学位論文内容の要旨

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学位論文題名

Mechanistic analysis of Thai medicinal plants on anti-obesogenic activity

（タイ薬用植物の抗肥満関連活性に関する作用機構解析）

Prevalence of overweight and obesity is rising dramatically. Numerous of research focus on the prevention and the treatment of obesity. One of the approaches is the application of medicinal plants. However, lack of scientific knowledge prevents the use of thousands of medicinal plants around the world. Thus, this study aims to study the anti-obesogenic activity of the selected medicinal plants on its mechanistic aspects.

Four medicinal plants were selected from the screening of seventy Thai medicinal plants using three *in vitro* assays, including enzymatic assay (pancreatic lipase inhibition) and cell-based assays (lipolysis enhancement and lipid accumulation reduction). The medicinal plants that exhibited at least dual activities, *Acacia concinna* (Willd.) DC., *Cymbopogon nardus* (L.) Rendle, *Cyperus rotundus* L., and *Tiliacora triandra* Diels, were selected for the current study.

1. Mechanistic study in 3T3-L1 adipocytes

Change in gene expression and an activation of protein associated to adipogenesis (*Cebpa*, *Pparg*, AMPK), lipogenesis (*Srebf1*, *Acaca*, *Fas*), lipolysis (*Plin-1*, *Lipe*, *Pnpla2*, PKA, ERK, β-adrenergic receptor) after stimulation by the plant extracts were examined in 3T3-L1 adipocytes.

The selected plants differently influence adipogenesis and lipid metabolism of adipocytes. *A. concinna* and *T. triandra* act as anti-adipogenic and anti-lipogenic agents, where both plants reduce the lipid accumulation during adipogenesis and in mature adipocytes. Meanwhile, *C. nardus* and *C. rotundus* do not reduce the lipid accumulation. Analysis revealed that one of the differences between these two groups of plants lie in the activation of AMPK. *T. triandra* has a milder effect on adipogenesis and lipogenesis

compared to *A. concinna*, analysis showed that this might be due to the upregulation of *Cebpa*.

Four plants enhance lipolysis of 3T3-L1 adipocytes. In all plants, changes in lipolytic gene expression did not reflect the activity, whereas activation of PKA or ERK pathways was found to be primarily responsible for activating lipolysis. Additionally, *A. concinna* were shown to activate both pathways and *T. triandra* were shown to partially act on the β-adrenergic receptor, the upstream of PKA.

2. Mechanistic study in NCTC 1469 hepatocytes

Four plants downregulated several lipogenesis-related genes showing a potential to reduce lipid synthesis in hepatocytes. However, the lipolytic genes and gene expression of PPARα, the regulator of fatty acid β-oxidation, were also downregulated which would reduce lipid metabolism. These downregulations might result from the limited lipid content in the cell, which leads to lessening the requirement for the production of proteins in lipolysis and fatty acid oxidation. However, the explicit effect of the plants on hepatocytes is needed to explain the effect of plants on hepatocytes.

3. Summary

From the study, the mechanistic aspects of Thai medicinal plants on anti-obesogenic activity were revealed. Gene expression changes are often used to explain the effect of medicinal plants, but in this study, the activation of protein is more concrete to explain the anti-obesogenic activity of the plants.

To conclude, this study revealed the promising plant candidates with anti-obesogenic potential and their underlying mechanism that provide their therapeutic targets. This information can be used in further studies, such as identifying bioactive compounds, *in vivo* study and further application in terms of obesity prevention and treatment.