

# Studies on Biological Activity of Indonesian Medicinal and Non-Medicinal Plants

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# 學位論文要旨

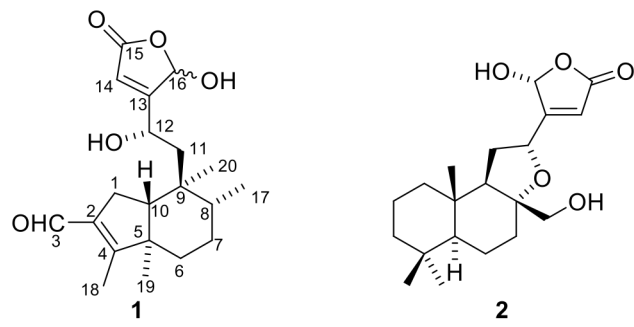
This research has revealed that 15 kinds of Indonesian plants show various antiproliferative activities by using preliminary screening against four cancer cell lines, namely: A549, KB, MDA-MB-231, MCF7. An anti-inflammatory assay that inhibited production of NO and MTT assay on J774.1 cells and an antiangiogenesis assay on HUVEC were conducted. The aim was to study the potential benefits and to isolate bioactive compounds of Indonesian medicinal and non-medicinal plants. Methods: The plants were extracted using methanol and water for the preliminary assay. The preliminary assay was performed in this research for the screening of these plants. Antiproliferative activity was evaluated with an RSB assay, anti-inflammatory activity was examined with inhibition of NO production on LPS-induced J774.1 cells, anti-angiogenesis was performed on the inhibition of VEGF on HUVEC, and anti-HIV was investigated by MTT assay. Based on the data of the assays, specific plants were chosen for extraction, isolation and purification to create isolated compounds. The isolated compound identified the structure and evaluated the activity by using an anti-proliferative activity on several cancer cell lines. Anti-inflammatory activity was examined by inhibition of NO production on LPS-induced J774.1 cells. Antiangiogenesis assay was performed on inhibition of VEGF on HUVEC , and anti-HIV assay was conducted on Cells MT4 and virus NL4-3.

It is recommended to further investigate the following six plants which are KNG, GHR, VCS, HJG, PDS, and KPS because they have shown significant activity during the preliminary assay. VCS was chosen for further investigation because it was the only plant that has yet to be explored. And also, one of the fractions after separation exhibited significant results against human cancer cell lines where the chloroform-soluble part of VCS was performed on silica gel flash column chromatography, recycle HPLC, and preparative TLC to derive 2 compounds. Both of the compounds were identified using Mass spectrum analysis, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, 2D NMR, ECD experiments and were compared with previous research. Compound 1 was identified as

(3a*R*,6*R*,7*S*,7a*R*)-7-[(*S*)-2-hydroxy-2-[(*R*&*S*)-2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl]ethyl]-3,3a,6,7-tetramethyl-3a,4,5,6,7,7a-hexahydro-1*H*-indene-2-carbaldehyde (IUPAC), namely 16-hydroxy-pentandralactone. Compound **2** can be identified as acuminolide. Both of the compounds were examined through the antiproliferative assay against five human cancer cell lines such as A549, MDA-MB-231, KB, KB-Vin, MCF-7. Compound **1** and compound **2** showed bioactivity against five cancer cell lines, with IC<sub>50</sub> 5.4 – 11.4 μM (Table 8). Antiangiogenesis assay was also performed on both of the extracts, and compound **1** inhibited VEGF in a dose-dependent manner, but displayed no cytotoxicity against HUVEC. Compound **2** had cytotoxicity against HUVEC with cell viability 47% at concentration 3.0 μM.

Conclusion: Six plants can be used as candidate plants for further examination because they show significant activity, which are flowers buds of *Cananga odorata*, stems of *Aquilaria* sp., seeds of *Azadirachta indica*, aerials of *Pseudelephantopus spicatus*, leaves of *Chromolaena odorata*, leaves of *Cordyline* and leaves of *Vitex cofassus* sp. Compound **1** was identified as

(3a*R*,6*R*,7*S*,7a*R*)-7-[(*S*)-2-hydroxy-2-[(*R*&*S*)-2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl]ethyl]-3,3a,6,7-tetramethyl-3a,4,5,6,7,7a-hexahydro-1*H*-indene-2-carbaldehyde (IUPAC), namely 16-hydroxy-pentandralactone could be explored as an agent for anti-cancer because it exhibited bioactivity against five cancer cell lines lung carcinoma (A549), triple-negative breast cancer (MDA-MB-231), estrogen receptor-positive breast cancer (MCF-7), epidermoid carcinoma (KB), vincristine-resistant KB subline (KB-VIN) with IC<sub>50</sub> 6.4 -11.9 μM. Compound (**1**) also showed evidence of ability in assisting in problem-solving in multi-resistant drugs because it showed activity on cancer cells that are resistant to chemotherapy such as KB-VIN. This is supported by antiangiogenesis data which inhibited VEGF in a dose-dependent manner, but no cytotoxicity appeared on the HUVEC. Compound **2** exhibited significant activity against all the tested tumour cell line, and the IC<sub>50</sub> 5.4 – 8.9 μM and also had cytotoxicity against HUVEC with cell viability of 47 % at concentration 3.0 μM.



**Figure:** Compounds isolated from leaves of *Vitex cofassus*

# 審査結果の要旨

発表者はインドネシアの植物資源の生理活性調査とその活性本体を得ることを研究目的とした。15種類の植物材料の各 MeOH 及び熱水抽出エキスに対し三種類の生物活性試験〔①ヒト由来がん細胞 (A549、MDA-MB-231、MCF-7、KB) に対する増殖抑制作用、②NO 産生阻害 (J774.1) による抗炎症作用、③血管内皮細胞増殖因子誘発ヒト臍帯静脈内皮細胞に対する血管新生抑制作用〕を実施した。その結果、クマツヅラ科 *Vitex cofassus* 葉の MeOH 抽出エキスを選択した。NO 産生阻害試験を指標に分離分画を繰り返した結果、新規化合物 (3aR,6R,7S,7aR)-7- $\{(S)\text{-}2\text{-hydroxy-}2\text{-}[(R\&S)\text{-}2\text{-hydroxy-}5\text{-oxo-}2,5\text{-dihydrofuran-}3\text{-yl]ethyl\}$ -3,3a,6,7-tetramethyl-3a,4,5,6,7,7a-hexahydro-1*H*-indene-2-carbaldehyde 及び既知化合物 acuminolide を得た。この新規化合物は生物活性試験①に対し、やや強い活性 (IC<sub>50</sub>; 6.4-11.4  $\mu\text{M}$ ) を、acuminolide は③に対し 53% の細胞毒性 (3  $\mu\text{m}$ ) を示すことを明らかにした。

以上、本研究ではインドネシア産資源植物 15 種の抽出液について 3 種の生理活性を調査した。さらに *Vitex cofassus* より新規を含む 2 化合物を単離し、得られた新規化合物ががん細胞増殖抑制効果を示すことを明らかにした。この成果は学術的な重要性が期待できることから審査委員会は本論文が博士 (学術) に値すると判断した。