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Title　：Studies on cholesterol metabolism in non-alcoholic fatty liver disease
(非アルコール性脂肪性肝疾患におけるコレステロール代謝に関する研究)

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Thesis Summary

Nonalcoholic fatty liver disease (NAFLD) is a series of liver diseases that starts with over 5% lipid accumulation in the liver. In addition to triacylglycerol (TAG), hepatic cholesterol accumulation has been reported to increase the severity of NAFLD. Thus, the prevention of dysregulated cholesterol metabolism may effectively prevent the progression of NAFLD. The purpose of this study is to investigate the effect of natural compounds derived from food ingredients on cholesterol metabolism with cell or animal models in NAFLD.

I used two animal models to demonstrate inhibition of NAFLD development. Rats were fed with either modified AIN-76 diets containing 0.2% cholesterol with 64.8% sucrose or starch for 4 weeks by pair feeding to verify how carbohydrates affects hepatic cholesterol metabolism. The sucrose diet significantly increased the fecal contents of total neutral steroids, including coprostanol, and phytosterols. The fecal conversion rate of cholesterol into coprostanol and hepatic contents of TAG showed an increasing trend in the sucrose diet. Serum and hepatic levels of phytosterols and hepatic contents of cholesterol were significantly lower in the sucrose diet. Serum levels of cholesterol, HDL-c, or non-HDL-c, and hepatic contents of cholesterol precursors and oxidized cholesterols were no significant differences between the two diets. From the above results, dietary sucrose reduces liver cholesterol levels by inhibiting in the intestine.

I investigated the effect of soyasaponin (SAP) on the lipid metabolism of high-fat diet (HFD)-induced NAFLD in C57BL/6J mice. The SAP significantly increased hepatic levels of total, free, and esterified cholesterol. The SAP significantly decreased fecal cholesterol content, hepatic cholesterol synthesis rate-limiting enzyme HMGCR mRNA level, and hepatic cholesterol effluxes ABCA1 mRNA level. CYP7A1 mRNA levels tended to be lower in the SAP group. In addition, SAP decreased hepatic TAG content and lipogenesis related gene expression (SREBP-1c and FAS). Therefore, SAP improved HFD-induced fatty liver but exacerbated the abnormality of hepatic cholesterol metabolism.

D-psicose is known as a rare sugar and inhibits the development of NAFLD via decreasing hepatic fatty acid synthesis. I examined the effect of d-psicose on cholesterol metabolism of the palmitic acid (PA)-induced as an NAFLD cell model in HepG2 cells. D-psicose reversed the PA-activated SREBP-2-PCSK9 pathway via improving ER stress. Moreover, d-psicose blocked *de novo* cholesterol synthesis, which was increased by PA treatment, and increased mRNA level of ABCA1, which excretes cholesterol extracellular, to lower cholesterol levels in the cells. Those results demonstrated that the effect of decreasing cholesterol accumulation by d-psicose explains

its protection against NAFLD development.

In summary, in animal models of NAFLD, sucrose increases hepatic TAG contents coincident with reducing hepatic cholesterol levels, whereas SAP improves hepatic TAG accumulation and simultaneously accelerates hepatic cholesterol deposition. In cell models of NAFLD, d-psicose prevents cholesterol accumulation in hepatocytes. These findings suggest that the regulations by each food ingredient on hepatic cholesterol metabolism in NAFLD development are in different mechanisms.