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Hypoglycaemic Effect of *Zizyphus jujuba* Leaves

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Abstract

Zizyphus jujuba leaves have been widely used as a hypoglycaemic agent by diabetics in some regions of Turkey. In this study, the effects of *Z. jujuba* leaves on plasma glucose levels in normo- and hyperglycaemic rats were investigated. In addition, the chronic toxicity of *Z. jujuba* leaves was investigated in normoglycaemic rats.

When 3 and 6% decoctions of *Z. jujuba* leaves were administered to rats, plasma glucose levels decreased significantly ($P < 0.01$). Biochemical and haematological parameters were not different from control groups ($P > 0.05$) and these parameters were within normal limits. No drug-related changes were observed in rats and there were no pathologic changes attributable to the drug in histopathologic examination of all tissues.

Since ancient times, diabetics have been treated orally with several medicinal plants or their extracts based on folk medicine (Akhtar & Ali 1984). The pathogenesis of diabetes mellitus and the possibility of its management by the oral administration of hypoglycaemic agents have stimulated great interest in recent years (Al-Awaidi et al 1985).

Zizyphus jujuba leaves have been widely used as a hypoglycaemic agent by diabetics in some regions of Turkey (Koker et al 1993). These leaves are collected after they begin to turn yellow in September, and dried. Two handfuls of leaves are boiled in 500 mL water for 30 min, and 100 mL of this decoction is drunk (a tea cup) 30 min, before each meal. This decoction has been used by type II diabetics.

In the present study, the effects of *Z. jujuba* leaves on plasma glucose levels in normo- and hyperglycaemic rats were investigated. The chronic toxicity of *Z. jujuba* was also evaluated in normoglycaemic rats.

Materials and Methods

The leaves used in this study were collected in September 1992 after they began to turn yellow, and were dried at room temperature. Leaves were identified as *Z. jujuba* by Prof. Dr. Mekin Tanker in Ankara University, Faculty of Pharmacy, Department of Pharmacognosy (Herbarium voucher number: AEF 3565).

Decoctions (3 and 6%) were prepared with dried leaves as follows: 12 and 24 g leaves were boiled in 600 mL tap water for 30 min until the residual liquid volume was 400 mL. Decoctions were prepared according to the traditional method. These decoctions were freely available to rats during experiments, in place of normally available tap water.

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Swiss albino, adult rats, 300–400 g, of either sex were used in the present study. Food and water or decoction were freely available. The animals were observed daily for signs of toxicity and behavioural changes.

Normoglycaemic rats

Thirty rats were divided into three equal groups (control, 3 and 6% decoction). Control animals received tap water, others the decoction. Animals were observed over three months. Rats were fasted for 18 h at the end of the study, then blood samples were obtained by decapitation and plasma was separated. Plasma was assayed for glucose, alkaline phosphatase, bilirubin, AST (aspartate aminotransferase), ALT (alanine aminotransferase), cholesterol, urea-N, creatinine, total protein, albumin, Na^+, K^+ and Cl^- using an AutoAnalyser.

Heart, lungs, liver, kidneys, brain and pancreas were preserved in 10% formalin and histopathologic examination was performed.

Hyperglycaemic rats

Thirty rats were divided into three equal groups (control, 3 and 6% decoction). They were made diabetic by a single intravenous injection of 50 mg kg^{-1} alloxan monohydrate (Merck). Seven days after administration, the hyperglycaemic animals were fasted for 18 h and initial plasma glucose levels (day 0) determined (Chucla et al 1988). Animals were then used in the decoction experiments as described above, except that glucose levels were re-determined at 2, 4, 6, 8 and 10 days following an 18-h fasting period. Blood for the glucose assay was obtained by snipping the tail with a sharp razor.

Statistics

Statistical comparisons were made according to a *t*-test for unpaired observations and expressed as ± s.e.m. $P < 0.05$ was considered to be statistically significant.

Table 1. Biochemical parameters of rats and effects of *Z. jujuba* leaves decoction on plasma glucose levels in normoglycaemic rats.

	Control	Decoction 3%	Decoction 6%
Glucose (mg dL^{-1})	161·81 ± 1·25	138·9 ± 12·99*	127·9 ± 10·82*
Urea-N (mg dL^{-1})	27·06 ± 7·19	24·56 ± 6·36	23·18 ± 6·28
Cholesterol (mg dL^{-1})	73·21 ± 3·64	85·83 ± 36·62	78·09 ± 15·34
Creatinine (mg dL^{-1})	0·42 ± 0·13	0·56 ± 0·25	0·52 ± 0·16
Uric acid (mg dL^{-1})	1·12 ± 1·08	1·82 ± 1·14	1·42 ± 1·11
Na^+ (mM)	136·2 ± 7·21	132·0 ± 14·07	142·3 ± 6·61
K^+ (mM)	5·6 ± 1·12	5·05 ± 1·04	5·83 ± 0·54
Cl^- (mM)	102·53 ± 7·46	104·0 ± 4·6	105·16 ± 4·84
Bilirubin (mg dL^{-1})	0·75 ± 0·08	0·73 ± 0·05	0·75 ± 0·06
AST (units L^{-1})	124·0 ± 40·89	131·36 ± 49·14	157·08 ± 68·26
ALT (units L^{-1})	51·06 ± 19·99	54·6 ± 11·99	52·5 ± 26·2
Alkaline phosphatase (units L^{-1})	135·73 ± 132·61	144·68 ± 59·6	124·87 ± 48·21
Total protein (g dL^{-1})	5·81 ± 0·84	5·9 ± 0·93	5·96 ± 0·91
Albumin (g dL^{-1})	1·88 ± 0·5	2·04 ± 0·38	1·66 ± 0·43

Values are mean ± s.e.m. n = 10 for each group. *$P < 0.01$ compared with control.

Results

Normoglycaemic rats

Glucose levels were significantly lower in animals receiving 3 and 6% *Z. jujuba* decoctions (Table 1).

Biochemical and haematological parameters (Tables 1, 2) were not different from controls in the experimental groups and all parameters were within normal limits (Schalm 1971; Canadian Council and Animal Care 1984). No drug-related changes were observed in rats. There were no pathologic changes attributable to the drug on histopathologic examination of the tissues.

Hyperglycaemic rats

Glucose levels were significantly lower in animals receiving 3 and 6% *Z. jujuba* decoctions in the alloxan-induced hyperglycaemic animals (Table 3).

Discussion

Although insulin has become one of the most important therapeutic agents known to medicine, efforts continue to find insulin substituted from synthetic or plant sources for the treatment of diabetes (Choi et al 1991). Over 150 plant extracts and some of their active principles including flavonoids are known to be used for the treatment of diabetes (Meiselman et al 1976; Choi et al 1991), but information on insulin substitutes from plant sources is still sparse.

We report for the first time a hypoglycaemic effect of *Z. jujuba*, without any apparent toxic properties on chronic administration. Several reports on *Z. jujuba* relate to tests on their effect on the perception of sweetness (Meiselman et al 1976; Smith & Halpern 1983; Yamada & Imoto 1987). According to these studies, *Z. jujuba* selectively suppressed

Table 2. Haematological parameters of rats.

	Control	Decoction 3%	Decoction 6%
Haemoglobin (g/100 mL)	14·75 ± 1·40	14·05 ± 1·92	13·80 ± 1·84
WBC (10^2 μL^{-1})	96·20 ± 38·53	10·180 ± 42·91	90·80 ± 42·10
RBC (10^6 μL^{-1})	6·16 ± 1·09	5·49 ± 1·67	5·47 ± 1·10
Haematocrit (vol %)	45·4 ± 6·00	46·7 ± 6·11	43·7 ± 4·13

Values are mean ± s.e.m. n = 10 for each group. WBC = white blood cells. RBC = red blood cells.

Table 3. Effect of *Z. jujuba* leaves decoction on plasma glucose levels in hyperglycaemic rats.

Day of treatment	Blood glucose (mg dL^{-1})		
	Control	Decoction 3%	Decoction 6%
0	321·3 ± 10·12	324·4 ± 9·8	310·8 ± 14·8
2	328·5 ± 11·9	228·1 ± 11·2*	210·7 ± 13·7*
4	338·5 ± 12·5	217·8 ± 10·5*	200·4 ± 12·0*
6	346·4 ± 14·9	236·4 ± 13·7*	192·3 ± 9·1*
8	351·6 ± 12·7	219·6 ± 13·1*	202·0 ± 8·9*
10	364·4 ± 15·1	203·2 ± 14·5*	188·4 ± 12·1*

Values are mean ± s.e.m. n = 10 for each group. *$P < 0.01$ compared with control.

sweetness perception in man. The taste-modifying ability of extracts from the leaves of *Z. jujuba* was first reported by Giordano & Kohlberg (as cited by Meiselman et al (1976)). Meiselman et al (1976) showed that *Z. jujuba* leaves reduced perceived sweetness of sucrose but did not produce any change in the other taste parameters (sourness, bitterness or saltiness). On the other hand, *Z. jujuba* leaves have been used to decrease the intake of sweets in Iran (as cited by Meiselman et al (1976)). The relevance of taste modification to the hypoglycaemic effect is an interesting topic and needs further investigation.

References

Akhtar, M. S., Ali, M. R. (1984) Study of antidiabetic effect of a compound medicinal plant prescription in normal and diabetic rabbits. J. Pakistan Med. Assoc. 34: 239–244

Al-Awaidi, F. M., Khattar, M. A., Gumaa, K. A. (1985) On the mechanism of the hypoglycaemic effect of a plant extract. Diabetologia 28: 432–434

Canadian Council and Animal Care (1984) Guide to the Care and Use of Experimental Animals. 2 vols CCAC, Ottawa, Ontario

Chucla, M. T., Lamela, M., Gato, A., Cadavid, I. (1988) *Centaurea corbionesis*: a study of its hypoglycemic activity in rats. Planta Med. 54: 107–109

Choi, J. S., Yokozawa, T., Oura, H. (1991) Improvement of hyperglycemia and hyperlipemia in streptozotocin-diabetic rats by a methanolic extract of *Prunus davidana* stems and its main component, prunin. Planta Med. 57: 208–211

Koker, A. H., Kelestimur, F., Erenmemisoglu, A., Ustun, H., Tekol, Y., Ustdal, M. (1993) Hunnap yapraginin hipoglisemik ve kronik toksik etkilernin arastirilmasi. XI Gevher Nesibe Tip Gunleri 19–22 April 1993, Kayseri, Turkey (abstract book p. 35)

Meiselman, H. L., Halpern, B. P., Dateo, G. P. (1976) Reduction of sweetness judgements by extracts from the leaves of *Z. jujuba*. Physiol. Behav. 17: 313–317

Schalm, O. W. (1971) Veterinary Hematology. Lea & Febiger, Philadelphia, p. 307

Smith, V. V., Halpern, B. P. (1983) Selective suppression of judged sweetness by ziziphins. Physiol. Behav. 30: 867–874

Yamada, H., Imoto, T. (1987) Inhibitory effect of the extract from *Z. jujuba* leaves on sweet taste responses of the chorda tympani in the rat and hamster. Comp. Biochem. Physiol. 88A: 355–360