Indian Journal of Pharmacology 1999; 31: 138-141 RESEARCH PAPER

INVESTIGATIONS INTO THE ANTI-DIABETIC ACTIVITY OF *AZADIRACHTA INDICA*

SONIA BAJAJ, SRINIVASAN B.P.

College of Pharmacy, Pushp Vihar, New Delhi-110 017.

Manuscript Received: 21.8.95 Revised: 29.10.98 Accepted: 1.12. 98

SUMMARY

Objective: To investigate the anti-diabetic activity of *Azadirachta Indica* using IDDM and NIDDM animal models .

Methods: Streptozotocin induced models of IDDM (65 mg/kg, *iv*) as well as NIDDM model (90 mg/kg, *i.p* in neonates) were given neem leaf extract (NLE, 1 g/kg, po) for 6 weeks and their anti-diabetic activity was assessed.

Result: The treatment with insulin, aqueous NLE, aqueous NLE with insulin and insulin with aminoguanidine showed a fall in blood glucose levels of 80, 45.4, 38.02 and 77-65% whereas in NIDDM model, a fall of 53.95 and 60.50% were observed with glibenclamide and NLE.

Conclusion: Aqueous extract of NLE has a good therapeutic potential as anti-hyperglycaemic agent in IDDM and NIDDM.

KEY WORDS *A.indica* IDDM NIDDM rats

INTRODUCTION

Azadirachata Indica (F: Meliaceae, Hindi: neem) has been shown to possess number of pharmacological effects like cardiovascular, antimicrobial, immunomodulatory [1]. One of the properties of neem has been its hypoglycaemic effect. Different parts like seed and leaf extract have been shown to possess hypoglycaemic effect [2,3,4,5]. Earlier observation in this laboratory has shown that NLE has moderate hypolycaemic activity and significant antihyperglycaemic activity in normal rats[6]. Hence the antidiabetic activity of NLE was evaluated in animal models of IDDM and NIDDM. The NLE was compared with aminoguanidine, an inhibitor of nonenzymic glycosylation and which prevents formation of advanced glycosylated end product (AGEP).

MATERIALS AND METHODS

Male albino rats of Wistar strains (200-300g) were used. IDDM was induced[7] by injecting streptozotocin (STZ) to adult rats in a dose of 65 mg/kg. *i.v.* in 0.1M citrated buffer, pH 4.5, Rats were kept fasted overnight but were given water *ad libitum*. After 48 hours of STZ injection, blood samples were taken from retroorbital plexus of conscious rats. Blood glucose estimations were done by glucose oxidase method[8]. The standardized aqueous neem leaf extract (NLE) was used for the treatment. Animals were divided into six groups. The drug or saline treatment was given daily in the morning for 4 weeks. Group I (non diabetic control) and Group II (diabetic control) were given distilled water. Groups III, IV, V and VI were administered insulin NPH (5U/kg, s.c.), NLE (1g/kg, p.o.), NLE (1g/kg, p.o.) with insulin NPH (5U/kg, s.c.) and insulin NPH (5U/kg,s.c.) aminoguanidine (AMG,100 mg/kg, p.o.) respectively. After 4 weeks of treatment, blood glucose estimations were done.

NIDDM was induced[9] by administration of STZ (90 mg/kg, i.p.) to 2 days old neonatal rats dissolved in 0.1M citrated buffer, pH 4.5. The rats were kept fasted overnight but had free access to water. After 6 weeks of STZ injection, glucose estimations were carried out. The rats were divided into 4 groups (6-10 animals in each) . Groups I and II (non-diabetic and diabetic control groups) were given distilled water (p.o.). Group III and IV received NLE (1g/kg, p.o.) and glibenclamide (0.025 mg/kg, p.o.) respectively daily in the morning. After 6 weeks of treatment, blood glucose estimations were done. Glucose tolerance test was done by administering glucose (50% w/v, 2.5 g/kg) and estimating blood glucose levels at

Correspondence: B.P. Srinivasan

Figure 1. Blood glucose levels after 4 weeks of treatment in IDDM animal model (mean ± SEM)
*P <0.05 when compared to control.

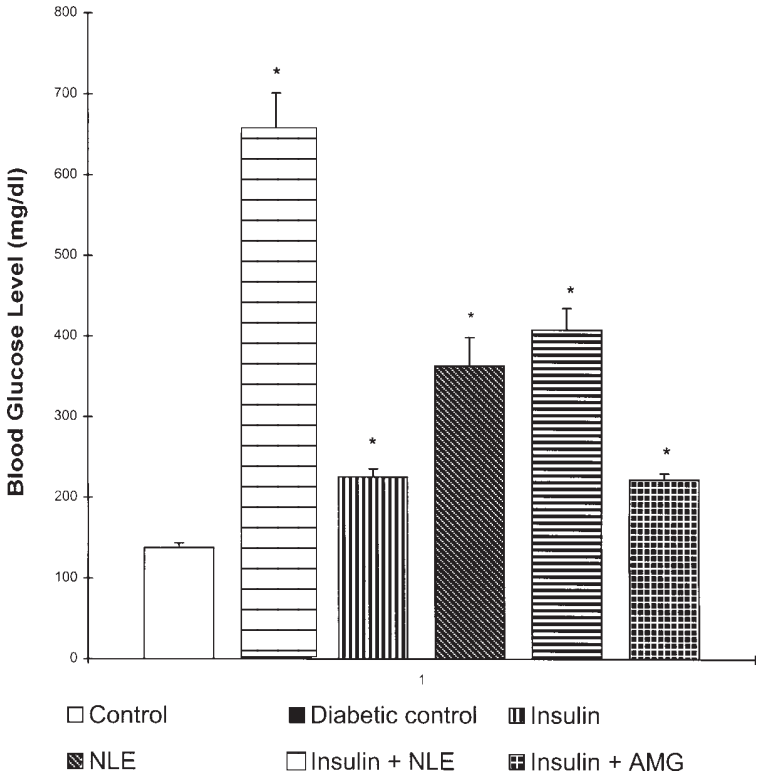
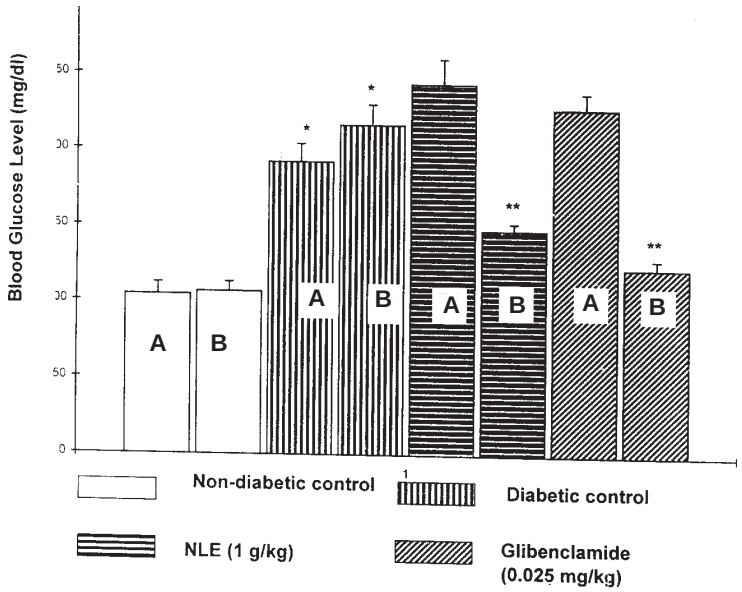
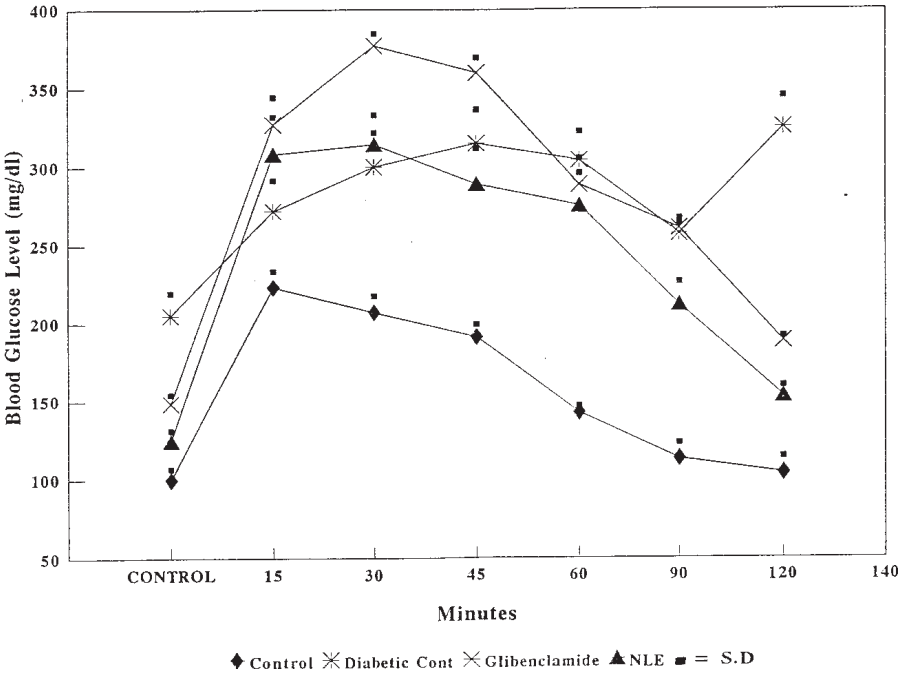


Figure 2. Blood glucose level after 6 weeks of treatment with NLE and glibenclamide in NIDDM animal model. A,B : Blood glucose levels before and after 6 weeks of treatment with saline/drug in diabetic animals respectively.



*P <0.001 when compared to non-diabetic control group; **P <0.001 when compared to diabetic control group.

Figure 3. Effect of NLE and Glibenlamide on Oral GTT in NIDDM model.



15,30,45,60,90 and 120 minutes. All the rats were subjected to oral GTT before and after 6 weeks of daily treatment of NLE (1g/kg) and glibenclamide (0.025 mg/kg). Results were statistically analysed using ANOVA. P values <0.05 were considered significant.

RESULTS

In IDDM animal models, a fall in blood glucose levels of 80, 45.4, 38.02 and 77.65% were observed in groups treated with insulin, NLE, NLE and insulin and insulin with AMG respectively as compared to diabetic control group (Figure 1).

In NIDDM models, both glibenclamide and NLE significantly reduced the blood glucose level ($p < 0.001$) and the effect of NLE (1g/kg) was greater than that of glibenclamide (Figure 2).

The NLE (1g/kg) and glibenclamide (0.025 mg/kg) significantly increased ($P < 0.001$) the tolerance for glucose (Figure 3). However in diabetic control animals, there was extreme rise in blood glucose which was not found to be normalised.

DISCUSSION

The study shows that in case of IDDM, both insulin as well as NLE treatment produced hypoglycaemia and the hypolycaemic effect of NLE was lesser than that of insulin. It was also observed that insulin effect was reduced when combined with NLE whereas the AMG had no effect. This is in conformity with the observation of Nicholls and Mandel[10]. However in IDDM model, where there is complete loss of b cells, NLE causes a reduction of blood sugar probably by increasing the uptake of glucose peripherally but inhibits the action of insulin by inhibiting glycogenesis. These results are in variance with the conclusion of Chattopadhyay *et al* [11] who showed that *A. Indica* failed to modify the effect of insulin. However the lack of NLE effect in IDDM model was indicated by Santoshkumari and Devi [2].

In case of NIDDM, NLE showed significant hypoglycaemic effect similar to glibenclamide. indicating a sulphonylurea like action as suggested by Luscombe and Taha[12]. It may also act by modifying the peripheral uptake of glucose and probably increasing the sensitivity of insulin receptor[5].

Our results also indicate that in case of NIDDM rats both first as well as second phase of insulin response to glucose load are impaired whereas NLE and reference drug treatment improved glucose tolerance . It may be due to restoration of delayed insulin response or due to inhibition of intestinal absorption of glucose.

Thus the present experiments show that NLE has significant hypoglycaemic effect in both IDDM as well as NIDDM models and also improved glucose tolerance. It has got potential as an oral hypoglycaemic agent in NIDDM.

ACKNOWLEDGMENT

The authors thank Professor S.S. Agrawal, Head of the department for his encouragement, M/S Dabur Research Foundation for providing us with NLE and other facilities, NVS Hoechst for supply of glibenclamide.

REFERENCES

1. Dhawan BN, Patnaik GK. Pharmacological studies for therapeutic potential. In neem research and development. Randhawa NS. and Pannai B S. (Eds.). Published by Soc. Pesticide. Sci., India; 1993:242-9.
2. Santoshkumari KS, Devi KS. Hypoglycaemic effects of medicinal plants. *Ancient Sci. Life* 1990;**9**: 221-3.
3. Murty KS, Rao DNI, Rao DK, Murty LBG. A preliminary study on hypoglycaemic and anti hyperglycaemic effect of *A. Indica*. *Indian J Pharmacol* 1978;**10**:247-50.
4. Dixit VP, Sinha R, Jank R. Effect of Neem seed oil on the blood glucose concentration of normal and alloxan induced diabetic rats. *J Ethnopharmacol* 1986;**17**:95-8.
5. Shukla R, Singh S, Bhandari CR. Preliminary clinical trials on antidiabetic actions of *A. Indica*. *Medicine and surgery* 1973;**134**:11-2.
6. Jain G. Pharmacological profile of *A.Indica*: A study. M.Pharm thesis, Delhi University, Delhi. 1984.
7. Pitkin RM, Reynold WA. Diabetogenic effect of streptozotocin in Rhesus monkey. *Diabetes* 1970;**19**:85-90.
8. Braham D, Trinder P. An improved color reagent for the determination of blood glucose by oxidase system. *Analyst* 1972;**97**:142-4.
9. Bonner weir S, Trent DF, Honey RN, Weir GC. Response of neonatal rats islets to streptozotocin. *Diabetes* 1981;**30**: 64-9.
10. Nicholls K, Mandel TE. Advanced glycosylation end product in experimental murine diabetic nephropathy. *Laboratory Invest*. 1992;**60**:486-91.
11. Chattopadhyay RR, Chattopadhyay RN, Maitra SK. Effect of *A. Indica* on hepatic glycogen in rats. *Indian J Pharmacol* 1993;**25**:174-5.
12. Luscombe DK, Taha SA. Pharmacological studies on the leaves of *A. Indica*. *J Pharm. Pharmacol* 1974;**(Supp. 26)**:111.