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Anti-obesity study of Indonesian medicinal plants: an *in vitro* study in adipocytes

（脂肪細胞を対象としたインドネシア薬用植物の抗肥満研究）

Obesity has become a global health problem due to its association with major life-threatening diseases including cardiovascular diseases, type 2 diabetes and numerous cancers. Over the past decades, only few anti-obesity drugs have been developed and approved. In fact, some drugs have been withdrawn from the market due to their serious side-effects. With the alarming rise of obese individuals globally, and in view of the dissatisfactions with synthetic drugs, there is a growing shift towards natural product-based medications.

In this thesis, investigation of potential anti-obesity plant materials and their active components was conducted from Indonesian medicinal plants. Two plants, *Eurycoma longifolia* and *Brucea javanica* (both from family Simaroubaceae) were investigated for their lipolytic activity, a bioactivity to break down triglyceride into glycerol in adipocytes. Several lipolytic compounds were isolated from these plants and were further studied for their cellular mechanisms of actions. In addition, an anti-lipogenesis screening was conducted to explore anti-obesity plants with different mode of action from Indonesian medicinal plants.

1. Study on lipolytic activity of *E. longifolia*

Based on glycerol release assay, the extract of *E. longifolia* (EL) was found to exert lipolytic activity in a concentration-dependent manner. Subsequent molecular mechanistic study using several specific inhibitors of lipolytic signaling pathways showed that protein kinase A (PKA) and extracellular signal-regulated kinase (ERK) are involved in the lipolytic activity of EL. Further immunoblotting analysis showed that EL activates PKA and ERK through enhanced phosphorylation confirming their involvements.

Based on bioassay-guided fractionation, two lipolytic compounds, eurycomanone and 13 β ,21-epoxyeurycomanone, were isolated from *E. longifolia*. Eurycomanone enhanced lipolysis in adipocytes with an EC₅₀ of 14.6 μ M, while 13 β ,21-epoxyeurycomanone had a stronger activity with an EC₅₀ of 8.6 μ M. Molecular mechanistic study showed that PKA inhibitor totally diminishes their lipolytic activity. Furthermore, immunoblotting analysis confirmed the enhanced phosphorylation of PKA through the stimulation by both compounds.

Additionally, when tested in WT-1 brown adipocytes, eurycomanone and 13 β ,21-epoxyeurycomanone also reduced lipid accumulation and exerted lipolytic activity, suggesting a potential to stimulate thermogenesis.

2. Lipolytic activity of *B. javanica*

The extract of *B. javanica* demonstrated strong lipolytic activity in white adipocytes, thus further study was conducted to identify its lipolytic compounds. Bioassay-guided fractionation from *B. javanica* lead to the isolation of several lipolytic compounds, including brucein A, brusatol, brucenatinol, brucein B, 3'-hydroxybrucein A, and bruceine C. Some isolated compounds from this plant have demonstrated much stronger lipolytic activity compared to two isolated compounds from *E. longifolia*.

3. Anti-lipogenesis screening of Indonesian medicinal plants

The 76 selected Indonesian plant extracts were subjected to two bioassays, namely lipid accumulation and glycerol release assays. There are plants that both reduced lipid accumulation and enhanced lipolysis, *B. javanica*, *Melaleuca leucadendra*, *Zingiber purpureum*, and *Clerodendrum serratum*. There are some plants that enhanced lipolysis but not reduced lipid accumulation, *Leucas lavandulifolia*, *Mentha arvensis*, *Pimpinella anisum*, *E. longifolia*, *Piper crocatum*, *Guazuma ulmifolia*, and *Sapindus rarak*. There is also plant that reduced lipid accumulation but not enhanced lipolysis, *Momordica charantia*.

Taken together, the findings of this study provide significant contributions to the body of knowledge in anti-obesity research of Indonesian medicinal plants. Not only has this study provided scientific basis and rationale for the use of those potential plants for medicinal purposes, but it has also provided information on different mode of anti-obesity effects to address this global health problem.