Ceylon J. Med. Sci. 30 (No. 2, December) 1987, *pp.* 73—77

ORAL HYPOGLYCAEMIC ACTIVITY OF THE STEM BARK OF *FICUS BENGHALENSIS*

M. R. FERNANDO, M. IRA THABREW

(*Department of Biochemistry, Faculty of Medicine, University of Ruhuna, Galle*)

AND

E. H. KARUNANAYAKE

(*Department of Biochemistry, Faculty of Medicine, University of Colombo, Colombo*)

SUMMARY. Investigations were carried out to determine whether the stem bark of *Ficus benghalensis* possesses oral hypoglycaemic activity. The ability of aqueous extracts of this plant material to lower the fasting blood glucose level and improve glucose tolerance was investigated using Sprague Dawley rats as the experimental model. The results indicate that the stem bark of *Ficus benghalensis* is capable of significantly lowering the fasting blood glucose level and markedly improving glucose tolerance in rats. The hypoglycaemic effect produced by a therapeutic dose (20 g/kg body weight) of the plant extract (49 mg/dl or 52% decrease in fasting blood glucose level in 3 hrs) was in fact better than that produced by a therapeutic dose (15mg/kg body weight) of tolbutamide (34 mg/dl or 36% decrease in fasting blood glucose level in 3 hrs). The magnitude of the hypoglycaemic effect was found to vary with the dosage administered and the storage time of the prepared extract. The maximum hypoglycaemic effect was observed with a dose of 40 g/kg body weight of the plant extract.

INDRODUCTION

Ficus benghalensis (S. Nuga) of the family Moraceae is often recommended by Ayurvedic and folk medical practitioners in Sri Lanka for the alleviation of various disease conditions including diabetes mellitus,[1-4] Although, in countries like India, the root bark of *Ficus benghalensis* is used as a hypoglycaemic agent, in Sri Lanka the stem bark is more commonly used for this purpose.

Despite the use over many years of the *Ficus benghalensis* stem extract for therapeutic purposes, no scientific investigations have so for been conducted to confirm or disprove the view held by many traditional medical practitioners about the hypoglycaemic activity of this plant. While the therapeutic efficacy as well as the most effective dosage of this plant preparation cannot be established without conducting sceintifically controlled trials any potential toxicity associated with these preparations cannot also be ruled out.

A controlled study of the oral hypoglycaemic activity of the stem bark of *Ficus benghalensis* was therefore started with the hope that such an investigation would help in a more rational use of this plant extract as a drug to control blood sugar levels. The results of preliminary investigations on the oral hypoglycaemic activity of this plant are reported here.

MATERIALS AND METHODS

Experimental animals

In all experiments male Sprague Dawley rats of body weight 150 ± 25g maintained on a standard laboratory diet were used. The animals were fasted overnight (14—16hrs) before the commencement of all experiments. After collecting blood samples for the determination of fasting blood glucose levels, the animals were randomly divided into different groups as required.

Preparation of drugs

Plant extract

The plant extract was prepared according to the method by which it is normally made by traditional medical practitioners for the administration to diabetic patients. The methods quoted in books on medicinal plant [1,4] were confirmed by discussions with serveral reputed traditional medical practitioners in southern Sri Lanka. Fresh bark from the stem of *Ficus benghalensis* (200g) was boiled with distilled water (1000ml) for 3 hrs and the final volume reduced to 100 ml *in vacuo*.

Tolbutamide

Tolbutamide (Hoechst Pharmaceuticals Ltd., 500 mg tablet) was finely powdered and 150 mg dispersed in distilled water (100 ml). Before administration the suspension was throughly mixed to ensure homogeneity.

Dosage and administration of drugs

In preliminary investigations, all drugs were administered via a stomach tube. The dosage administered was 1ml/100g body weight.

Determination of blood glucose

Blood samples (0.1ml) were drawn at regular intervals by tail puncture using a microcap (Drummond Scientific Company, U.S.A.) into distilled water (3.5ml). The proteins were precipitated by adding barium hydroxide (0.2 ml, 10% w/v) and zinc suphate (0.2ml, 5% w/v). The precipitated proteins were removed by centrifugation and the supernatant was collected. The glucose content in the supernatant was assayed by the glucose oxidase method.[3]

Effect of Drugs on fasting blood glucose level

In these studies, animals (n=18) were fasted overnight. After taking blood samples for the determination of fasting blood glucose level, animals were randomly divided into three groups of six each. Group one was given distilled water (1ml/100g body wt) and and group 2 was given the plant extract (1ml/100mg body wt.). Group 3 was given tolbutamide (1ml/100g body wt). Blood samples were collected at 1h intervals post-administration and assayed for glucose.

Effect of drug on Glucose Tolerance Test (GTT)

Animals (n=12) were fasted overnight. After collecting samples (0.1ml) of blood, animals were randomly divided into two groups of six each. Group one was given distilled water (1ml/100g body wt.) and group 2 was given the *Ficus* extract (1ml/100g body wt.)

Thirty minutes after the administration of drugs, both groups were given an oral dose of glucose (1ml/100g body wt. 50% w/v). Samples of blood were then collected at 1h intervals for 5h and blood glucose content estimated as before.

Dose response studies

In dose response studies, dosages used were 2ml, 1ml, and 0.5ml per 100g body wt. respectively.

Effect of storage of extracts on biological activity

The effect of storage on biological activity was studied with the drug prepared as described above. The drug was stored at room temperature for 24h, 48h and 72h and the biological activity was measured at each stage of storage.

RESULTS

Effects of the plant extract on fasting blood sugar levels

The effect of a therapeutic dose *Ficus benghalensis* extract on the fasting blood glucose levels is shown in Fig 1. The extract caused a marked reduction in the mean blood sugar concentration as compared with initial levels and with water treated controls. The maximum effect which occured at 3h was equivalent to a reduction of 49mg/dl or 52% in the level of blood sugar. This effect is significantly better than the 34mg/dl or 36.0% decrease in the level of blood sugar elicited by the equivalent of a normally recommended therapeutic dose of tolbutamide (15mg/kg body wt) (Fig. 1). The maximum effect with tolbutamide was also observed at 3h.

Effects of plant extract on the Glucose Tolerance

The results of the effect of aqueous plant extract on oral glucose tolerance are illustrated in Figure 2, In the control group of animals receiving distilled water (1ml/100g body weight) followed 0.5h later by an oral dose of glucose (1ml/100g body weight, 50%w/v), the peak increase in blood glucose concentration (65%) was observed between 1—2 hrs after glucose administration. The blood glucose concentration remained high over the next 3 hrs. In contrast, the group receiving the *Ficus* extract showed significant improvement in their ability to utilize the external glucose load. This group showed only a 30% increase in blood glucose concentration after 2 hrs. This value is 35% less than the peak value attained by the control group during the same period.

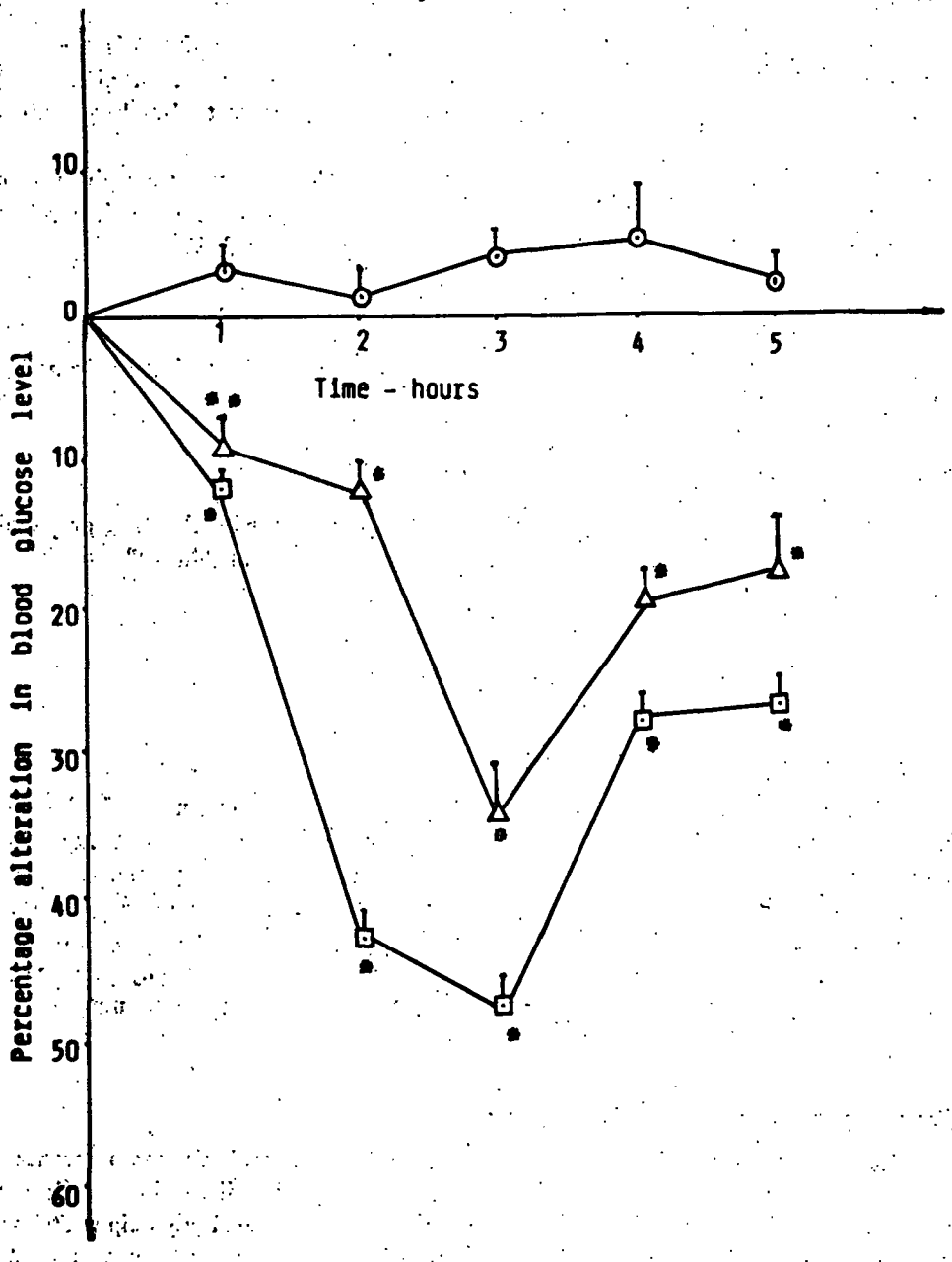

Fig. 1. Effects of the aqueous extract of *Ficus benghalensis* (20g/kg) and tolbutamide (15mg/kg) on the fasting blood glucose level in normal rats. Rats (n=6) were orally administered 1 ml/100 g body weight of distilled water (o—o), plant extract (□—□) or tolbutamide (Δ — Δ). Blood samples (0.1 ml.) were taken at 1 h intervals and assayed for glucose. Each point on the graph is the mean of 6 determinations ± S.E.M. When examined by the students t-test, the effect of the drugs was significantly different from control: * $p < 0.001$, ** $p < 0.05$.

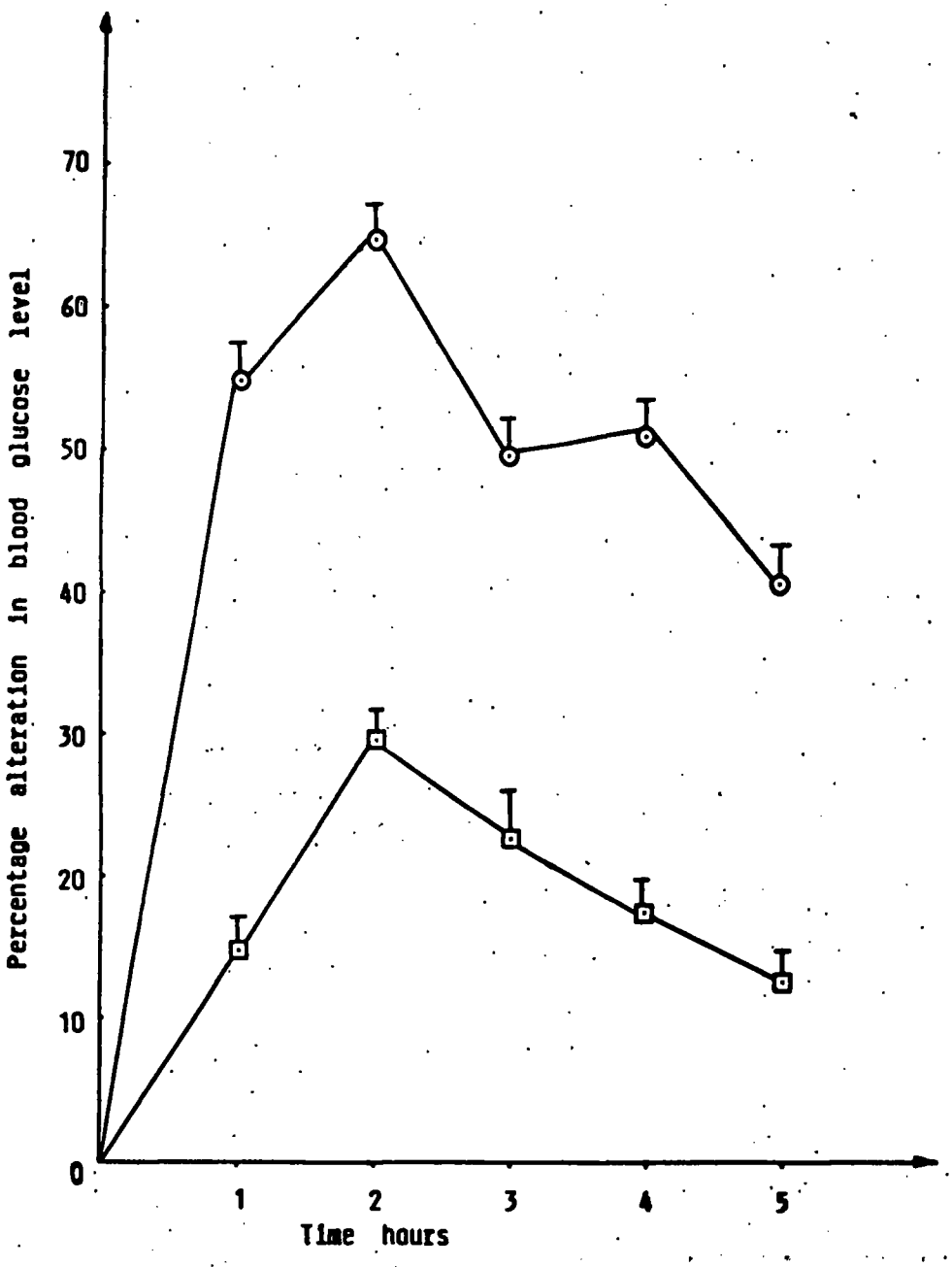

Fig. 2. Effect of an aqueous extract of *Ficus benghalensis* (20g/kg) on oral glucose tolerance of normal rats. Rats (n=6) were administered 1 ml/100g body weight of distilled water or the drug. Blood samples (0.1 ml) were taken at 1h intervals and assayed for glucose. The results are expressed as the percentage increase in the blood glucose level. Each point is the mean of 6 determinations. When examined by the student's t-test, all the points on the *Ficus benghalensis* graph were found to be significantly different from those in the control graph at $p < 0.001$.

o—o control □—□ *Ficus benghalensis*

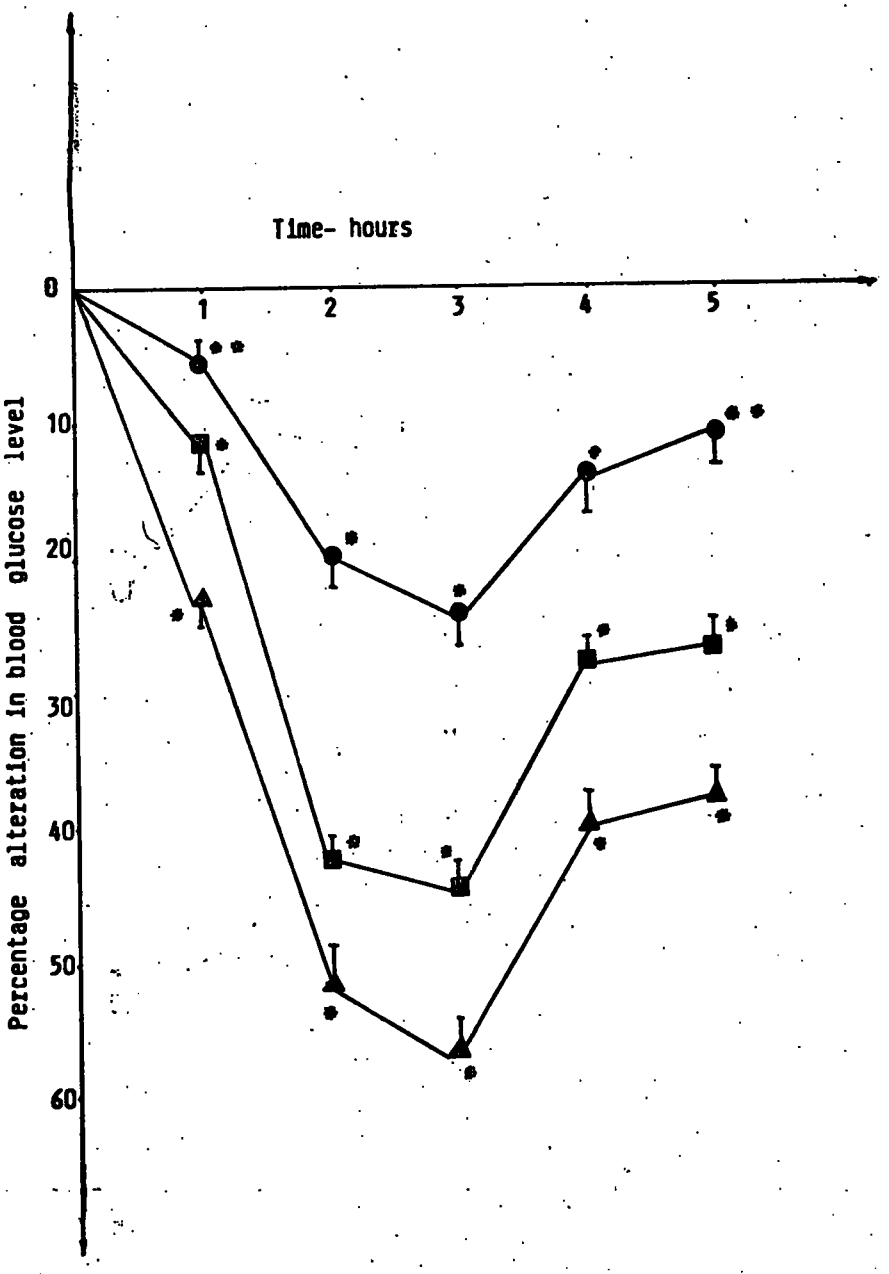

Fig. 3. Effect of different dosages (10g/kg, 20g/kg, and 40g/kg) of *Ficus benghalensis* on the fasting blood glucose levels of rats. Blood samples from each group (n = 6 rats) were collected at 1 h intervals and the glucose levels compared with that from animals treated with distilled water (10mg/kg). The results are given as the percentage change of the blood glucose level. Each point is the mean of 6 determinations ± S.E.M. When examined by the student's t-test, the values were significantly different from control : * $p < 0.001$ ** $p < 0.05$.

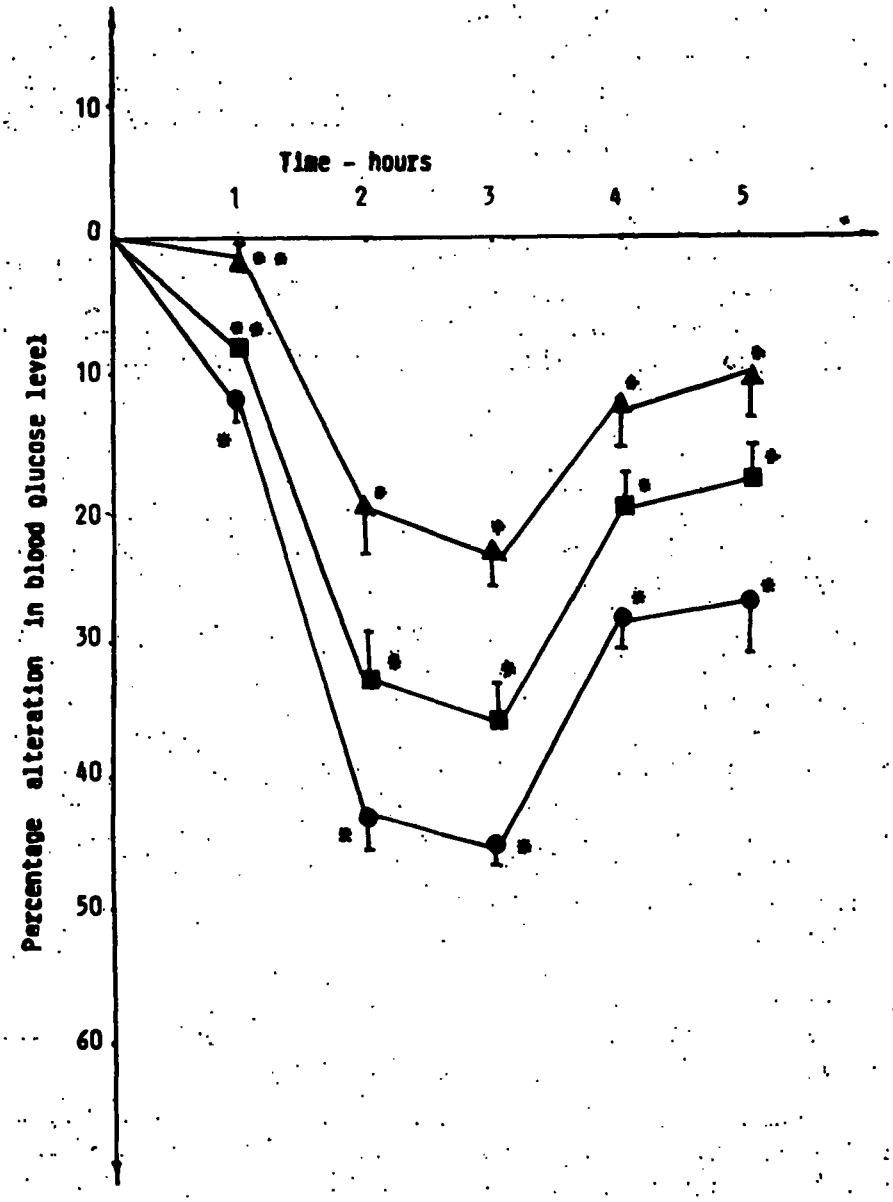

Fig. 4. Effect of storage of an aqueous extract of *Ficus benghalensis* on hypoglycaemic activity. Rats (n=6) were administered 1ml/100g body weight of the extract of *Ficus benghalensis* 24h, 48h, and 72h after preparation. Blood samples were taken at 1h intervals and assayed for glucose. The results are given as the percentage decrease of the blood glucose level. Each point represents the mean of 6 determinations. When examined by the student's t-test, the values were significantly different from control : * $p < 0.001$, ** $p < 0.05$.

●—● 24h, ■—■ 48h, ▲—▲ 72h

Effect of dosage on the hypoglycaemic activity

Figure 3 summarizes the different responses obtained by varying dosages of aqueous extracts of *Ficus benghalensis*. The hypoglycaemic activity increased with increasing dosage, the maximum activity being at a dose of 40g/kg body weight (double the normally recommended therapeutic dose).

Effect of storage on hypoglycaemic activity

The effect of storage at room temperature on the hypoglycaemic activity of aqueous extracts of *Ficus benghalensis* is illustrated in Figure 4. There was a gradual decrease in biological activity with storage. After 72 hrs storage, the maximum hypoglycaemic response was only 23% as compared to 40% elicited by the fresh extract.

DISCUSSION

The overall results obtained in the present investigation provides supportive scientific evidence in favour of the view that aqueous extracts of *Ficus benghalensis* possess significant hypoglycaemic activity.

On administration of the normally recommended therapeutic dose (20g/kg body weight) of the plant extract (Fig. 1) to rats, a fairly significant hypoglcaemic effect was seen even up to 5 hours. However, the maximum hypoglycaemic effect was produced only by double the normal therapeutic dosage (Fig 3). In previous investigations with other hypoglycaemic plants such as *Mormordica charantia, Aegle marmelos Salacia reticulata*[3] and *Asteracanthus longifolia*[2] it was also observed that the maximum hypogly caemic activity was not produced by the normally recommended therapeutic dose of the plant extract. These observations further emphasize the importance of clinical trials to establish the most effective therapeutic dosage in treatment with medicinal plant extracts. The loss of activity of the plant extract with storage time can be due either to bacterial action or some other mechanism. Such a decrease in biological activity with storage time seems to be a fairly common characteristic of many medicinal plants.[2,5] These observations strongly support the advice of ayurvedic physicians who insist on daily preparations of the decoctions for oral administration.

On comparison of the effects on the fasting blood glucose levels of therapeutic dosages of the aqueous extract of *Ficus benghalensis* and tolbutamide, the *Ficus* extract appeared to be a stronger hypoglycaemic agent than tolbutamide, even though they both produced the maximum hypoglycaemic effect at 3 hrs after administration. The differences in the magnitudes of the maximum hypoglycaemic activity produced by the two drugs may have been due to the fact that the dose of the active ingredient the animals received with the crude plant extract was not equimolar to the tolbutamide dose. The fact that the plant extract could also significantly improve the ability of animals to utilize an external glucose load (Fig. 2) seems to suggest that the *Ficus benghalensis* extract may have a mechanism of action similar to that of sulfonyl ureas rather than to that of biguanides.

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