

Medicinal Properties of *Plantago major* : Hypoglycaemic and Male Fertility Studies

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Keywords : *Plantago major*, antidiabetic, hypoglycaemia, diabetes mellitus, OGTT, male fertility, sperm count, medicinal plant

ABSTRAK

Kajian ini dijalankan untuk menentukan keberkesanan ekstrak berakua *Plantago major* untuk merawat diabetes mellitus dan meningkatkan kesuburan lelaki. Ciri-ciri hipoglisemia ekstrak daun *P. major* ditentukan dengan memberikan empat dos rawatan secara oral (100, 200, 400 dan 600 mg/kg berat badan). Salin dan glibenklamida disediakan sebagai kawalan. Ujian Toleransi Glukosa dilakukan pada masa -10, 0, 5, 15, 30, 60, 120 dan 180 minit lalu kepekatan glukosa plasma darah ditentukan dengan ujian oksidase glukosa. Keputusan kajian menunjukkan bahawa dos rawatan 600 mg/kg berupaya merendahkan aras glukosa darah tikus diabetik. Walau bagaimanapun, kesan ekstrak kurang ketara berbanding dengan glibenklamida. Dalam kajian kesuburan, ekstrak berakua biji *P. major* pada dos rawatan berbeza (30, 60, 100 dan 200 mg/kg berat badan) diberikan secara oral kepada tikus. Kesan setiap dos ke atas kepekatan sperma vas deferens selepas 120 hari ditentukan. Keputusan kajian menunjukkan bahawa dos-dos 60, 100 dan 200 mg/kg meningkatkan kepekatan sperma. Walau bagaimanapun, peningkatan aras testosteron adalah tidak ketara pada hari ke-8 dan ke-14 untuk dos 60 dan 200 mg/kg. Faktor lain yang mungkin mempengaruhi keputusan ini ialah ciri antiestrogen bijinya yang mempunyai kesan spermatigenik. Keputusan kajian ini menunjukkan bahawa ekstrak berakua *P. major* mungkin mengandungi bahan kimia untuk merawat diabetes mellitus dan masalah ketidaksuburan lelaki.

ABSTRACT

Plantago major extract has been traditionally used for treating diabetes and to increase male fertility. This study was conducted to verify its efficacy. The hypoglycaemic property of *P. major* aqueous leaf extract was determined by oral administration of four treatment doses (100, 200, 400 and 600 mg/kg body weight). Saline and glibenclamide were used as controls. Glucose Tolerance Test was done at -10, 0, 5, 15, 30, 60, 90, 120 and 180 minutes and the plasma glucose concentration was determined by the glucose oxidase assay. The study showed that only the 600 mg/kg dose had a significant effect in reducing blood glucose level in diabetic rats. However, the effect of the aqueous extracts was less pronounced compared to glibenclamide. In the fertility study, an aqueous extract from *P. major* seeds was given orally to rats at 30, 60, 100 and 200 mg/kg body weight respectively. The effect of each dose on vas deferens sperm concentrations after 20 days of treatment was determined. Analysis of the data showed significant increases in sperm concentrations in the 60, 100 and 200 mg/kg body weight groups. However, the trend in increased testosterone levels from day 8 to 14 in the 60 and 200 mg/kg groups was insignificant, suggestive of other factors, possibly antiestrogens in the seed extract contributing to the spermatogenic effect. The studies suggest that aqueous extract from *P. major* could contain chemicals for treating diabetes mellitus and male infertility problems.

INTRODUCTION

In Malaysia, *Plantago major* ('Ekor Anjing' in Malay) has been used by the Chinese and Malays as a diuretic, tonic (Hyatt 1978) and cough mixture (Muhammad and Mustafa 1994). It is also a folk remedy for the blacks in South Africa (Veale *et al.* 1992), Spanish and Mexican (Conway and Slocumb 1979) and the natives in Brazil (Franca *et al.* 1996). Recent research on *P. major* has touched on anti-cancer (Lithander 1992), anti-inflammation (Nunez-Guillen *et al.* 1997), anti-oedema (Than *et al.* 1996) and anti-ulcerogenic properties (Yesilada *et al.* 1993) to name but a few. Other uses of the plant for treatment of various diseases are summarized in Table 1.

TABLE 1
Other medicinal uses of *P. major*

| Usage | References |
|--|----------------------------------|
| 1 Treatment for panaritium | Dharma 1987 |
| 2 To induce abortion | Conway and Slocumb 1979 |
| 3 Promote blood coagulation | Hornok 1992 |
| 4 Treatment against Leishmanial ulcers on skin | Franca <i>et al.</i> 1996 |
| 5 Remedy for gall and renal stones | Riawan and Sangat-Roemantyo 1992 |
| 6 Chronic bronchitis | Matev <i>et al.</i> 1982 |
| 7 Anti-parasitic properties against <i>G. duodenalis</i> | Ponce <i>et al.</i> 1994 |
| 10 Stimulate mucus and proteolytic activity of gastric juice | Vymyatnina 1997 |
| 11 Anti-bacterial activity | Ravn and Brimer 1988 |
| 12 Anti-nematodal | Insunza and Valenzuela 1995 |
| 13 Treatment against <i>Amanita sp. poisoning</i> | Perez-Silva and Herrera 1992 |
| 14 Treatment of mastitis | Deryabin 1991 |
| 15 Promote wound healing | Salas-Auvert <i>et al.</i> 1985 |

The prevalence of diabetes mellitus in the general population is on the upswing while over the past 40 years, male fertility has declined alarmingly. In traditional Malay medicine, *Plantago major* is used for treating diabetes mellitus (Muhammad and Mustafa 1994). Hypoglycaemic studies had been done locally on plant

extracts such as *Akar Seruntun (Tinospora crispa)* (Noor and Ashcroft 1998), *Petai Papan (Parkia speciosa)* (Fathaiya *et al.* 1995) and fenugreek seeds (*Trigonella foenum-graecum*) (Mariam *et al.* 1995). Modern treatments such as with oral hypoglycaemic like glibenclamide and troglitazone unfortunately could cause hepatic dysfunction to the patient, which in several instances has been fatal (Watkin and Whitcomb 1998). Therefore Ajoankar (1979) had suggested alternative treatment of diabetes mellitus, using oral administration of plant extracts based on traditional medicine.

Meanwhile, in traditional Chinese medicine, *P. major* is said to be able to increase sperm and fertility (Hyatt 1978). Historically, a number of plants have been used as sex hormones in native medicine (Farnsworth *et al.* 1975). Plants that have been used in fertility enhancement include *Panax schinseng*, *Trigonella foenum-graecum* (Lucas 1978) and *Epimedium brevicornum* Maxim. (Lu 1994).

The objective of this study is to verify the hypoglycaemic and fertility enhancing properties of *Plantago major* extract.

MATERIALS AND METHODS

Preparation of Extracts

Plantago major seeds were obtained from Sibul, Sarawak and were planted at UPM Biology Department's nursery for three months. The leaves were dried and boiled in 0.5 liter of water for 5 minutes. In the male fertility study, the aqueous seed extract of *Plantago major* was used. The aqueous extract was prepared using the Soxhlet extraction apparatus (Soxhlet Electrothermal, England). Both extracts were then concentrated and later freeze dried at -70°C to obtain the powder form.

Experimental Procedure

The experimental animals used were white albino rats (250-350g) of the Sprague Dawley strain. They were given food pellets (Gold Coin (M) Bhd. Pelabuhan Kelang, Selangor) and drinking water *ad libitum*.

Hypoglycaemic Study

The rats were intravenously injected with 40 mg/kg body weight of alloxan monohydrate to induce diabetes. Only rats with blood glucose concentration of 250 - 400 mg/dl were selected for the experiment.

The diabetic rats were divided into 6 groups (5 rats each). The first two groups were treated with saline 0.95% (5ml/kg) and glibenclamide (10mg/kg) as controls. The other four groups were treated with water extracts of various doses (100, 200, 400 and 600 mg/kg). Saline, glibenclamide and the water extracts were administered through oral catheter. The rats were anaesthetized with Zoletil 50 and blood samples were obtained from the tip of the tail (Noor and Ashcroft 1989).

For the Oral Glucose Tolerance Test, the rats were fasted overnight before the test. The first sampling was obtained at time -10 minute and another sampling at time 0 minute, followed by treatment administration. After 15 minutes, a glucose load of 1.5g/kg rat body weight was orally administered. Consecutive blood samples were taken at 5, 15, 30, 60, 90, 120 and 180 minutes after the oral glucose load. The blood glucose concentrations in the samples (mg% or mg/100ml) were analyzed by Glucose Oxidase method (GOD-Perid Method, Boehringer Mannheim).

Areas under the blood glucose concentration curves (AUC) were calculated by trapezoidal integration method (Campbell and Madden, 1990) whereby
Area under curve (AUC)

$$= \sum_{i=1}^{n-1} [(Y_i + Y_{i+1}) / 2] [t_{i+1} - t_i]$$

In which

- n is the number of replicates
- $(Y_i + Y_{i+1}) / 2$ is the height of the rectangle (estimated as the midpoint between Y_i and Y_{i+1}) in mg%
- $t_{i+1} - t_i$ is the width of the rectangle in minutes

Male Fertility Study

The seed extract was given orally to four groups of rats with doses of 30, 60, 100, and 200 mg/kg body weight. 0.95% saline solution was used for control purpose. Treatment was given every day immediately after blood sampling using an oral catheter that was connected to a syringe. Blood samples were taken from the tail tip at days 0, 8, 14 and 20. The blood and later the serum were both centrifuged at 6500 rpm for 15 minutes and stored at -20°C before Testosterone RIA analysis (Gamma-B Testosterone Kit, IDS Ltd.).

Sperm concentrations were determined on the last day of treatment (day 20). The rats were killed and the vas deferens fluid was taken immediately using a fine needle syringe, which was inserted into the vas deferens. A 10(1 aliquot of vas deferens fluid was aspirated into the syringe and then diluted to 2 ml in 0.95% saline solution and examined under light microscope. The sperm concentration was determined using a haemocytometer (Hafez 1987).

RESULTS AND DISCUSSION

Hypoglycaemic Study

The basal plasma glucose levels in the experimental animals (230-300 mg%) were higher compared to normal animals which have basal levels in the range of 80 mg% to 100 mg% (Noor and Ashcroft 1989 and Abdel-Barry *et al.* 1997). The high basal values confirmed the diabetic condition in the experimental animals. Furthermore, there is no significant difference in the readings at -10 minutes and 0 minute for all treatment groups (Figure 1). This shows that the diabetic condition in the animals was stable. After the rats were given a glucose load of 1.5g/kg body weight at time 0 minute, the plasma glucose level of the rat group treated with saline reached a peak at 30 minutes (388.38 mg%) and very gradually became lower until it reached the basal diabetic level after 120 minutes (Figure 1). Although Alloxan is believed to specifically destroy the β -cells (Chattopadhyay *et al.* 1997) there might be a chance of recovery from the drug and the surviving β -cells could still produce insulin (Chattopadhyay *et al.* 1997). This explains the gradual lowering of the blood glucose level from the peak to the basal diabetic level. In the glibenclamide-administered group, the peak blood glucose level was significantly lower (ANOVA, $p < 0.05$, $n = 5$) (349.56 mg%) compared to the saline control (388.38 mg%). This shows that the drug (glibenclamide) was effective in slowing the rate of increase in blood glucose level after a glucose load. The decrease in the blood glucose level might be due to the possibility of stimulation of the β cells to release insulin (Ligtenberg *et al.* 1997).

Since the treatment of saline and glibenclamide showed the ability of the blood glucose level to reach basal diabetic level, the results could indicate that the rats are from the Type II diabetes mellitus (Non-Insulin Dependent Diabetes Mellitus) categorised by insulin

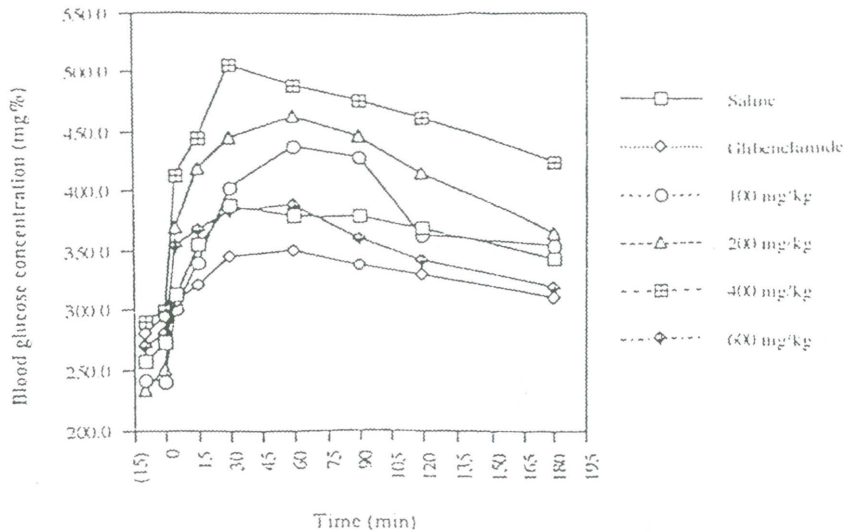


Fig. 1. Blood glucose concentration (mg%) at different time intervals (min) in diabetic rats

deficiency or insulin resistance (Ferrannini 1998). Invariably, the time taken for the high blood glucose level in saline and glibenclamide groups to reach basal diabetic level is longer (120 and 180 minutes respectively) compared to normal rats where the blood glucose returned to basal within 90 minutes to 120 minutes (Trejo-González *et al.* 1996 and Peungvicha *et al.* 1998)

The area under the graphs has been used to indicate the amount of blood glucose level due to the glucose load and also to see the effect of the extracts (Leatherdale *et al.* 1981). The area from the time of glucose load (0 minute) until the end of the experiment (180 minutes) was calculated for each treatment (Table 2). The area under the glibenclamide graph ($7.4358 \times$

10^3 mg%minute) is significantly lower than the rest (ANOVA, $p < 0.05$, $n = 5$) (Figure 1). This could be due to the increase in insulin release and/or increase in glucose uptake by the peripheral cells stimulated by glibenclamide (Grodsky *et al.* 1963).

The extract of 600 mg/kg dose has an area of 13.5818×10^3 mg%minute, which is significantly less than that of the saline control (16.7434×10^3 mg%minute) but greater compared to glibenclamide control graph (Figure 1). The results showed that the extract might contain some unidentified substances that can lower the blood glucose level. However, three other lower doses of the extracts (100 mg/kg, 200 mg/kg and 400 mg/kg) did not show any hypoglycaemic properties or dose dependent effect as statistical data analysis (ANOVA, $p < 0.05$, $n = 5$) did not show any significant increase in blood glucose level compared to saline at all time intervals.

TABLE 2

Area under graph indicating blood glucose concentration for each treatment

| Treatment | Area under graph ($\times 10^3$ mg%minute) |
|---------------|---|
| Glibenclamide | 7.4358 ^a |
| Saline | 16.7434 ^b |
| 100 mg/kg | 25.9535 ^c |
| 200 mg/kg | 30.4419 ^c |
| 400 mg/kg | 29.4215 ^c |
| 600 mg/kg | 13.5818 ^d |

Note : Groups labeled with different letters are significantly different compared to saline control, $P < 0.05$

Male Fertility Study

After 20 days of treatment, the extract doses of 60, 100 and 200 mg/kg body weight significantly increased the sperm concentrations (Table 3) by an average of 18% as compared to the control group. The 30 mg/kg group failed to show any significant increase in sperm concentration compared to the control. There were also no significant differences in sperm concentrations between the 60, 100 and 200 mg groups. The

TABLE 3

Sperm concentrations of treatment groups after 20 days of treatment

| Treatment | Sperm concentrations (× 107 cells per ml) |
|-----------|--|
| Control | 123 ± 6.60 a |
| 30 mg/kg | 127 ± 6.16 a |
| 60 mg/kg | 144 ± 10.05 b |
| 100 mg/kg | 146 ± 7.04 b |
| 200 mg/kg | 144 ± 11.23 b |

Note : Groups labeled with different letters are significantly different, P<0.05.

Data presented as mean ± s.d., n=4.

testosterone levels (Table 4) show a trend increase for the 60 and 200 mg/kg groups for days 8 and 14 but it is not statistically significant due to high standard error and a limited sample. The sperm characteristics on all treatment groups did not show any signs of abnormality.

The results failed to show concrete evidence to suggest testosterone's direct role in increasing sperm concentration. Other factors may have contributed to the extract's spermatogenic action. One possible explanation is that the seed extract has anti-estrogenic properties. No studies has yet been done on *P. major's* anti estrogenic properties but other plants have been known to possess this property (Kallela 1974). Anti estrogens act on the pituitary gland to stimulate the production of FSH (Teoh 1987). FSH increases the availability of germ cells at certain steps of development during spermatogenesis for entry into androgen dependant stages which included stage 19 where spermatids are released (Sharpe 1994). This coupled with the trend increase in testosterone levels may have helped to significantly increase the sperm concentrations.

CONCLUSION

Results from the hypoglycaemic studies showed that only the 600mg/kg *P. major* water extract demonstrated hypoglycaemic effect on blood glucose level in diabetic rats. The effect is, however, less pronounced compared to the established hypoglycaemic agent, glibenclamide. The use of the plant as a drug in treatment of diabetes will depend on the proper processing and dosages of the extracts in order to obtain the desired hypoglycaemic effect. In the male fertility study, the doses of 60, 100 and 200 mg/kg were able to significantly increase sperm concentrations. There was also a trend in increased testosterone levels from day 8 to 14 in the 60 and 200 mg/kg groups but it was insignificant and suggested other factors, possibly antiestrogens in the seed extract contributing to the spermatogenic effect. All together, the studies suggest that aqueous extract from *P. major* could contain chemicals for treating diabetes mellitus and male fertility problems. Further studies should be carried out to verify its hypoglycaemic and male antifertility effects.

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TABLE 4

Testosterone levels of serum (ng/ml) during the course of treatment

Data presented as mean ± s.e.m.

| Treatment | Days | | | | |
|-----------|-------------|--------------|-------------|-------------|--------------|
| | 0 | 4 | 8 | 14 | 20 |
| Control | 1.21 ± 0.49 | 0.72 ± 0.31 | 1.07 ± 0.66 | 0.68 ± 0.27 | 1.16 ± 0.741 |
| 60mg/kg | 1.28 ± 0.99 | 0.728 ± 0.44 | 1.53 ± 0.58 | 1.67 ± 0.72 | 0.44 ± 0.21 |
| 200mg/kg | 0.83 ± 0.51 | 0.76 ± 0.14 | 1.42 ± 0.56 | 1.55 ± 0.74 | 0.35 ± 0.58 |

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Received: 23 February 1999

Accepted: 10 February 2000