New Antidiabetic Compounds, Mangiferin and Its Glucoside

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Mangiferin (MF) and its glucosides (mangiferin-7-*O*- β -glucoside) (MG) isolated from *Anemarrhena asphodeloides* Bunge rhizome, were tested for their antidiabetic activity in KK-Ay mice, an animal model of non-insulin-dependent diabetes mellitus (NIDDM). MF and MG lowered the blood glucose level of KK-Ay mice after oral administration. However, no effect on the blood glucose level in normal mice was seen, indicating that MF and MG are useful in treating NIDDM. In addition, MF or MG improved hyperinsulinemia in KK-Ay mice. From these findings, it seems likely that MF and MG exert their antidiabetic activity by increasing insulin sensitivity.

Key words mangiferin; mangiferin-7-*O*- β -glucoside; KK-Ay mice; antidiabetic activity

Many natural branched glucosides participate in a variety of biochemical functions *in vivo*.^{1–3)} In an attempt to obtain effective new glucosides to reduce blood glucose levels in diabetics, we isolated xanthone compounds associated with antidiabetic activity by bioassay-guided fractionation. However, there is no evidence that xanthone glucoside has antidiabetic activity. The aim of this study was therefore to examine the effect of xanthone glucoside on glycemic metabolism in KK-Ay mice, an animal model of obese-type genetic NIDDM with hyperinsulinemia.

MATERIALS AND METHODS

Mangiferin and Mangiferin-7-*O*- β -Glucosides Mangiferin (MF) and mangiferin-7-*O*- β -glucoside (MG) were isolated by the conventional method (Fig. 1).^{4,5)} The structures of MF and MG were confirmed by spectroscopic methods.^{4–6)}

Antidiabetic Activity Normal male mice (ddY, 12 weeks old) and KK-Ay mice (12 weeks old) were used. The mice were given free access to drinking water and food. MF and MG were dissolved in distilled water and administered to the mice orally. As a control experiment, the distilled water solution was also administered to the mice. Seven hours after administration, blood was drawn from the eye with a capillary. The glucose level of the drawn blood was determined by the glucose oxidase method⁷⁾ and serum insulin was measured by the double-antibody method.⁸⁾

Fig. 1. Structure of MF and MG

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STATISTICAL ANALYSIS

All data are expressed as mean $\pm$ SEM. Student's *t* test was used for statistical analysis. Values were considered to be significantly different when the *p* value was less than 0.05.

RESULTS AND DISCUSSION

The present study clearly showed that MF or MG from an extract of rhizomes of *Anemarrhena asphodeloides* produces consistent antidiabetic activity in KK-Ay mice. Results in the KK-Ay mice are summarized in Table 1. In the basic study, we examined the time dependence (0, 4, 7, 10 h) after treatment of MF with MG, and found that both showed a peak 7 h after oral administration. MF and MG similarly showed antidiabetic activities at a dosage of 90 mg/kg ($p < 0.001$). Seven hours after the administration of MF (90 mg/kg), the blood glucose level was in the range of 56% of the 0 hour value. The activity of MF was stronger than that of tolbutamide, a synthetic antidiabetic drug. MF or MG (30 mg/kg) also lowered blood glucose (MF, $p < 0.01$; MG, $p < 0.001$). In normal mice, no change in blood glucose was observed in MF- or MG-treated mice (Table 2). Thus it appears that MF or MG could be useful in therapy for NIDDM. The serum insulin concentration in MF- or MG-treated KK-Ay mice decreased (Fig. 2). KK-Ay mice, including ob/ob mice and KK

Table 1. Effects of MF and MG in KK-Ay Mice

	Dose (mg/kg)	N	Blood glucose (mg/dl)	
			0 h	7 h
Control		5	535 $\pm$ 26	530 $\pm$ 16
MF	10	5	545 $\pm$ 42	427 $\pm$ 62
	30	6	555 $\pm$ 24	343 $\pm$ 42**
	90	5	521 $\pm$ 17	290 $\pm$ 36***
MG	10	5	542 $\pm$ 20	481 $\pm$ 21
	30	5	546 $\pm$ 18	339 $\pm$ 25***
	90	5	565 $\pm$ 19	312 $\pm$ 44***
Tolbutamide	50	4	537 $\pm$ 44	370 $\pm$ 37*

Each value represents the mean $\pm$ SE. Significantly different from 0 h, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. N, number of mice.

Table 2. Effects of MF and MG in Normal Mice

	Dose (mg/kg)	N	Blood glucose (mg/dl)	
			0 h	7 h
Normal		5	157±7	155±8
MF	90	5	163±11	160±5
MG	90	5	163±2	169±4

Each value represents the mean±SE. N, number of mice.

Fig. 2. Effects of MF and MG on Insulin Concentration in KK-Ay Mice

Each value represents the mean±S.E. from 5 mice. Significantly different from control, *** $p<0.001$.

mice, genetically induced diabetes and are hyperinsulinemic as a result of insulin resistance.⁹⁾ From these findings, it seems likely that MF and MG exert their antidiabetic activity by increasing insulin sensitivity. Many active glucosides associated with antidiabetic activity have been discovered, including triterpenoid glucoside,³⁾ steroidal glucoside,¹⁾ and iridoidal glucoside.²⁾ It is therefore interesting that xanthone glucosides have a significant antidiabetic effect. Further study will indicate how MF and MG could become useful in the clinical treatment of diabetes.

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