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Effect of Four Flavonoids on Blood Glucose of Rats

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Abstract □ The effects of aglycones morin and quercetin and their corresponding glycosides quercitrin and rutin were studied on the blood glucose levels of rats. Quercetin and quercetrin caused hypoglycaemia in rats, while rutin and morin showed almost no difference. Quercetin, which showed 50% pronounced hypoglycaemic effect, reduced significantly the blood glucose level of alloxan diabetic rats.

Keywords □ quercetrin, rutin, morin, hypoglycaemic activity

Flavonoids are naturally occuring substances which have widespread biological activities including a hypoglycaemic effect.[1] Kovalev *et al.* studied 17 flavonoids which proved to have a hypoglycaemic effect. Bengalenoside, an uncharacterized flavonoid glycoside isolated by Augusti[3] from the bark of *Ficus bengalensis* (Moraceae) reduced the blood glucose level of normal and alloxan diabetic rats. The flavonoids of *Bauhinia purpurea* leaf are proved to be effective hypoglycaemic agents.[4] Phloridzin inhibited renal sugar transport.[5] When administered to pregrant rats starved for 18 hours, the fetal blood glucose concentration ıell by 36%. Flavonoids have also been used to treat diabetic complications. Some flavonoids[6-9] inhibit the human lens aldose reductase, and they delay or even stop the cataract process in experimental animals and possibly in man.

The purpose of our research is to compare the hypoglycaemic effect, not previously described, of quercetin, its corresponding glycosides quercitrin and rutin, and the pentahydroxy flavone morin on rat blood glucose levels.

EXPERIMENTAL PROCEDURE

Flavonoid Compounds

Four flavonoid compounds, quercetin, quercitrin, rutin and morin, were kindly supplied by Dr. Bruce Jarvis, University of Maryland, U.S.A.

Animals

Abino rats of Sprague-Dawley strain weighing 160-180 g were used in this experiment.

Methods

The experiment consists of two stages. In the first stage, rats were divided into five groups: A, a control group of 6 rats; B, four test groups each of 6 rats.

After determining the fasting blood glucose (rats were fasted 18 hrs), each test rat received a single oral dose 200 mg/kg of quercetin, quercetrin, rutin or morin through a stomach tube. Glucose solution (1 mg/g rat body weight) was given through stomach tube[10] to all rats and 2 hours later blood glucose levels were estimated immediately by an enzymatic method.[11]

In the second stage, quercetin the most potent hypoglycaemic flavonoid was tested in alloxan-diabetic rats. Diabetes was induced in rats by an intramuscular injection of alloxan 60 mg/kg (10% solution).[12]

Alloxan-diabetic rats were divided into a control group ($n = 6$) and a tested group ($n = 6$) which received a single oral dose of quercetin 200 mg/kg through stomach tube. Blood glucose was determined in the fasting state (rats were fasted 18 hrs) and again two hours after oral ingestion of glucose solution (1 mg/g rat body weight) through stomach tube.

RESULTS

The blood glucose of control fasting rats was 2.731 ± 0.186 m mol/L, and 2 hours after glucose ingestion was 3.804 ± 0.246, *i.e.* an increase of 1.073 ± 0.203 m mol/L (Table I). When rats received quercetin, the increase in blood glucose after giv-

Table I. Blood glucose levels of fasted rats before and 2 hours after glucose ingestion. Quercetin and quercetrin lowered the blood glucose levels. Rutin shown asimilar tendency, but morin had little or no effect.

	Blood Glucose (m mol/L)		
	A (Fasting)	B (2 hours after glucose ingestion)	B-A
Controls	2.731 ±0.186	3.804 ±0.246	1.073 ±0.203
Quercetin	3.305 ±0.323	3.839 ±0.376	0.534** ±0.077
Quercetrin	3.230 ±0.148	3.774 ±0.052	0.544* ±0.102
Rutin	3.313 ±0.241	3.992 ±0.191	0.679*** ±0.078
Morin	3.592 ±0.358	4.589 ±0.413	0.996*** ±0.176

* $p < 0.05$, ** $p < 0.025$, *** $p > 0.05$

Table II. Blood glucose levels of fasted diabetic rats before and 2 hours after glucose ingestion. Quercetin lowered the blood glucose levels of diabetic rats.

	Blood Glucose (m mol/L)		
	A (Fasting)	B (2 hours after glucose ingestion)	B-A
Control	7.123 ±0.523	9.900 ±0.939	2.776 ±0.755
Quercetin	7.259 ±1.619	7.974 ±1.198	0.715* ±0.429

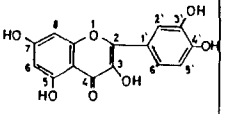
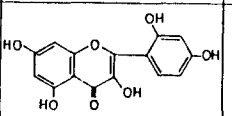
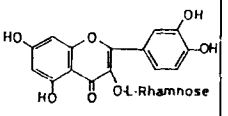
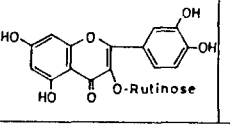
* $p < 0.05$

ing glucose orally was 0.534 ± 0.077 m mol/L, 50% less than control ($p < 0.025$). After quercetrin the increase in fasting blood glucose after glucose ingestion was 0.544 ± 0.102 m mol/L, 49% less than control ($p < 0.05$).

The increase in fasting blood glucose of rutin treated rats after glucose ingestion was 0.679 ± 0.078 m mol/L, 36.7% less than control ($p > 0.05$). In case of rats received morin, the flavonoid showed little or no hypoglycaemic effect since an increase in fasting blood glucose after giving glucose orally was 0.996 ± 0.176, 7.7% less than control ($p > 0.05$).

The fasting blood glucose of alloxan-diabetic rats was 7.123 ± 0.523, rising 2 hours after glucose ingestion to 9.900 ± 0.939, an increase of 2.776 ± 0.755 m mol/L. When quercetin was given to diabetic rats, the increase in blood glucose after giving glucose orally was 0.715 ± 0.429 m mol/L, 74% less than control ($p < 0.05$). This result showed significant hypoglycaemic effect of quercetin in diabetic rats.

Table III. Name, structure and percent reduction of hypoglycaemia by flavonoids used

Name	Structure	Hypoglycaemic %	
		Normal rats	Alloxan diabetic rats
Quercetin		50	74
Morin*		7.7	—
Quercetrin		49	—
Rutin		36.7	—

*The OH arrangment in ring B in case of morin is not good for hypoglycaemia.

DISCUSSION

We evaluated in this study the ability of four flavonoids, quercetin, quercetrin, rutin and morin to reduce the blood sugar of fasting rats after giving glucose orally by stomach tube (Table III). Quercetin (3,5,7,3′,4′-penta-OH) flavone was the most potent inhibitor of the blood sugar rise (50% reduction). However, morin (3,5,7,2′,4′-penta-OH) flavone with resorcinol (meta) hydroxyls in ring B was much less potent (7.7%) than quercetin where the hydroxyl groups have a catechol (ortho) orientation. This result clarified the beneficial effect of hydroxylation in the 3′ (or ortho) position. In addition of the orientation of the hydroxyls in ring B, glycosylation may affect the hypoglycaemic activity. The glycosylating carbohydrate and the number of sugar constituents seem to be an important factor, since quercetrin (quercetin-3-O-L-rhamnoside), decreased slightly the hypoglycaemic effect of quercetin from 50% to 49% but still have

significant hypoglycaemic effect, where as rutin (quercetin-3-O-rutinose) decreased mean blood sugar by about 37% but its hypoglycaemic effect was non significant and less potent than the parent aglycone quercetin and its corresponding monoglycoside quercetrin.

Based on this study we can conclude the following structure activity relationship:

1. The aglycone quercetin is more potent than its corresponding glycosides, glycosylation of ring A by a monosaccharide slightly decreases the hypoglycaemic activity while 3-O-glycosylation with a disaccharide leads to more reduction of the hypoglycaemic effect.
2. In the penta hydroxy flavones, an ortho dihydroxy catechol orientation in ring B (3',4'-dihydroxy) possess more hypoglycaemic property as compared to meta dihydroxy (2',4'-dihydroxy) orientation.

The mechanism of action of flavonoids as hypoglycaemic agents may be due to inhibition of intestinal sugar absorption by an effect on enzymes.[13] Nicole *et al.*,[5] proved that some flavonoids inhibit renal sugar transport, producing a loss of glucose in the urine. Moreover, the hypoglycaemic activity may be due to stimulating pancreatic B cells to produce more insulin. The latter mechanism may not be the case in our study, since quercetin reduced blood sugar in both normal and alloxan-diabetic rats. However, Hii and Howell[14] reported that quercetin may exert at least part of its hypoglycaemic effect on insulin release via changes in Ca^{2+} metabolism.

While this study with flavonoids looks very interesting, the side effects, toxicity, mechanism of action and metabolism of these natural compounds should be studied to examine their value as hypoglycaemic agents in man.

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