C and resveratrol</td>
<td>Gnetin C and resveratrol were inhibitory of DOPA oxidation by 25.2 and 64.1% 16 µM. (Yanagihara et al., 2012)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Allium cepa</td>
<td>dried skin</td>
<td>methanol</td>
<td>quercetin-3’-O-β-D-glucoside</td>
<td>It inhibits melanin formation in B16 melanoma cells at IC50 38.8 µM of IC50 and inhibitory both tyrosinase activity, L-tyrosinase and L-DOPA (IC50 6.5 and 48.5 µM respectively). (Arung et al., 2011d)</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Eleutherine americana</td>
<td>bulb</td>
<td>methanol</td>
<td>naphthoquinone eleutherin</td>
<td>It inhibits melanin formation in B16 melanoma cells by 87% at 50 µg/mL. (Kusuma et al., 2010)</td>
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<td>23</td>
<td>Cuscuta japonica</td>
<td>seed</td>
<td>water</td>
<td>-</td>
<td>It inhibited α-MSH-induced melanin synthesis and tyrosinase activity. (Jang et al., 2012).</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Nardostachys chinensis</td>
<td>seed</td>
<td>water</td>
<td>-</td>
<td>It inhibits melanin synthesis and tyrosinase activity &gt;50% at 0.1–2.5 g/ml. (Jang et al., 2011).</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Artocarpus communis</td>
<td>Heartwood</td>
<td>methanolic</td>
<td>-</td>
<td>It decreases melanin content and tyrosinase activity at 39.50 µg/mL of IC50. (Fu et al., 2014)</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Sargassum polycystum</td>
<td>Seaweed</td>
<td>ethanol 95%</td>
<td>-</td>
<td>It inhibits cellular tyrosinase activity by 87% at 100 µg/mL. (Chan et al., 2011).</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Syzygium polyanthum</td>
<td>leaf</td>
<td>Methanol extract (4E)-1-(2, 3, 5-trihydroxy-4-methylphenyl)decan-1-one</td>
<td>It diminished extracellular melanin in B16 melanoma cells by &gt;80% and inhibits tyrosinase activity at 83.98 µM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Arung TE, Shimizu K, Hiroyuki T and Kondo R (2010d) 3-Prenyl luteolin, a new prenylated flavone with melanin biosynthesis inhibitory activity from wood of *Artocarpus heterophyllus*. Fitoterapia, 81: 640-643
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Fig. 9 Chemical compounds isolated from folk medicinal plant Bengkoang (Pachyrhizus erosus) for use as whitening agents and commercially used as cosmetic products.

Arung TE, Yoshikawa K, Shimizu K and Kondo R (2010a) Isoprenoid-substituted flavonoids from wood of Artocarpus heterophyllus on B16 melanoma cells: Cytotoxicity and structural criteria. Fitoterapia, 81: 120-123
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cells by influencing the expression of melanin biosynthesis proteins MITF and p38 MAPK. Bioorganic Med. Chem., 22: 3331-3340


