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Influence of *Coleus forskohlii* on non-alcoholic steatohepatitis

Sachina SUZUKI

Non-alcoholic fatty liver disease (NAFLD) and the more progressive non-alcoholic steatohepatitis (NASH) have recently become recognized liver diseases in developed countries. NASH progresses to fatty degeneration, inflammation, hepatocellular damage (ballooning degeneration), fibrosis, cirrhosis, and ultimately cancer. NASH is associated with obesity and metabolic syndrome, such as dyslipidemia, insulin resistance, and diabetes, therefore medication for these diseases combined with diet-treatment and exercise are prescribed to NASH patients.

The use of dietary supplements including herbal products has increased in worldwide. *C. forskohlii* is the most popular herbal ingredient for commercial weight-loss supplements in Japan. The influence of weight-loss supplement, especially CFE supplement on NASH patients is of increasing concern. In the present study, we examined the influence of CFE, especially on major CYP subtype activities, during progression or diet and/or exercise treatment of NASH using diet-induced NASH model mouse.

Male C57BL/6J mice (8 weeks old) were fed a NASH diet for 4 weeks or 12 weeks. The 12 week-feeding of NASH diet induced NASH. These mice indicated increased plasma lipid levels and liver functional markers, hepatic lipid contents. In this mice model, we measured major CYP subtype activities (CYP1A1, CYP1A2, CYP2C, CYP3A, which are associated to metabolize approximately three-quarters of drugs). We showed that CYP1A1, 1A2, and CYP3A activities were increased, whereas CYP2C activity was decreased in the liver in NASH mice. To evaluate the efficacy of drugs in NASH, statin or tolbutamide were administered into NASH mice. These drug efficacies were attenuated in NASH mice compared to control mice.

Next, we examined whether CFE and forskolin that is an active ingredients in CFE, affect prior to the establishment/ development of NASH because the influence of weight loss supplements on NASH patients is of increasing concern. Furthermore, we measured major CYP subtype activities. Male C57BL/6J mice (8 weeks old) were fed a NASH diet with or without CFE or forskolin for 12 weeks. In this study, we examined the effects of CFE on progression and treatment of NASH in mice model. Both of CFE and forskolin, suppressed hepatic TG accumulation and inflammatory gene expressions in the liver during the progression of NASH, according to suppressed body weight and adipose tissue weight gain. On the other hand, CFE induced major CYP subtype activities during progression of NASH, even though forskolin did not. We demonstrated that ingestion of CFE suppressed the development of NASH. Furthermore, CFE induced CYP

activities. A similar trend was observed in 4 week feeding that is prior to the establishment of NASH.

We also examined the influence of CFE during diet-treatment and exercise to improve NASH. Male C57BL/6J mice (8 weeks old) were fed a NASH diet for 12 weeks. After establishment of NASH, mice were subjected to diet-treatment and/or exercise with/without CFE for 3 weeks. Diet-treatment was more effective in NASH improvement compared to exercise, and CFE suppressed this improvement of NASH by diet-treatment. Furthermore, CFE induced CYP1A1, CYP1A2, CYP2C, and CYP3A activities during diet-treatment and exercise. These results suggest that CFE not only suppress the beneficial effects of diet-treatment, but also influences the medication on NASH.

In conclusion, ingestion of CFE suppressed the development of NASH, according to suppressed body weight and adipose tissue weight gain. However, CFE suppressed improvement of NASH by diet-treatment. Furthermore, CFE might influence in medication on NASH via induction of major CYP subtypes activities. In this regards, NASH patients should avoid to use CFE. Further investigation is needed to clarify the influence of CFE and it's active ingredient, forskolin, on NASH in human.