A limonene-derivative purified from peels of Citrus Sudachi ameliorates lipid and glucose metabolism through upregulating sirt1

Licht Miyamoto¹, Haruna Aihara¹, Wenting Xu¹, Meina Jin¹,², Yosuke Tomida¹, Naonobu Tanaka², Yasumasa Ikeda³, Toshiaki Tamaki³, Yoshiki Kashiwada², Koichiro Tsuchiya¹

¹Medical Pharmacology, Inst. of Biomedical Sciences, Tokushima University, Japan, ²Pharmacognosy, Inst. of Biomedical Sciences, Tokushima University, Japan, ³Pharmacology, Inst. of Biomedical Sciences, Tokushima University, Japan

Sudachi (Citrus Sudachi) is a small sour citrus, and it is a typical seasoning for fish dishes in Japanese cuisine. Interestingly, it grows exclusively in Tokushima region of Japan, and Sudachi is a specialty of Tokushima prefecture. Recently our collaborators have reported that administration of Sudachi peel decreases serum triglyceride (TG) levels in obese human subjects.

The effects of crude Sudachi peel were evaluated in Zucker diabetic fatty (ZDF) rats. Hexane-extract of Sudachi peel was fractionated by silica gel column and subjected to a cell-based screening using C2C12 myotubes by an index of intracellular TG content. The positive fractions were then purified using octadecylsilyl column. Activities of the compound were evaluated in high fat diet-fed male ddY mice as well as C2C12 cells.

A daily administration of Sudachi peel improved serum TG levels and extended lifespan of ZDF rats. It also reduced TG levels in cultured C2C12 myotubes. We found a limonene-derivative from Sudachi peel as an active compound by the screening. The TG-lowering effects of the compound was sensitive to nicotinamide, a sirt1 inhibitor, and the molecule increased sirt1 expression levels in a dose-responsive manner. In high fat diet-fed mice, repetitive administration of the compound for 10 days improved glucose tolerance, fatty liver, serum TG and cholesterol to the same levels as those of healthy mice with increase in sirt1 activities in the gastrocnemius muscle and liver.

Therefore, it will be one of the active components of Sudachi peel regulating metabolism, which should be mediated by sirt1 activation. The sirt1 activation is supposed principally due to upregulation of the expressions.

In conclusion, we identified a limonene-derivative which ameliorates metabolism in cultured cells and in vivo with increase in the activities and expression levels of sirt1 which should be involved in the metabolic action. It will be a novel lead compound regulating metabolic homeostasis by modulating sirt1 expression levels.