HYPOGLYCAEMIC ACTIVITIES OF SOME INDIGENOUS MEDICINAL PLANTS TRADITIONALLY USED AS ANTIDIABETIC DRUGS

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INTRODUCTION

In the modern therapy of diabetes mellitus, insulin and the sulfonylureas provide excellent relief from the acute symptoms of the disease. However, these agents are neither curative nor efficacious to reduce or prevent chronic complications of the disease[1]. Therefore, research on antidiabetic medicaments of any other source including the plants must be continued[2]. The plants have been used since ancient times in the traditional medicine for the treatment of various diseases of man and animals. It is not surprising, therefore, that many of them have also been employed in this part of the world to cure diabetes mellitus[3-5]. The present paper reviews several studies made on some indigenous medicinal plants and herbs which have been pharmacologically evaluated for hypoglycaemic activity in the normal and alloxan diabetic rabbits during the last ten years in the department.

MATERIALS AND METHODS

Plant materials used

Hypoglycaemic/antidiabetic activities of a total of 22 indigenous medicinal plants/herbs and a compound herbal preparation containing equal parts of 4 plants have been described in the review. These plants have been claimed inAyurvedic, Unani and Eastern medicines to possess antidiabetic properties. These indigenous plant drugs included fresh and green over-the-ground (aerial) parts of achyranthes aspera, fin (puthkanda) and gymnema sylvestre, R. Br. (gurmar booti), eupborbia prostrata, Lit. (dhodi-khurd), fumaria parvlflora, lin (kulfa) fruits of cassla fistula, lin (amaltas), ficus glomerata, in (gular), momordica charantla, lin (karela), green barks ofgrewia asiatica, lin (phalsa) and seeds of eugenia jambolana, lam (jaman). All these plants were obtained in sufficient amounts from the experimental fields and gardens of the Agricultural University, Faisalabad. However, the fresh and green leaves of whole plants ofportulaca olerecae, lin (kulfa), zizyp bus sativa, Gaertn. (unab) while green, aerial parts of taraxacum officinale, wigg (dudhal) were collected from the hills ofAbbottabad (NWFP). They were carefully washed with tap-water and dried under shade at a temperature below 40°C. In addition, completely dried seeds of mucuna pruriens, lin (kowanch), roots of onosma echioldes, lin (rattanjot), cuminum nigrum, lin (kala zira), roots of asparagus racemosus, wild (satwar) and caralluma edulis, benth. (chung), fruits of acacia arabica, lin (kiker), lodiocea sechellarum, comm. (naryal-daryal) and gossypium birsutum, lin (cottonseed) and dried-stalks ofpterocarpus marsupium, roxb. (chop-bejasar) were procured from the local medicinal plant market of Faisalabad. A compound medicinal plants based prescription containing roots of bergenia ligulata wild (Pakistan-bed), seeds of asteracantha longzfolia, nees (tal makhana), roots of argyria speciosa, sweet (sumandar-sokh) and bark of cinnamomum cassia, blume (tej) was also purchased from the local herbal dealers. The identity of the above mentioned plant drugs was first established with the aid of treatise on regional flora and comparison with herbarium sheets of the authentic species. All the plants were then finally powdered in an electric grinder and stored in well closed cellophane bags at 4°C in the refrigerator.

Chemicals used

Alloxan monohydrate, alpha-D-glucose (anhydrous) and methanol were obtained from B.D.H.

Laboratories (Chemical Division), Poole, England. Glacial acetic acid, benzoic acid, 0-toluidine, thiourea and tnchloracetic acid were obtained from E. Merck Darmstadt, West Germany. All other chemicals and reagents used were of analytical grade prepared either by E. Merck of B.D.H. Laboratories. Tolbutamide or acetohexamide were obtained from Hoechest or Lilly Laboratories Ltd., Karachi respectively.

Experimental animals used

Adult, healthy rabbits of a local strain weighing between 1000. 1500 grams were used in these experiments. The animals were kept in an air-conditioned animal-room. The animals were offered a balanced rabbit feed. The hypoglycaemic effects of most plant drugs were first studied on the blood glucose levels of normally fed (non-fasted) rabbits. Then, separate experiments were performed to study their effects on blood glucose levels of the non-fasted alloxan-treated diabetic rabbits. For acute toxicity and behavioural pattern studies, local strain of rabbits of either sex were used.

Preparation and administration of drug suspensions

The amount of powdered plants or their aqueous and methanol extracts required for each rabbit was calculated on body weight basis and their appropriate amounts were weighed, well triturated with 10 ml of 2% aqueous gum tragacanth solution and the final volume was made upto 20 ml and then administered orally to each animal by using a feeding needle connected to a 20 ml syringe. Control animals received an equivalent amount of 20% gum tragacanth solution only. Similarly, tolbutamide or acetohexamide were administered after suspending in the 2% gum orally as aqueous solution.

Preparation and administration of aqueous and methanol extracts

Aqueous extracts were prepared by cold maceration[6] and the methanol extracts were prepared by the continuous extraction technique using Soxhiet apparatus. The extracts obtained were evaporated by slow heating and continuous stirring at 40°C. The process of evaporation was continued till complete evaporation was ensured. The extracts obtained were suspended in 2% gum solution just before administration to rabbits.

Collection of blood samples

Just after drug administration, the animal was held in a wooden rabbit holder and immediately, after pricking the vein with a needle 0.2 ml of blood was collected from saphenous vein (zero hour sample). Similarly, samples of blood glucose were again collected after +2, +4, +8, +12 and +24 hours.

Determination of blood glucose levels

Blood glucose was determined by using the Otoluidine reagent. This method gives results very close to the glucose oxidase method and is one of the most widely used manual methods[7].

Acute toxicity and behavioural pattern studies

In order to study any possible toxic effects of the plant drugs, rabbits were randomly divided into 5 groups (I-V) of six animals each. The rabbits of group I served as a control. These animals received orally 20 ml of water only. The animals of group II, III, Wand V were treated orally with various doses of the powdered plant drugs suspended in 20 ml of water, respectively. The number of animals that die in a 7 day period after a single dose was recorded. The animals were also closely examined for signs of intoxication, lethargy, behavioural modification and morbidity. The symptoms including awareness, mood, motor activity, CNS excitation, posture, motor incoordination muscle tone, reflexes, autonomic response, etc. were checked for seven days[8].

Statistical analysis

Mean blood glucose levels and effects of the powdered plant drugs observed in the rabbits have been expressed as the means ± SEM and the Student's t-test was used to check for significance[9].

RESULTS

The important data of the reviewed studies on the screening of the indigenous medicinal plants for

hypoglycaemic/antidiabetic activity including their vernacular names of the plants, part used, effect on blood glucose of normal and diabetic rabbits, durations of action, possible mechanism(s) of action and the refer. ences of publications describing the results in detail have been given in Table I.

TABLE I. Indigenous medicinal plants screened for antidiabetic/hypoglycaemic activity in rabbits.

S. botanical name of No. plant (vernacular name) and the family	Part(s) used (dried and powdered)	Effect on blood glucose		Duration of action (hours)	Possible mechanism(s) of action	Reference(s)
		In normal rabbits	In diabetic rabbits			
1. Acacia arabica, wild (kikar) mimosaceae	Fruit	Decrease	Nil	2-24	Insulin release	Akhtar and Khan[10]
2. Achyranthes aspera, Lin (Puthkanda) amaranthaceae	Aerial parts	Decrease	Decrease	2-24	Insulin release and insulin-like effect due to organic and mineral contents	Akhtar and Iqbal[11]
3. Asparagus racemosus, wild (sarwar) liliaceae	Root	Decrease	Nil	2-24	Insulin release	Akhtar et al.[12]
4. Cassia fistula, Lin (amaltas) leguminosae	Fruit	Decreases	Decrease	2-8	Insulin release and insulin-like	Akhtar and Riffat[13]
5. Caralluma edulis, benth (chung) Asclepiadaceae	Root	Nil	Nil	-	Not hypoglycaemic	Akhtar and Khan[10]
6. Cuminum nigrum, Lin (kala-zira) umbelliferae	Seed	Decrease	Decrease	2-24	Insulin release and insulin-like	Akhtar and Ali[14]
7. Eugenia jambolana, Lin (jaman) myrtaceae	Seed	Decrease	Decrease	2-12	As above	Farooqi[15]
8. Euphorbia prostrata, Lit. (dhodhi-khurd) Euphorbiaceae	Whole plant	Decrease	Nil	8-24	Insulin release	Akhtar et al.[16]
9. Ficus glomerata, Roxb. (gular) urticaceae	Fruit	Decrease	Decrease	2-12	Insulin release and insulin-like due to organic and mineral contents	Akhtar and Qureshi[17]
10. Fumaria parviflora, Lam. (shahtarah) Fumariaceae	Whole plant	Decrease	Nil	4-12	Insulin release	Akhtar et al.[16]
11. Gossypium hirsutum, Lin (benola) Malvaceae	Seed	Nil	Decrease	2-12	Biguanide-like	Dogar[18]
12. Grevia asiatica, Lin (falsa) Tiliaceae	Green bark	Decrease	Decrease	6-12	Insulin release and insulin-like	Akhtar[19], Dogar[18]
13. Gymnema sylvestre R.L. (gurmar) Asclepiadaceae	Aerial parts	Decrease	Nil	4-12	Insulin release	Dogar[18]
14. Lodoicex seychellarum (naryal-daryai) Pulmae	Fruit	Decrease	Nil	4-24	As above	Akhtar et al.[12]
15. Momordica charantia, Lin (karela) Cucurbitaceae	Fruit	Decrease	Decrease	4-24	Insulin release and insulin-like action	Akhtar et al.[20], *Akhtar[21]
16. Mucuna pruriens, Bak. (kowanch) Leguminosae	Seed	Decrease	Decrease	2-12	Insulin release and insulin-like	Akhtar et al.[22]
17. Onosma echioides, Lin (rattan jot) Boraginaceae	Root	Decrease	Decrease	2-8	As above	Akhtar and Riffat[23]
18. Portulaca oleracae, Lin (kulfa) Portulacaceae	Whole plant	Decrease	Nil	8-24	Insulin release	Akhtar et al.[24]
19. Pterocarpus marsupium, Roxb (chob-bejasar) Leguminasae	Stalks	Decrease	Nil	8-24	As above	Akhtar[19]
20. Taraxacum officinale, Wigg. (dhudal) Compositae	Whole plant	Decrease	Nil	4-12	As above	Akhtar et al.[24]
21. Zizyphus sativa, Gaertn. (unab) Rhamnaceae	Leaf	Decrease	Nil	8-12	As above	Akhtar[19]
22. Compound plant prescription containing bergenia ligulata, wall; asteracantha longifolia, nees; argyria speciosa, sweet; cinnamomum cassia, blume; (pakhan-bed, tal-makhana, summundar sokh and tej) equal parts saxifragaceae, acanthaceae, convolvulaceae, lauraceae	Root Bark Seed, Bark, respectively	Decrease	Decrease	4-24	Insulin release and insulin-like	Akhtar and Ali[25]

*Study carried out in maturity-onset (type II) human diabetes mellitus patients.

However, certain other features of the results, especially their effective doses are described in detail under following groups.

1. Plants producing hypoglycaemia in normal rabbits only

Powdered whole plants of euphorbia prostrata and fumaria parviflora in 1-3g/kg doses and the methanol extract of E. prostrata produced significant hypoglycaemic effect in the normal (non-diabetic) rabbits only. Decoction of gymnema sylvestre (aerial parts) in doses equivalent to 5.20g/kg of the powder decreased the blood glucose in the normal rabbits but not in ailoxan diabetics. Similarly, powdered asparagus racernosus (roots) whole plants of portulaca oleracae and taraxacum

officinale,pterocarpus marsupium (stacks) and a prescription containing equal parts of bergenia ligulata (root barks), asteracantha longifolia (seeds), argyria speciosa (seeds) and cinnamomum cassia (barks) in doses ranging from 1 to 3g/kg orally showed hypoglycaemic action in normal rabbits only.
2. Plants producing hypoglycaemia in both normal and diabetic rabbits Oral administration of 2-4g/kg of powdered achycanthes aspera (aerial parts), cuminum nigrum (seeds) and onosma ecbioides (roots) produced a significant hypoglycaethic effect in normal as well as in alloxan diabetic rabbits. The water and methanol extracts also decreased blood glucose levels in both types of rabbits. Powdered cassia fistula (fruits) in 30 and 40 mg/kg doses produced significant hypoglycaemia in normal and diabetic rabbits. However, its extracts in water and methanol were ineffective in both types of rabbits. The herbal drug showed a mild laxative effect in the toxicity studies. The oral administration of 1-4g/kg of powdered eugeniajambolana (seeds) ficus glomerata (fruits) and their methanol extracts significantly lowered the blood glucose levels in normal and diabetic rabbits. The aqueous extracts, however, could not produce this effect Grewiaasiatica (green bark) powder in 5- 20g/kg doses significantly lowered the blood glucose level of normal and diabetic rabbits but its extracts in water and methanol were nottested.Momordica charantia (fruits) and mucunapruriens (seeds) in 0.5 and L5g/kg doses produced a dose dependent decrease in blood glucose levels in normal and alloxan diabetic rabbits. The M. charantia powder in 50 mg/kg dose given orally to eight maturity onset (type II) human diabetic patients produced a consistent hypoglycaemic effect (Figures 1-3).

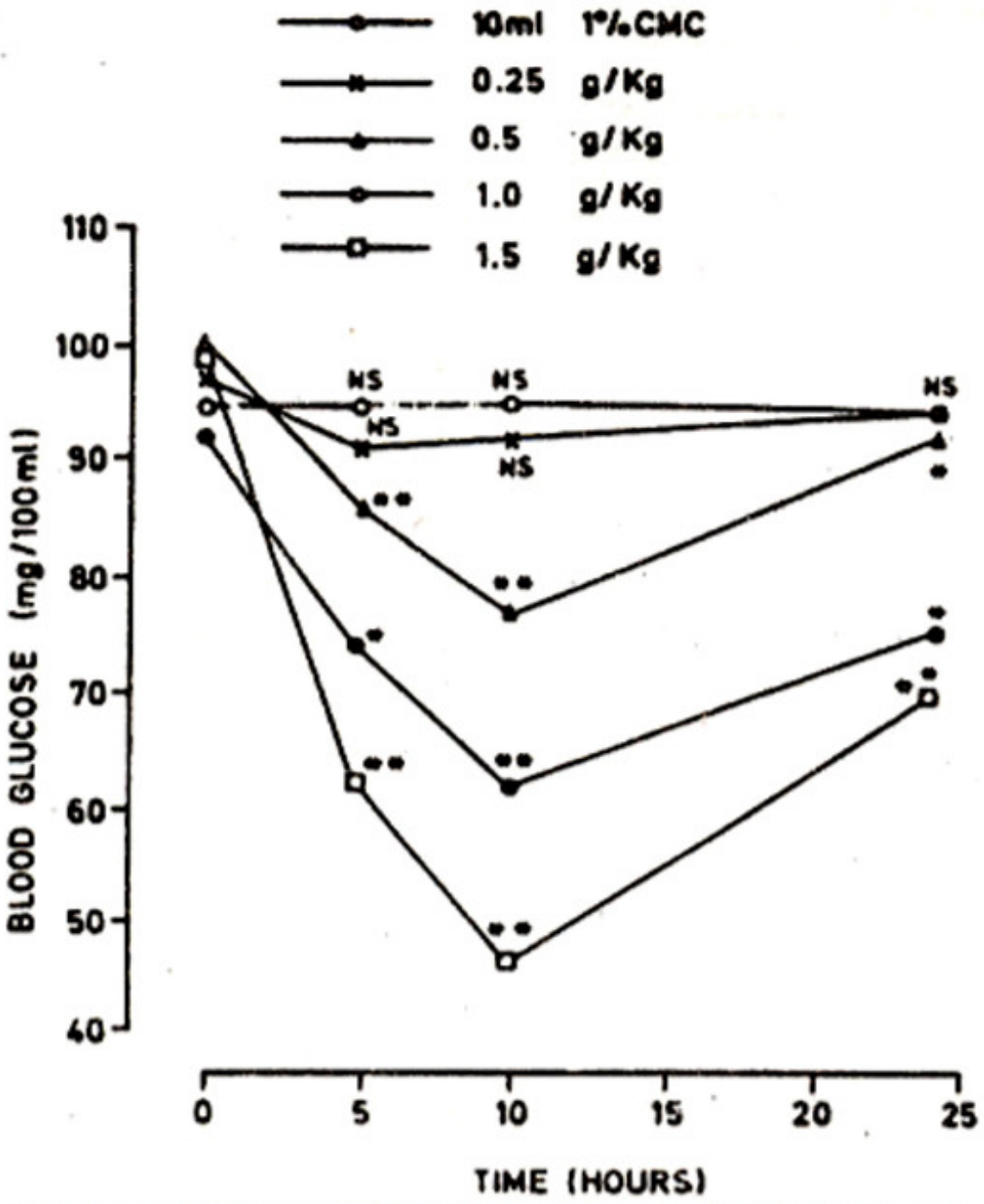

Figure 1. Blood glucose levels of normal rabbits (mg/100) at various time intervals after oral administration of 1% CMC solution and momordica charantia dried fruit powder (0.25, 0.5, 1.0 and 1.5g/kg) body weight orally, suspended in 1% CMC.
NS = Non-significant difference from the zero level ($P > 0.05$).
• = Significant decrease as compared to the zero level ($P < 0.05$).
•• = Highly significant decrease as compared to the zero level ($P < 0.001$).
Number of animals in each group = 6;
CMC = Carboxymethylcellulose.

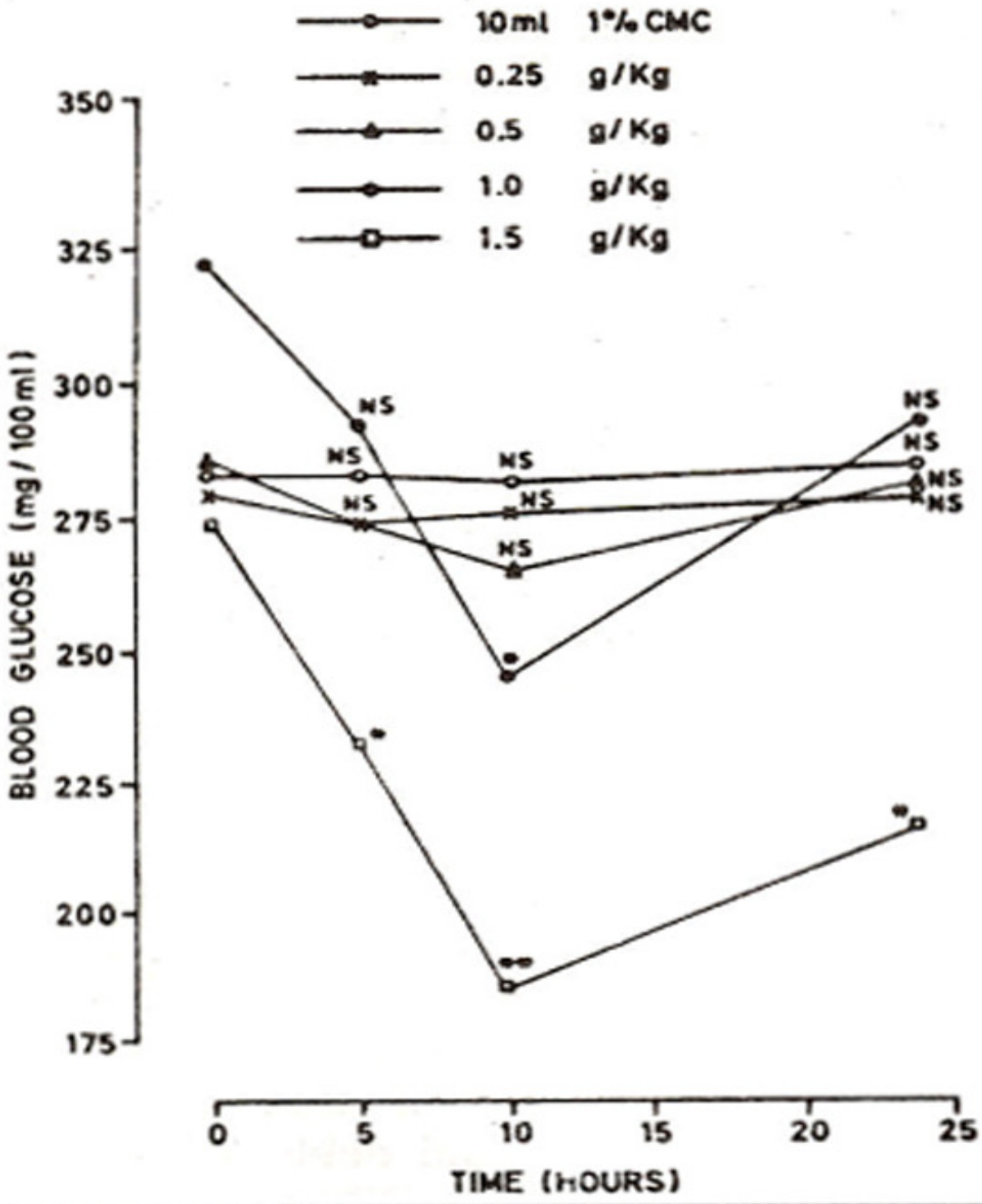

Figure 2. Blood glucose levels of diabetic rabbits (mg/100 ml) at various time intervals after oral administration of 1% CMC solution and Momordica charantia dried fruit powder (0.25, 0.5, 1.0 and 1.5g/kg) body weight orally; suspended in 1% CMC.
NS = Non-significant difference from the zero level ($P > 0.05$).
* = Significant decrease as compared to the zero level ($P < 0.05$).
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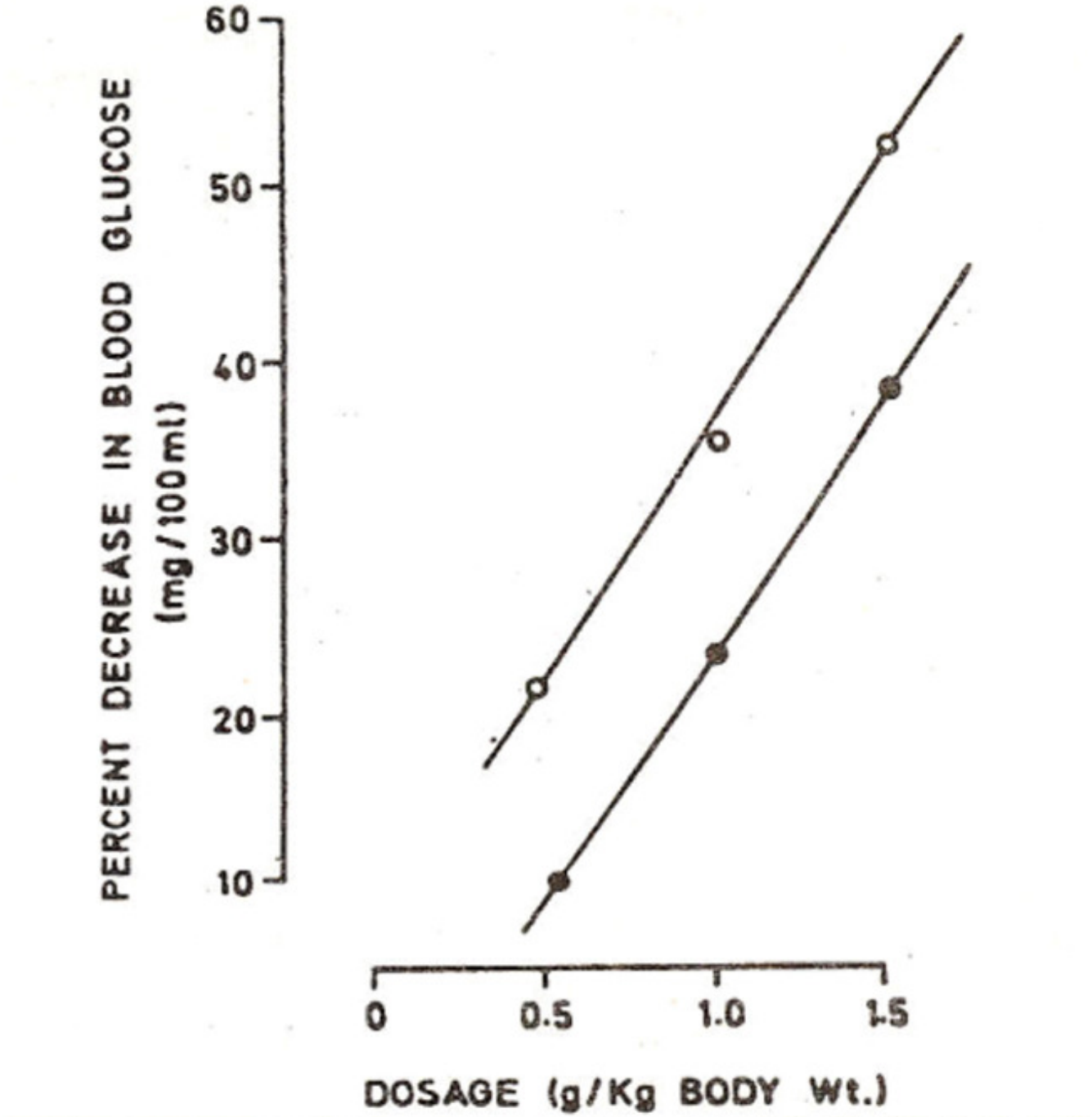

Figure 3. Percent decreases in blood glucose level of normal and diabetic rabbits at 10 hour intervals after treatment with momordica charantia 0.5, 1.0 and 1.5g/kg body weight, orally.

Note: The percent decreases shown in the above figure have been calculated from the data shown in Figure 1 and 2.

O-O, Normal rabbits; 0-0, Alloxan-diabetic rabbits.

3. Plants producing hypogiycaemia action In diabetic rabbits only Gossypium hirsutum (seeds) in 5, 10 and 20g/kg produced significant reduction of blood glucose in the diabetic rabbits only. However, the effect was not noted in the non-diabetic normal rabbits.

4. Plant producing no hypoglycaemia in both normal and diabetic rabbits Caralluma edulis (roots) powder did not produce significant hypoglycaemia in both normal and diabetic rabbits in any of the doses (1-4g/kg) checked. Higher doses, however, could not be tested due to administration difficulty.

Acute toxicity and behavioural pattern studies

The rabbits treated with all the tested plant drugs, even in high doses upto 8g/kg, kept under close observation for 7 days remained alive and did not show any visible symptoms of toxicity of these dosages. Administration of the powders above these doses was not possible as aqueous suspensions of these crude drugs were then too thick to be administered orally by feeding needle. Even at the highest doses tested, the treated animals showed no restlessness, respiratory distress, diarrhoea, convulsions, coma etc.

Elemental constituents

The levels of zinc, calcium, magnesium manganese, iron and phosphorus as determined by atomic absorption spectroscopy are given in Table II.

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*Study carried out in maturity-onset (type II) human diabetes mellitus patients.

It is clear that the levels of these elements in these plants are relatively high as compared to those found in common vegetables, fruits and other plant materials.

DISCUSSION

The data obtained clearly show that significant and consistent reduction in the blood glucose levels of the normoglycaemic and alloxan-diabetic rabbits was produced by the plants including A. asp era, C.fistula, C. nigrum, E. jambolana, F. glornerata, G. asiatica, M. charantia, M. pruriens, 0. echioides and the compound plant prescription as well as their methanolic and/or aqueous extracts (Table I). It has been well established that the sulphonylureas, including acetohexamide or tolbutamide which were used as controls in the present studies, produce hypoglycaemia in normal animals by stimulating the

pancreatic J3-cells to release more insulin[1]. In contrast to the oral hypoglycaemic agents, the exogenous administration of insulin is well known to produce hypoglycaemia in both normal and alloxan diabetic subjects[1]. It is, therefore, conceivable that the hypoglycaemic principle(s) in these antidiabetic plants and in their aqueous and methanol extracts exert not only an indirect insulin releasing effect but also a direct insulin like effect in the normal rabbits. In alloxan-diabetic rabbits, however, these plants exerted a direct insulin-like effect as they cannot act indirectly by initiating the release of insulin since alloxan treatment causes permanent destruction of the /3-cells. Acetohexamide and tolbutamide (500 mg/kg) were ineffective in the alloxan diabetic rabbits. The biguanides produce hypoglycaemia by increasing the glycolysis and uptake of glucose in muscles and by decreasing gluconeogenesis in the liver and absorption of glucose from the intestines. However, the biguanides do not produce hypoglycaemia in normal subjects because increase in peripheral glucose utilization is compensated by an increase in hepatic glucose output[26]. Therefore, it may be postulated that the active principle(s) of the above mentioned plants do not act like biguanides as the blood glucose levels were decreased by these crude drugs in both normal and alloxan-diabetic rabbits. Table I also shows that the plant drug including A. arabica, A racemosus, C. edulis, E. prostrata, F. parviflora, G. sylvescre, L. sachellarum, P. oleracae, P. mars upium, T. officinale and Z. sativa have been found to lower blood glucose levels only in the non-diabetic normoglycaemic rabbits as they have failed to significantly affect the blood glucose levels of the alloxan- diabetic animals (Table I). These plants exert hypoglycaemic effects only in the rabbits with intact pancreatic beta cells bytriggeringinsulin release. The G. birsutum seeds were found to be effective only in the diabetic rabbits. Thus it may be suggested that they possess active principles which might act like biguanides, i.e., by increasing glycolysis and uptake of glucose in muscles and by decreasing gluconeogenesis in liver and absorption of glucose from intestines. The table also shows that C. edulis roots which are popularly used by the diabetics do not seem to possess any hypoglycaemic substance(s). It is just possible that the plant is considered antidiabetic in folklore merely because of the bitter ingredients. However, use of C. edulis as an adjunct therapy to help the diabetic patients in some entirely different way cannot be denied as present. Powdered bark of G. asiatica produced at first a significant increase in blood glucose at 4 hours which was followed by a decrease. The increase could be attributed to its high sugar contents (e.g., maltose, etc.) or alkaloids (e.g., hordenine, etc.). Similar results have already been obtained with this plant and some others like allium cepa, brassica vulgaris,fastida borrida and phaseolus vulgaris as reported by Bever and Zahnd[27]. Table I also tells that the hypoglycaemic effects of most of the plants had begun by + 4 hours and had reached its maximum at +12 hours. By + 24 hours blood glucose levels were back to normal, showing that their onset is not as quick as i.e. with those of suiphonylureas but these plants do possess relatively longer durations of action. The present experiments have also shown that the hypoglycaemic principle(s) of A aspera, C. nigrum and 0. ecbioides plants are extractable in both water and methanol while those of F. pro strata, F. jambolana and F. glomerata are soluble only in methanol while those of G. birsutum are soluble in water only. In Table II, the plants containing high amounts of trace elements have been given. Thus A. aspera, F. prostrata, F. glonierata and F. parviflora plants contain high amounts of minerals, namely manganese, magnesium, zinc, calcium and phosphorus. It has been reported that alloxan causes complexation with biologically significant metals in/3-cells producingtheir deficiency[28]. Since A aspera powder exerted a rapid hypoglycaemic action in normal as well as alloxandiabetic rabbits, it might have acted by providing the cells with appropriate amounts of needed elements. This plant drug may initiate the release of insulin due to its trace mineral content which could deblock the enzymatic processes[28,29]. Virtually the preliminary acute toxicity studies done here revealed no visible signs and symptoms of toxicity and none of the rabbits died after 7 days, even at the highest oral dosage of 8g/kg body weight. It is just possible that these plants prove to be especially valuable antidiabetic agents since, in addition to their non-toxic also insulin-releasing and/or insulin-like activities, they could also compensate for the mineral deficiency that occurs in diabetics

due to osmotic diuresis. Furthermore, comprehensive chemical and pharmacological investigations were needed to elucidate the exact mechanism(s) of the hypoglycaemic effect and to isolate the active principle(s). Hence detailed data on pharmacological activity,mechanism of action, toxicity and other properties of some of the above discussed medicinal plants have even been recently reported on the Spainish by Ivorra and Villar[30]. Generally, it has been demonstrated that there are many hypoglycaemic plants and the chemical structures of their active principles varies widely. Therefore, there must also be considerable diversity in the mechanisms of action. Some act by increasing the release of insulin and require a minimum of B-cells to exert their action. Other plants or their constituents act by modifying glucose metabolism and finally there are some that appear to correct the complications of diabetes. All are important since they potentially can be used to treat the different aspects of diabetes mellitus. Therefore, they are a fertile source for new hypoglycaemic agents. For the study of antidiabetic plants, it has been found that alloxan-induced diabetic rabbits, glucose-induced hyperglycaemic rats and streptozotocin-induced diabetic rats are equally good preliminary models for hypoglycaemic screening. It is important to do a toxicity study because, as is known, hepatotoxic agents can influence the activity of certain hepatic enzymes involved in gluconeogenesis. This can lead to a reduction in the amount of glucose that reaches the blood resulting in false-positive results. As is the case with any ethnopharmacologic study, careful collection of plant material and proper identification/verification is of primary importance. The molecular mechanism of insulin release recently put forward by Ammon and Wahl[31] is shown in the Figure 4.

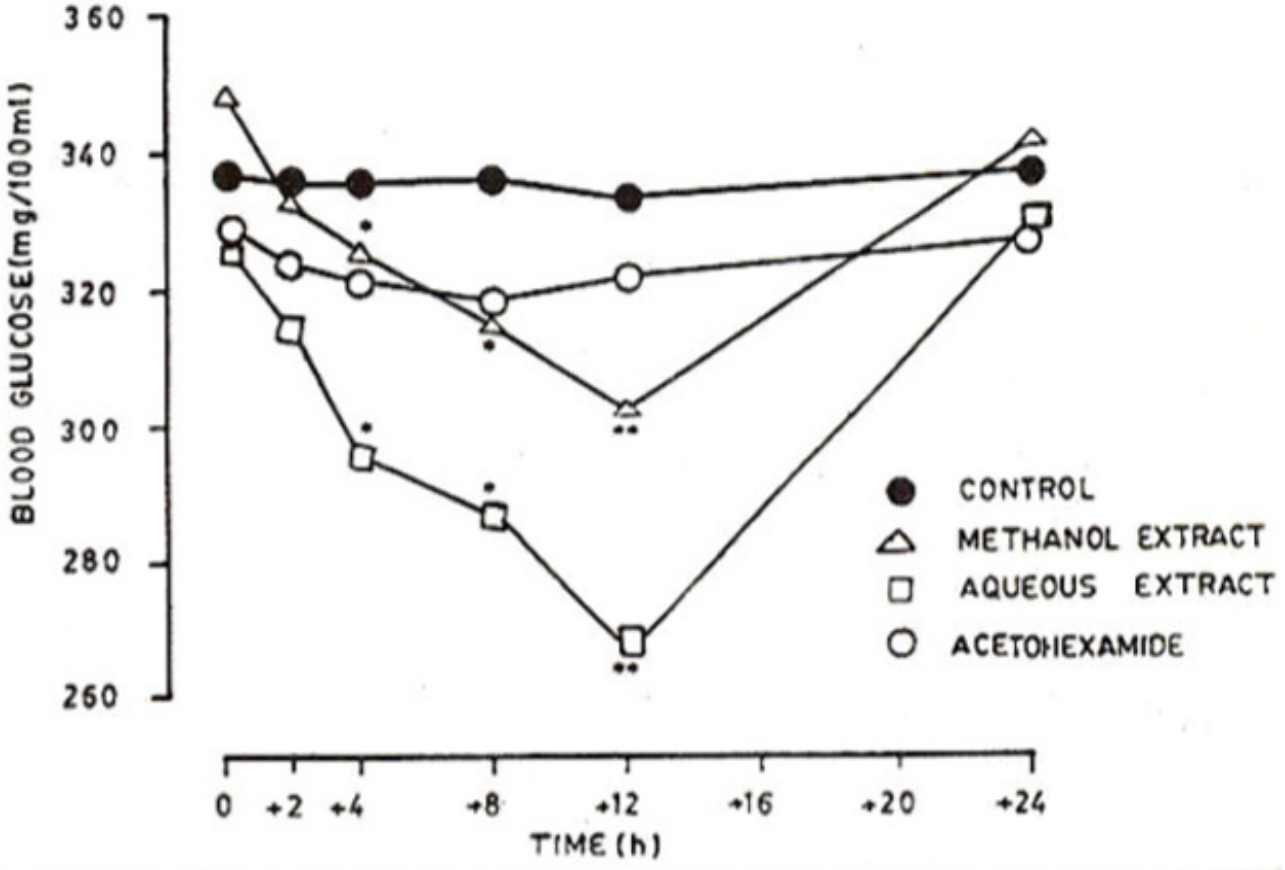

Figure 4. Mean blood glucose levels of alloxan-diabetic rabbits after oral administration of the methanol and aqueous extracts at a dosage equivalent to 4g/kg dose of A. aspera and of acetohexamide at 500 mg/kg. Significant from 0 tine value: *P<0.05, **P<0.001.

It is, therefore, possible that the active principles present in the insulin releasing plants might be acting

by elevating the ATP/ADP, NADPH/NADP, GSH/GSSG ratios in j3-ceits of the islets of langerhans. Incidently, Hii and Howell[32] have shortly reported that the flavones present in the P. marsupium wood (chob bejasar) lowers blood glucose by increasing the glucose mediated uptake of calcium. This step is important in the mechanism of insulin release (Figure 4). In the end it may be further emphasised that the plants usually possess more than one active principles which might even exert opposite actions. Thus due attention should be given to this aspect as well in the screening of medicinal plants for antidiabetic/hypoglycaemic activity. In conclusion, the studies reviewed have encouraged the possible use of these cheap and relatively non-hazardous natural remedies of plant origin for the treatment of diabetes mellitus. However, large scale double blind clinical trials in diabetic human patients are still required to find out their real worth in the cure of diabetes. The isolation of their active principles may help in finding newer model chemical compounds for the treatment of diabetic syndrome. It may be that here lies one of the major contributions that the herbal medicine can make to the advancement of the world health. In the end, it also seems appropriate to mention that laboratory animals including rabbits, rats, etc. have generally much higher basal metabolic rates (BMR). Thus their recommended dosages for almost all drugs per kg body weight appear much higher than those for human patients. In view of our experience with some of the antidiabetic plants and the doses given byAwan[33] for use in the traditional medicine for the treatment of various human diseases since centuries it may be suggested to clinically, try the proven Pakistani hypoglycaemic plants listed in the Table I on the human diabetic patients in the doses suggested in the Table III.

TABLE III. Suggested median effective doses of dried and powdered proven hypoglycaemic plant drugs for trials in human diabetic patients.

S.No.	Botanical name	Common Urdu name	Parts used	Type of diabetes	Suggested daily oral doses* (for adults)
1.	A. arabica	Kikar	Fruits	Type II	2-4 grams b.i.d.
2.	A. aspera	Puthkanda	Aerial parts	Types I and II	2-4g b.i.d.
3.	A. racemosus	Satwar	Roots	Type I	3-12g
4.	C. fistula	Amaltas	Fruits	Type I and II	4-12g b.i.d.
5.	C. nigrum	Kala zera	Seeds	Type I and II	1.5-3g b.i.d.
6.	E. jambolana	Jaman	Seeds	Type I and II	2-3g b.i.d.
7.	E. prostrata	Dhodhi khurd	Whole plants	Type I	1.5-3g b.i.d.
8.	F. glomerata	Gular	Fruits	Type I and II	2.5-3g b.i.d.
9.	F. parviflora	Shahtarah	Whole plant	Type I	2.5-3g b.i.d.
10.	G. hirsutum	Banola	Seeds	Type I and II	10-20g b.i.d.
11.	G. asiatica	Falsa	Green barks	Type I and II	4-8g b.i.d.
12.	G. sylvestre	Gurmar	Aerial parts	Type I	2.5-10g b.i.d.
13.	L. seychellarum	Naryal daryai	Fruits	Type I	0.25-1g b.i.d.
14.	M. charantia	Karela	Fruits	Type I and II	0.5-2g b.i.d.
15.	M. pruriens	Kowanch	Seeds	Type I and II	1.5-3g b.i.d.
16.	O. echioides	Rattan jot	Roots	Type I and II	1.5-3g b.i.d.
17.	P. oleracae	Kulfa	Whole plants	Type I	2-4g b.i.d.
18.	P. marsupium	Chob-bejasar	Stalks	Type I	1-3g b.i.d.
19.	T. officinale	Dhudal	Whole plants	Type I	1-3g b.i.d.
20.	Z. sativa	Unab	Leaves	Type I	1-3g b.i.d.
21.	Compound Prescription: B. ligulata A. longifolia, A. speciosa, C. cassia	Pakhan bed Talmakhana Sumundar sokh Teg	Root barks Seeds Seeds Barks	Type I and II	2-4g b.i.d. 1-3g b.i.d.

*Dose can be doubled and administered once a day only.

Important notes:

1. Powders may be administered after meals.
2. Sulphonylurea tablets or insulin if already in use should not be stopped immediately but should be slowly and gradually withdrawn after checking the blood sugar levels in about 3 days.

However, further clinical work must be carried out to establish the real dosage schedule of these economical and relatively side effects free drugs of indigenous plants origin.

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REFERENCES

1. Larner,J. Insulin and oral hypoglocaemic drugs. Glucogon, in the pharmacological basis of therapeutics. Editors Alfred Goodman et. al 7th ed. New York, Macmillan, 1985, pp.1490-1516.
2. Ammon, H.P.T. Arzneipflanzen mit hypoglykaemischer Wirkung, Zeitschrift fuer Phytotherapie. 1989;10:111-16
3. Nadkarni, A.K. Indian materia medics. 3rd ed. Bombay, Popular Book Depot, 1954, vol.1, p.21.
4. Said, M. Hamdard pharinacopia of eastern medicine. Karachi, Hamdard National Foundation, 1969; p. 407.
5. Satyavati, G.V., Gupta, A. and Tandon, N.T. Medicinal plants of India. New Delhi, Indian Corn. Med.Res., 1987;vol.2, p.875.
6. Riebling. P.W. and Walker, G.C. Extractions and extractives, in Remington's phar. maceutical sciences. Edited by A. Osol and J.E. Hoover. 15th ed. Easton. Pennsylvania, Mack PubL, 1975, pp.1509-10.
7. Fings. CS., Tatliff, C.R. and Dunn, R.T. Glucose determination by O-toluidine method using acetic acid, in practical clinical chemistry. Edited by C. Torn and P.G. Ackerman. Boston, Little Brown, 1970, pp.115-18.
8. Laurence, D.R. and Bacharach, A.L. Evaluation of drug activities; pharmacometrica. NewYork, Academic Press, 1964, vol. 1, p.33.
9. Steel, R..G.D. and Torrie, J.H. Principles and procedures of statistics. New York, McGraw Hill, 1960, pp.37-150.
10. Akbtar, M.S. and Khan, G.M. Studies on the effect of acacia arabica fruits (kikar) and caralluma edulis roots (chung) on blood glucose levels in normal and alloxan-diabetic rabbits. Pak.J. Agri.Sci., 1985;22:252-59.
11. Akbtar, M.S. and Iqbal, J. Evaluation of the hypoglycaemic effect of achyranthea aspera Unn. in normal diabetic rabbits. J. Ethnopharmacol., 1991;31:49-57.
12. Akhtar,.MS., Khan, Q.M. and Khaliq, T. Pharmacological screening of hypoglycaemic activity of asparagus racemosus (roots) and lodoicea sechellarum fruits in rabbits. J.Pharm. (Univ. of Punjab, Lahore), 1987;8:63-70.
13. Akhtar, M.S. and Riffat, S. Effect of cassia fistula Linn, (amaltaa) on blood glucose levels of normal and bypergtycaemic rabbits. Pak.J. Pharmacol., 1987;4:5-13.
14. Akhtar, M.S. and Ali, M.R. Study of hypoglycaemic activity of cuminum nigrum Lànn. seeds in normal and alloxan.diabetic rabbits. Plants Med., 1985;51:81-85.
15. Farooqi, M.M. Effect of eugenia jaunbolana Lam, seeds on blood glucose levels of normal and alloxan diabeticrabbils (dissertation). Faisalabad, UniversityofAgriculture, 1986, p. 69.
16. Akhtar, M.S., Khan, G.M. and Khaliq, T. Effect of prostrata fumaria parviflora in normoglycaaemic and alloxan-treated hyperglycaemic rabbits. Plants Med., 1984;50:138-42.
17. Dogar, l.A. Effectof grewia asiatica (post phalia), gossypium herbacium (cotton seed) and gymnema sylvestre (parpatra) on blood glucose, total cholesterol and triglycerides levelsin normoglycaemic and alloxan diabetic rabbits (thesis). University of Agriculture, Faisalabad, 1987, p. 105.
18. Akhtar, M.S. and Qureshi, A.Q. Phytopharmacological evaluation of ficus glomerulata roxb. fruit for hypoglycaemic activity in normal and diabetic rabbits. Pak.J.Pharm.Sci., 1988;1:87-96.
19. Akhtar, MS. Pharmacological screeningof indigenous medicinal plants forantidiabetic activity. Final

Research report. Faisalabad, Punjab Agricultural Research Coordination Board, Universityof Agriculture, Faisalabad, 1985, p.55.
20. Akhtar, M.S., Akhtar, M.A. and Yaqub, M. Effect of rnomordica charantia on blood glucose level of normal and alloxan.diabetic rabbits. Plants Med., 1981;42:205-9.
21. Akhtar, M.S. Trial of momordica charantia Linn, (karela) powder in patients with maturity-onset diabetics. J.Pak.Med.Assoc., 1982;32.106-7.
22. Akbtar, M.S., Oureshi, AG. and Iqbal, J. Antidiabetic evaluation of mucuna pruriena, Linn. seeds. J.Pak.Med.Assoc., 1990;40:147-49.
23. Akhtar, M.S. and Riffat, S. Hypoglycaemic evaluation of onosma echiodies (rattan jot) roots in normal and alloxan-diabetic rabbits. Ann. Jinnab Postgrad. Med. Centre Karachi, 1986;3:9-18
24. Akhtar, M.S., Kban, M.K. and Khaliq, T. Effects of portulaca oleracae (kulfa) and taraxacum officinale (dudhal) in normogiycaemic and alloxan-treated hyperglycaemic rabbits. J.Pak.Med.Assoc., 1985;35:207-10.
25. Akhtar, M.S. and Ali, M.R. Study of anti-diabetic effect of a compound medicinal plant prescription in normal and diabetic rabbits. J.Pak.Med. Assoc., 1984;34:239-43.
26. Goth,A. Medical pharmacology, 9th ed. Saint Louis, Mosby, 1978, p.471.
27. Sever, B.O. and Zahnd, G.R. Plants with oral hypoglycaemic action. Q.J. Crude Drug Res., 1979;17:139-96.
28. Leopold, LH. Zinc deficiency and visual impairment. Am.J. Opthalmol., 1978;85:871-75.
29. Donsbach, K. Physiological functions of minerals in man in cheluted mineral nutrition in plants animals and man chelated minerals. Edited by D.W. Ashmead. Springfield, Thomas, 1982, pp.247,57.
30. Ivorra, M.D., Pays, M. and Villar, A.A. Review of natural products and plants as potential antidiabetic drugs. J. EthnopharmacoL, 1989;29:240-75.
31. Ammon, H.P.T. and WahI, MA. The impact of thiois for insulin secretion. Exp. Clin. Endocrinol., 1989;43:136-42.
32. Hii, C.S.T. and Howell, S.L. Effects of flavonoids. on insulin secretion and 45 Cahandling in rat islets of langerhans. J.Endocrinol., 1985;107:1-8.
33. Awan, M.H. Kitabul-Mufredat, Lahore, Sheikh Ghulam Ali and Sons, 1981; p.552.