Insulin resistance in peripheral tissues, together with the impairment of glucose-induced insulin secretion from pancreatic beta cells, is known as one of the major pathogenic factors of type 2 diabetes. Therapeutic agents to stimulate insulin secretion (for example, sulfonylureas) have been used for type 2 diabetic patients. But, in the first stage of type 2 diabetes, exercise therapy and diet is done.

The rhizoma of *Anemarrhena asphodeloides* has been used as an Oriental traditional medicine to treat diabetes (polyuria and polydipsia). It contains the xanthone compound, mangiferin (MF) (Fig. 1).1) In a previous study, we reported the antidiabetic effect of MF.2) Furthermore, we investigated the effect of MF with exercise on glucose metabolism in type 2 diabetic mice.3) Type 2 diabetes also often involves elevated blood lipid levels by metabolic derangement. Therefore, we examined the hypolipidemic effect of MF with exercise in type 2 diabetes using an animal model.

MATERIALS AND METHODS

**Materials** MF was isolated by a conventional method as previously reported.1) The structure of MF was confirmed by the spectroscopic method.4) MF was stored at room temperature until use.

**Animals** Male KK-A' mice (Clea, Tokyo, Japan), 6—11 weeks, were used. Under non-fasting, those with blood glucose levels above 300 mg/dl were considered to be diabetic patients. But, in the first stage of type 2 diabetes, exercise therapy and diet is done.

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**Animals** Male KK-A' mice (Clea, Tokyo, Japan), 6—11 weeks, were used. Under non-fasting, those with blood glucose levels above 300 mg/dl were considered to be diabetic and were used in this study. They were housed individually in an air-conditioned room at an ambient temperature of 22±2 °C with a 12 h light—dark cycle. The animals were kept in this experimental animal room for 7 d with free access to food and water.

To determine blood lipid levels, blood samples were taken from the cavernous sinus using a capillary.

**Exercise** For exercise studies, KK-A' mice were run on a motorized treadmill (Muromachi Kikai Co., Ltd., Osaka, Japan) for 120 min (5 m/min, 7% grade).5) MF was administered 30 min before the exercise once a day. The administration of MF was started at 13:00—14:00 pm. For exercise studies, mice went without food. MF (30 mg/kg body weight) was administered orally for 2 weeks.

**Determination of Blood Cholesterol and Triglyceride Level** Blood cholesterol levels in mice were determined using commercial reagents (Cholesterol E-Test Wako6) and Triglyceride G-Test Wako,7) Wako Pure Chemical Ind., Ltd., Osaka, Japan).

All data were expressed as means±S.E.M., and Student's *t*-test was used for the statistical analysis. Values were considered to be significantly different when the *p*-value was less than 0.05.

RESULTS

**Effect of MF with Exercise on Blood Cholesterol in KK-A' Mice** The mean blood cholesterol levels in KK-A' mice after oral administration of MF with exercise are shown in Fig. 2. MF (30 mg/kg) reduced the blood cholesterol (*p*<0.05) and triglyceride level (*p*<0.01) of KK-A' mice with exercise 2 weeks after oral administration when compared with the control group. Diabetes also often has elevated lipid levels. Therefore, it may be that MF has beneficial effects on hyperlipidemia in type 2 diabetes.

Key words mangiferin; hypolipidemic effect; type 2 diabetes

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**Fig. 1.** Structure of Mangiferin (MF)

**Fig. 2.** Effect of MF with Exercise on Blood Cholesterol in KK-A' Mice

Each value represents the mean±S.E.M. from 3—5 mice.

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compared with controls ($p<0.05$).

**Effect of MF with Exercise on Blood Triglyceride in KK-A'y Mice** The hypotriglyceride effects of MF with exercise in KK-A'y mice are shown in Fig. 3. MF (30 mg/kg) with exercise decreased blood triglyceride at 2 weeks when compared with the controls ($p<0.01$), MF only ($p<0.05$), and exercise only ($p<0.05$).

**DISCUSSION**

The present results show that MF with exercise reduces blood cholesterol and triglyceride levels in KK-A'y diabetic mice. KK-A'y mice have been known to genetically induce diabetes, including ob/ob mice$^3$ and KK mice.$^9$ Hyperinsulinemia occurred as a result of insulin resistance, and hyperlipidemia by metabolic derangement. KK-A'y mice exhibit an increase in blood cholesterol and triglyceride level (Figs. 2, 3). These findings indicate that MF with exercise decreases blood lipids by metabolic improvement. The blood triglyceride of MF treatment with exercise was lower than that of MF only or exercise only. From this finding, it could be suggested that the hypotriglycemic effect of MF with exercise is a synergistic effect.

In a preliminary study, we examined the dose-dependence (10, 30, 90 mg/kg) after treatment of MF, and found that it showed antidiabetic activity at 30 and 90 mg/kg after oral administration. Therefore, we studied the effect of lipid metabolism of MF at the dosage of 30 mg/kg body weight.

MF-treated mice did not show any obvious stimulus action, suggesting that MF did not affect exercise action.

In a previous study, we also showed the antidiabetic activity of MF in mice.$^2,3$ Diabetics also often have elevated blood lipid levels by metabolic derangement. It may be that MF has a beneficial effect on hyperglycemia and hyperlipemia in type 2 diabetics.

Further investigations will be needed to elucidate the mechanism of these effects.

**REFERENCES**