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学 位 論 文 要 旨
Dissertation Abstract

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学位論文題目：
Title of Dissertation

Structure-Cytotoxic Activity Relationship of Dietary Lignans and Their Apoptosis Induction
(食物性リグナン類の構造と細胞毒性活性との関係及びアポトーシス誘導)

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Cytotoxicity of dietary lignans and their derivatives against HL-60 and HeLa cell lines were determined and compared. To evaluate the role of structure and stereochemistry, stereoisomers and derivatives of dihydroguaretic acid (DGA), secoisolariciresinol, 1,7-seco-2,7′-cyclolignane (SCL), 9,9′-epoxylignane, lariciresinol, 9-dehydroxylariciresinol, 7,7′-epoxylignane, pinoresinol, and matairesinol were employed.

Cytotoxicity of 9-dehydroxylariciresinol and 7,7′-epoxylignane were found to be stereochemistry-dependent against both HL-60 and HeLa cell lines while dihydroguaretic acid only showed stereochemistry-dependent toward HeLa cell line. Insignificant activities at 100 μM against all cell lines were exhibited by all compounds bearing primary hydroxy group; suggested that the presence of primary hydroxy group was disadvantageous for the cytotoxicity of dietary lignans. As the next stage, further research on active stereoisomer were conducted by preparing derivatives of (–)-DGA, SCL, (–)-verrucosin, and (–)-matairesinol. Substituents of 7- and 7′-phenyl groups were focused on (–)-dihydroguaiaretic acid, (–)-verrucosin, and (–)-matairesinol derivatives; whereas substituent on 7- and 9′-position were highlighted on SCL derivatives. This research has revealed new compounds having higher cytotoxicity than the natural dietary lignans. Compared with the natural (–)-DGA, (8*R*,8′*R*)-2′-ethoxy-4-methoxy-3-lignanol of DGA derivative was 30-fold stronger against HL-60 (IC_{50} = 0.8 μM) and 13-fold stronger against HeLa cell line (IC_{50} = 1.7 μM). For SCL, (*R*)-9′-heptyl derivative was a highest active compound (IC_{50} = 3.7 μM against HL-60, IC_{50} = 3.1 μM

against HL-60). Hydrophobicity was advantageous for the cytotoxicity of SCL. (7*S*,7′*R*,8*R*,8'*R*)-3′,4,4′-Trimethoxy-7,7'-epoxylignane was a derivative of (–)-verrucosin with notable activity (IC_{50} = 2.4 μM against HeLa). Dichloro derivatives of (–)-matairesinol (8*R*,8′*R*)-2,4-dichlorolignano-9,9′-lactone, (8*R*,8′*R*)-3,4-dichlorolignano-9,9′-lactone, and (8*R*,8′*R*)-3,5-dichlorolignano-9,9′-lactone exhibited almost 4-fold stronger cytotoxicity than the natural compound (IC_{50} = around 20 μM against HL-60). Finally, apoptosis induction by lignans was recognized based on the observation of cell morphology or further experiment on flow cytometry, western blotting, DNA laddering, or fluorescence microscopy analyses.