学位論文内容の要旨

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学位論文題名

Search for α-glucosidase inhibitors from Indonesian indigenous plants

（インドネシア産植物からのα-グルコシダーゼ阻害物質の探索研究）

A promising approach for treating diabetes mellitus (DM) is to decrease postprandial hyperglycemia by suppressing carbohydrate digestion using α-glucosidase inhibitors. This work has demonstrated the effective finding of potential Indonesian medicinal plants as an alternative for antihyperglycemic sources. Aqueous methanol extracts of twenty-eight Indonesian indigenous herbs were used for searching active compounds against intestinal maltase. Among seven plants showing high maltase inhibitory activity (above 60%), *Pluchea indica* leaves and *Caesalpinia sappan* wood were chosen for further investigation to identify the active principles responsible for an antihyperglycemic effect through the inhibition of intestinal maltase. Chemical identification of the active principles was done by *in vitro* assay-guided isolation and extensive instrumental analyses. The overall results suggested that these plants could be used for promising DM treatments.

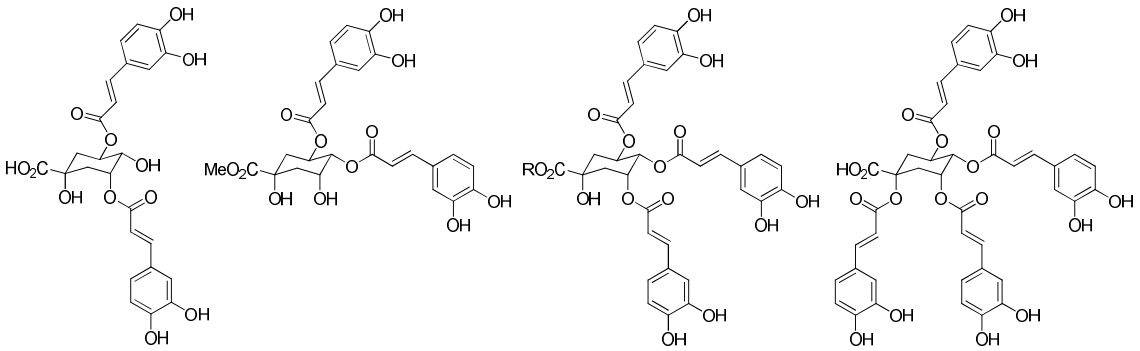
1. Intestinal maltase inhibitors from *Pluchea indica* leaves

The ethyl acetate-soluble layer from aqueous methanol extracts of *P. indica* leaves was fractionated successively by silica gel column chromatography (chloroform-methanol) and HPLC (ODS, methanol-water) to yield five active caffeoylquinic acid derivatives, 3,5-di-*O*-caffeoylquinic acid (**1**, 0.01% yield, IC_{50}=1.16 mM), 4,5-di-*O*-caffeoylquinic acid methyl ester (**2**, 0.08%, 0.21 mM), 3,4,5-tri-*O*-caffeoylquinic acid methyl ester (**3**, 0.04%, 0.002 mM), 1,3,4,5-tetra-*O*-caffeoylquinic acid (**4**, 0.04%, 0.013 mM), and 3,4,5-tri-*O*-caffeoylquinic acid (**5**, 0.02%, 0.011 mM), as intestinal maltase inhibitors. Comparison of the activities of each isolate indicated that both methyl esterification of quinic acid and the number of caffeate groups in the molecule were

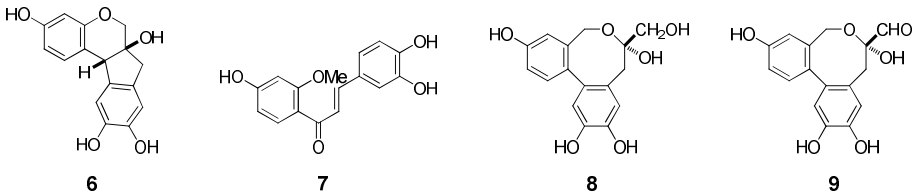
important to the inhibitory activity. Considering the yield of the isolates from *P. indica* leaves, the intestinal maltase inhibitory activity of the crude extract would be arising from **3** and partially contributed by **4** and **5**.

2. Intestinal maltase inhibitors from *Caesalpinia sappan* wood and their additional promising activities

The ethyl acetate-soluble layer from aqueous methanol extracts of *C. sappan* wood was fractionated successively by silica gel column chromatography (chloroform-methanol and hexane-ethyl acetate) and HPLC (ODS, methanol-water) to yield four phenolic compounds, brazilin (**6**, 0.03% yield, IC_{50}=3.83 mM), sappanchalcone (**7**, 0.01%, 0.96 mM), protosappanin B (**8**, 0.5%, 0.81 mM) and protosappanin C (**9**, 0.12%, 2.59 mM), as intestinal maltase inhibitors. The isolated compounds were also investigated for their intestinal sucrase and α-amylase (PPA) inhibitory activities, as well as an enhancement activity for glucose uptake on skeletal muscle cells. Compound **6** showed a moderate inhibition against intestinal sucrase (IC_{50}= 1.12 mM), whereas **7**, **8**, and **9** showed no inhibition. A weak PPA inhibitory activity was found only in **7**. Compounds **6** and **7** showed a significant enhancement of glucose uptake in skeletal muscle cell line. These results imply **6** and **8** might contribute mainly to the antihyperglycemic activity of the plant.



1 **2** **3**: R=Me **5**: R=H **4**



6 **7** **8** **9**