

Melanogenesis regulatory constituents from *Premna serratifolia* wood collected in Myanmar

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Melanin is a mixture of pigmented biopolymers synthesized by epidermal melanocytes that determine the skin, eye, and hair colors. Melanocytes produce two different kinds of melanin, eumelanin (dark brown/black insoluble pigments found in dark skin and dark hair and pheomelanin (lighter red/yellow). The biological role of melanin is to prevent skin damage by ultraviolet (UV) radiation. However, the overproduction or deficiency of melanin synthesis could lead to serious dermatological problems, which include melasma, melanoderma, lentigo, and vitiligo. Therefore, regulating melanin production is important to prevent the pigmentation disorders.

Myanmar has a rich in natural resources. However, the chemical constituents of these natural resources in Myanmar have not been fully investigated. In the effort to search for compounds with anti-melanin deposition activity from Myanmar natural resources, five plants were collected in Myanmar. Extracts of these collected five plants were tested for anti-melanin deposition activity against a mouse melanoma cell line (B16-F10) induced with α -melanocyte-stimulating hormone (α -MSH) and 3-isobutyl-1-methylxanthine (IBMX), and their anti-melanin deposition activities were compared with the positive control, arbutin. Among the tested extracts, the CHCl₃ extracts of the *Premna serratifolia* (syn: *P. integrifolia*) wood showed anti-melanin deposition activities with IC₅₀ values of 81.3 μ g/mL. Hence, this study aims to identify secondary metabolites with anti-melanin deposition activity from *P. serratifolia* wood of Myanmar.

P. serratifolia belongs to the Verbenaceae family and is widely distributed in near western sea coast from South Asia to South East Asia, which include India, Malaysia, Vietnam, Cambodia, and Sri Lanka. People in Tanintharyi region located in the southern part of Myanmar utilize the *P. serratifolia*, *Sperethusa crenulata*, *Naringi crenulata*, and *Limonia acidissima* as Thanaka, traditional cosmetics in Myanmar. Thanaka is applied in the form of paste onto skins to make it smooth and clear, as well as to prevent wrinkles, skin aging, excessive facial oil, pimples, blackheads, and whiteheads. However, the chemical constituents responsible for their cosmetic properties are yet to be identified. Moreover, the chemical constituents of *P. serratifolia* was almost uncharacterized. Investigation of the *P. serratifolia* chemical constituents is thus an attractive endeavor to discover new anti-melanin deposition active compounds.

The investigation of the chemical constituents of the active CHCl₃ extract of *P. serratifolia* led to isolation of four new lignoids, premnan A (1), premnan B (2), taungtangyiol C (3), and 7,9-dihydroxydolichanthin B (4), together with premnan C (5) (assumed to be an artifact), one natural newlignoid, (3R,4S)-4-(1,3-benzodioxol-5-ylcarbonyl)-3-[(R)-1-(1,3-benzo dioxol-5-yl)-1-

hydroxy methyl]tetrahydro-2-furanone (6), and five known compounds (7-11)^{1,2}). The structures of all isolated compounds were determined on the basis of their spectroscopic data and by comparison with the reported literatures. The absolute configurations of 1-3 and 5 were also determined by optical rotation and circular dichroism (CD) data analyses¹).

The anti-melanin deposition activities of all the isolated compounds were evaluated against B16-F10 cell line. 7,9-Dihydroxydolichanthin B (4) and (2 α ,3 α)-olean-12-en-28-oic acid (11) showed strong anti-melanin deposition activities with IC₅₀ values of 18.4 and 11.2 μ M, respectively, without cytotoxicity²). On the other hand, compounds 1-3, 5, and 7 showed melanogenesis enhancing activities¹).

To better understand their anti-melanin deposition mechanism, the effects of 4 and 11 on tyrosinase activities were investigated. The assay indicated that compounds 4 and 11 did not inhibit tyrosinase. Furthermore, we also examined the mRNA expression of microphthalmia-associated transcription factor (MITF), tyrosinase (TYR), tyrosinase-related protein-1 (TRP-1), and tyrosinase-related protein-2 (TRP-2). Compounds 4 and 11 down-regulated the expression of Tyr and Mitf mRNAs, respectively. Although the *P. serratifolia* wood has been used as traditional cosmetics in Myanmar for centuries, there are no scientific evidences to support its effectiveness as cosmetics. Investigation of the anti-melanin deposition activity of the chemical constituents of *P. serratifolia* thus provided insight into the effectiveness of the *P. serratifolia* wood as a cosmetic agent.

References

1. Woo S-Y, Hoshino S, Wong CP, Win NN, Awouafack MD, Prema, Ngwe H, Zhang H, Hayashi F, Abe I, Morita H (2019) Lignans with melanogenesis effects from *Premna serratifolia* wood. *Fitoterapia* 133:35-42.
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