UNIVERSITI TEKNOLOGI MARA

PHYTOCHEMICAL STUDY OF DRYOBALANOPS FROM MALAYSIAN DIPTEROCARPACEAE AND STRUCTURE-ACTIVITY RELATIONSHIP STUDIES

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Thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy

Faculty of Applied Sciences

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CONFIRMATION BY PANEL OF EXAMINERS

I certify that a Panel of Examiners has met on 14\textsuperscript{th} May 2014 to conduct the final examination of Agustono Wibowo on his Doctor of Philosophy thesis entitled "Phytochemical study of \textit{Dryobalanops} from Malaysian Dipterocarpaceae and structure-activity relationship studies" in accordance with Universiti Teknologi MARA Act 1976 (Akta 173). The Panel of Examiners recommends that the student be awarded the relevant degree. The panel of Examiners was as follows:

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I declare the work in this thesis/dissertation was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, Regulating the conduct of my study and research.

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ABSTRACT

Dryobalanops is one of the genera in the Dipterocarpaceae family, which is distributed as major species in emergent canopy of Lambir Forest and Sarawak lowland dipterocarps forest. The genus is very unique, as there are only seven species available in the whole world, which confined to the tropical forests of West Malesia. The chemical constituents of Dipterocarpaceae are reported to possess various biological activities such as cytotoxicity, antiviral, antibacterial and anti-inflammatory activities. The aims of this study are to isolate secondary metabolites, to determine their antibacterial, DPPH scavenging and cytotoxic activities, to study structure-activity relationship, and to propose biogenesis pathway and chemotaxonomic significance in Dryobalanops. The dried powder of the stem bark of D. aromatica, D. lanceolata, D. rappa and D. becarii were macerated with acetone and evaporated under reduced pressure. The crude acetone extract was subjected to vacuum liquid chromatography to give several fractions. Purification of fraction with combination of several chromatography techniques gave four new oligostilbenoid derivatives; malaysianol A (1), B (2), C (3) and D (4), and a new galloylglucoside derivative; malaysin A (5), together with 15 known oligostilbenoid (6-20) and six known non-oligomeric compounds (21-26). The chemical structures of isolated compounds were elucidated based on the spectroscopic data evidences and comparison with reported authentic data. Biogenetically, the biosynthesis routes of non-oligomeric compounds were formed from the shikimate pathway, while oligomeric compounds were from the combination of shikimate and acetate malonate pathways. Based on the radical species and their condensation types, 19 oligostilbenoids isolated from this study were formed from the oxidative coupling reaction of two radicals with active site at carbons C-8 and C-14 (C8-C14 type), carbons C-8 and C-8 (C8-C8 type), carbons C-3 and C-8 (C3-C8 type), and oxygen O-13 and carbon C-8 (C7-C14 type). The finding of oligostilbenoids with the condensation types C3-C8 and C7-C14 are not commonly found in Dipterocarpaceae family. Based on the chemotaxonomic study, the presence of several compounds that were only found in the tribe Dipterocarpeae and never reported in the tribe Shoreae supported the previous studies on the morphological character that suggested the placement of Dryobalanops under the tribe Dipterocarpeae. In the antibacterial assay, flexuosol A (16) and upunaphenol D (18) showed moderately antibacterial activity against S. epidermidis, S. aureus, S. xylosus with MIC value of 50.0/16.7, 66.7/33.3 and 50.0/16.7 μM, respectively. In the cytotoxic assay, vaticanol C (20) were found to be moderately active against A549 cell line (IC50 11.8 μM), as well as α-viniferin (11) and ampelopsin E (12) against MCF-7 cell line (IC50 23.1 and 21.0 μM, respectively), while other compounds were either weak or not active. In the DPPH assay, malaysianol A (1), flexuosol A (16) and vaticanol B (19) displayed great scavenging activity with IC50 values 15.7, 15.0 and 11.8 μM, respectively. In the structure-activity relationship study, the scavenging activity of oligostilbenoid depend on the number of hydroxyl group and their stereochemistry, otherwise no definitive correlation between unit structures of oligostilbenoid and cytotoxicity was observed, but its conformation seem to be responsible for the cytotoxic properties.
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