



Antidiabetic Potential Of *Momordica Balsamina* L. Fruit Pulp And Its Extracts In Streptozotocin Induced Diabetic Wistar Rats

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Momordica balsamina L. fruit pulp and its extracts were evaluated for antidiabetic potential. The study was carried out on whole fruit pulp powder (FPP), aqueous methanolic extract 90% (AME) and aqueous extract for 3 weeks on streptozotocin (STZ) induced diabetic Wistar rats. The biochemical parameters studied were serum glucose level, lipid profile and liver glycogen content along with this body weight was also measured. The ME showed significant ($P < 0.05$) serum glucose lowering effect, improvement in the complete lipid profile and check on the loss of body weight in comparison to control diabetic rats. The results were comparable with glibenclamide (GLB) 500 $\mu\text{g}/\text{kg}$, standard antidiabetic drug. Phytochemical screening of the AME revealed the presence of alkaloids, flavonoids and steroids. Our findings suggest, the FPP and AME have significant ($P < 0.05$) antidiabetic potential and can act as an effective oral hypoglycemic drug in diabetes.

Key words: Cucurbitaceae; Diabetes; Momordicin; Streptozotocin, Glibenclamide

Introduction

Diabetes mellitus is a heterogeneous primary disorder of carbohydrates metabolism with multiple etiologic factors, generally involves absolute or relative insulin deficiency or insulin resistance or both, results in hyperglycemia. The characteristic symptoms of diabetes are polyuria, polydipsia, polyphagia, pruritis and unexpected weight loss, etc. along with hyperglycemia and abnormalities in serum lipids (1-4). Diabetes is associated with microvascular and macrovascular complications which are major causes of morbidity and death in diabetic subjects (5,6). There is an increasing demand by diabetic patients to use natural products for the management of diabetes, due to the side effects associated with the use of synthetic oral hypoglycemic agents. There are large number of plants used in the treatment of diabetes e.g. *Momordica charantia*, *Eugenia jambolana*, *Cuminum cyminum*, *Salvadora persica*, *Catharanthus roseus*, *Azadirachta indica*, *Allium cepa*, *Allium sativum*, *Gymnema sylvestre* etc. (7-12).

Momordica balsamina L. (Family: Cucurbitaceae) commonly known as Jungle karela is a monoecious climber found in the Punjab, western Uttar Pradesh, Rajasthan and Saurashtra. Various parts of the plant have been reported to possess antimicrobial, hypoglycemic (13) anti-diarrhoeal (14) anti-HIV and immunostimulatory properties (15, 16).

In many African countries the fruit is taken as a purgative and vermifuge. The fruit is used as a vegetable and is also used prophylactically in diabetes but no systematic scientific antihyperglycemic study has been reported till date on these fruits.

The present study was designed to investigate the ethno pharmacological claim of its antihyperglycemic activity in experimental diabetes in rats.

Materials And Methods

Plant material

M. balsamina fruits were procured from the local market, Moga and were authenticated by Dr. H.B. Singh, Director, Department of Raw Material Herbarium & Museum, National Institute of Science communication and Information Resources (NISCAIR), New Delhi, India with reference no.(NISCAIR/ RHM 1062/93). The fruit pulp was separated, shade dried, and this fruit pulp powder (FPP) was used for the present study.

2.2 Extraction

One hundred g FPP was defatted with petroleum ether (60°-80°C) followed by extraction with aqueous-methanol (90% methanol) using Soxhlet apparatus. The aqueous methanol extract (AME) was concentrated under vacuum evaporator (Roteva). Dried marc was re-extracted three times with distilled water at room temperature for 24 h and prepared aqueous extract (AE) was dried by rotary evaporator. Both the extracts were kept in desiccator till further use.

2.3 Phytochemical Screening

These two extracts were tested for the presence of alkaloids, steroids, carbohydrates, tannins, phenolic compounds, flavonoids, triterpenoids, proteins and saponins, using standard procedures (17).

2.4 Animals

Wistar rats (either sex) weighing 180-220 g were procured from the animal house of I.S.F. College of Pharmacy, Moga (Reg. No.816/04/c/CPCSEA). The animals were kept in polypropylene cages (3 in each cage) at an ambient temperature of 25±2°C and 55-65% relative humidity. A 12 h light/dark cycle each was maintained in the animal house. The rats had free access to water and were fed with commercially available feed. The animal study was carried out as per the guidelines of animal ethical committee.

2.5 Chemicals/Instruments

STZ was procured from Sigma Chemical Co. (St Louis, MO, USA) and glibenclamide (GLB) from Torrent Pharmaceuticals, Ahmedabad, India. The kit for glucose estimation was purchased from Beacon Diagnostics Pvt. Ltd, Navsari, India and for total cholesterol, triglycerides, HDL-C kits were obtained from Carol Company, Goa, India. Animal feed was purchased from Ashirwad Industries, Ropar, India. All other chemicals and reagents were of the highest commercial grade available. Cooling Centrifuge (REMI), Rotary evaporator (Roteva), and UV/Visible Spectrophotometer (UV 1700, Pharmaspec, Shimadzu) were used during study.

2.6 Preparation of test drug material

Finally FPP, AME and AE were suspended in 1% w/v carboxymethylcellulose (CMC) to yield a concentration of 50 mg/ml suspension of these test samples.

2.7 Preparation of standard drug material

The GLB was dissolved in distilled water to obtain a solution of concentration of 1 mg/ml.

2.8 Induction of experimental diabetes

Rats were fasted for 16 h prior to the induction of diabetes by injecting a single dose of 50 mg STZ/kg, *i.p.*, for this STZ solution was freshly prepared by dissolving in cold sodium citrate buffer (pH 4.3). Animals were allowed to free access of 5% glucose solution overnight to overcome the drug-induced hypoglycemia. Hyperglycemia was confirmed one week after induction *via* serum glucose level measurements after 16 h fasting. Animals with a fasting serum glucose level 200-300 mg/dl were considered as a diabetic for the present study (18).

2.9 Drug administration in STZ model

In normal fasting serum glucose model, FPP at two doses (250 and 500 mg/kg) and AME (500 mg/kg) were administered orally with the help of gastric canula. Blood samples were collected at 0, 1 and 2 h after the administration of drug.

In OGTT model, glucose load (1.5 g/kg, *p.o.*) was given 1 h after the pretreatment of animals with test drugs, FPP at two doses (250 and 500 mg/kg, *p.o.*), extract at two doses (250 and 500 mg/kg, *p.o.*), the aqueous extract (500 mg/kg, *p.o.*) and glibenclamide (0.5 mg/kg, *p.o.*). Blood collection was done at 0, 1 and

2 h after the glucose administration. OGTT was carried out to find effective dose of *M. balsamina* extract for further STZ-induced diabetes model.

In STZ-induced diabetic model, the methanol extract (500 mg/kg, p.o.) and glibenclamide (0.5 mg/kg, p.o.) were administered orally with the help of gastric canula at 24 h intervals during the entire period of the experiment. Blood collection was done on the 0, 7th, 14th and 21st days.

2.10 Blood Collection

Blood samples were withdrawn by retro-orbital plexus under mild anesthesia. Blood was allowed to clot and centrifuged at 3000 rpm for 15 min to get clear serum. The serum was analyzed for serum glucose level and lipid profile estimation (19).

2.11 Collection of tissue

Animals were sacrificed by an overdose of anesthetic ether at the end of experimental protocol. The liver was immediately excised and transferred into ice cold 0.9% sodium chloride solution. The tissue was stored at -20°C for further study (20).

2.12 Grouping of Animals

A. Normal Fasting Blood Glucose model (21): The rats were divided into five groups with six animals in each group.

Group 1: Normal Control: Rats received 1% w/v CMC p.o.

Group 2: Test IA (FPP 250 mg/kg): Rats received fruit pulp powder 250 mg/kg, p.o.

Group 3: Test IIA (FPP 500 mg/kg): Rats received fruit pulp powder 500 mg/kg, p.o.

Group 4: Test IIIA (ME 500 mg/kg): Rats received methanol extract 500 mg/kg, p.o.

Group 5: Test IVA (AE 500 mg/kg): Rats received aqueous extract 500 mg/kg, p.o.

B. Oral glucose tolerance test (OGTT) (22): The rats were divided into seven groups with six animals in each group.

Group 1: Normal Control: Rats received 1% w/v CMC p.o.

Group 2: Test IB (FPP 250 mg/kg): Rats received fruit pulp powder 250 mg/kg, p.o.

Group 3: Test IIB (FPP 500 mg/kg): Rats received fruit pulp powder 500 mg/kg, p.o.

Group 4: Test IIIB (ME 250 mg/kg): Rats received methanol extract 250 mg/kg, p.o.

Group 5: Test IVB (ME 500 mg/kg): Rats received methanol extract 500 mg/kg, p.o.

Group 6: Test VB (AE 500 mg/kg): Rats received aqueous extract 500 mg/kg, p.o.

Group 7: Test VIB (GLB 500 mg/kg): Rats received glibenclamide 500 mg/kg, p.o.

C. STZ-induced diabetic model

Group 1: Normal Control: Rats received 1% w/v CMC, p.o.

Group 2: Diabetic Control: STZ-induced diabetic rats received only 1% w/v CMC p.o.

Group 3: Test I (ME 500 mg/kg): Diabetic rats treated with methanol extract of the fruit pulp in the dose of 500 mg/kg, p.o. at 24 h intervals during the entire period of the experiment.

Group 4: Test IIC (GLB 500 mg/kg): Diabetic rats treated with glibenclamide in the dose of 500 mg/kg, p.o. at 24 h intervals during the entire period of the experiment.

2.13 Biochemical studies

Fasting serum glucose level, lipid profile and liver glycogen were evaluated. Serum glucose was determined according to the GOD/POD methods (21). Serum lipid profiles including total cholesterol (CHOD/PAP method), triglycerides (GPO/PAP method), HDL-C (PEG Precipitation method), LDL-C (Freidwald's Formula), and VLDL-C was determined (23-25). Liver glycogen level was measured according to standard procedure (26).

2.14 Body weight

Animals were weighed on 0, 7th, 14th and 21st days to detect any changes in their body weights (27).

2.15 Calculations

Percent variation in serum glucose was calculated for each group in OGTT and STZ-induced diabetes models using following formula:

Where G_i and G_t are the values of initial glucose concentration (60 min in OGTT and 0 day in STZ-induced diabetes model) and glucose concentration at different interval (0 min in OGTT and 7th, 14th and 21st day in STZ-induced diabetes model) respectively (28).

2.16 Statistical analysis

All results were expressed as means \pm S.D and one way ANOVA was used to evaluate differences between the groups. The differences among the means were analyzed by Tukey's multiple comparison test using computerized program at 95% ($P < 0.05$) confidence level (20).

RESULTS

Phytochemical screening

The yields of the methanol (90%) and the aqueous extracts were 15.8% w/w and 7.90% w/w. Phytochemical investigations revealed the presence of carbohydrates, proteins, steroids, saponins, alkaloids, phenolic compounds and flavonoids.

Normal fasting blood glucose

Momordica balsamina fruit pulp powder (250 and 500 mg/kg), the methanol extract (500 mg/kg) and the aqueous extract (500 mg/kg) showed no significant effect on serum glucose level in normal rats (table 1).

Table 1: Effect of FPP, AE and AME on fasting serum glucose level of normal rats

Groups	Serum glucose levels (mg/dl)		
	0 min	60 min	120 min
Normal Control	86.34 \pm 2.10	85.68 \pm 2.09	83.32 \pm 2.10
Test IA (FPP 250 mg/kg)	89.66 \pm 2.85	88.27 \pm 2.74	86.41 \pm 2.44
Test IIA (FPP 500 mg/kg)	92.84 \pm 2.64	91.65 \pm 2.51	89.80 \pm 2.84
Test IIIA (AME 500 mg/kg)	91.70 \pm 1.59	90.88 \pm 1.84	90.10 \pm 2.05
Test IVA (AE 500 mg/kg)	86.24 \pm 4.07	84.71 \pm 2.14	81.98 \pm 3.46

All values represent mean \pm S.D. (n=6)

3.3 Oral glucose tolerance test (OGTT)

Animals of vehicle control group showed 43.45% and GLB pretreated group showed 5.62% increase in serum glucose level 1 h after glucose administration in comparison to the 0 h serum glucose level (table 2).

Table 2: Effect of FPP, AME and AE on serum glucose levels on glucose loaded normal rats

Groups	Serum glucose level (mg/dl)		
	0 min	60 min	120 min
Normal Control	90.64 \pm 3.24	129.98 \pm 2.41 ^a (\uparrow 43.40%)	94.46 \pm 4.12
Test IB (FPP 250 mg/kg)	97.60 \pm 2.47	135.20 \pm 4.04 ^a (\uparrow 38.52%)	102.09 \pm 4.17
Test IIB (FPP 500 mg/kg)	94.18 \pm 2.16	113.77 \pm 2.51 ^a (\uparrow 20.80%)	94.11 \pm 3.17

Test IIIB (AME 250 mg/kg)	93.06±3.15	117.20±4.22 ^a (↑29.60%)	98.71±3.39
Test IVB (AME 500 mg/kg)	91.43±4.21	106.48±3.84 ^a (↑13.41%)	99.83±3.40
Test VB (AE 500 mg/kg)	95.45±3.11	113.45±4.90 ^a (↑18.62%)	97.65±3.59
Test VIB (GLB 500 mg/kg)	95.53±3.51	100.90±3.90 ^a (↑5.62%)	92.16±3.53

All values represent mean ±S.D. (n=6)

a = $P < 0.05$ vs normal

The group of animals pretreated with the fruit pulp powder (250 and 500 mg/kg) showed 38.52% and 20.79% increase respectively. Similarly, the methanol extract at dose levels of 250 and 500 mg/kg pretreated group of rats showed 25.94% and 16.46% increase respectively. The aqueous extract (500 mg/kg) pretreated group showed 18.85% increase in serum glucose level 1 h after of glucose administration in comparison to 0 h serum glucose level. However control, glibenclamide and test drug pretreated groups of animals normalize the serum glucose level within 2 h.

3.4 STZ-induced diabetic model

Table 3 shows the effects of 3 weeks treatment of the methanol extract of the fruit pulp (500 mg/kg) and of glibenclamide (0.5 mg/kg) on serum glucose level in diabetic rats.

Table 3: Effect of AME treated rats at the dose of 500 mg/kg on serum glucose in STZ induced diabetic rats

Groups	0 day	7 day	14 day	21 day
Normal Control	93.90±4.70	94.70±3.34	94.78±3.80	94.11±3.72
Diabetic Control	268.18±9.91 ^a	271.83±10.86 ^a	275.05±10.29 ^a	280.59±12.75 ^a
Test IIC (GLB 500 mg/kg)	259.01±9.14	188.16±11.50 ^b (↓ 37.65%)	146.96±8.01 ^b (↓ 72.35%)	119.61±4.02 ^b (↓ 116.50%)
Test IC (AME 500 mg/kg)	242.93±10.51	208.33±10.84 ^b (↓ 16.60%)	140.95±8.01 ^b (↓ 72.35%)	110.28±8.49 ^b (↓ 120.28%)

All values represent mean ±S.D. (n=6)

a = $P < 0.05$ vs normal group; b = $P < 0.05$ vs diabetic control group

Diabetic control rats not given any drug treatment showed no significant change in the serum glucose level as compared to the 0 day. The diabetic rats treated with the methanol extract (500 mg/kg) showed significant ($P < 0.05$) reduction in fasting serum glucose level as compared to 0 day after 7th, 14th and 21st day treatment. The fall in serum glucose level was gradual and consistent by 37.65%, 76.24% and 116.50% respectively after 7th, 14th and 21st day treatment. Diabetic rats treated with 0.5 mg/kg of GLB showed consistent fall in serum glucose by 16.60%, 72.35% and 120.28% respectively after 7th, 14th and 21st day treatment.

Table 4 shows the average weekly body weights of both the control and treated groups. Reduction in body weight was 20.41%, 49.56% and 82.47% by the 7th, 14th and 21st day respectively. However, animals treated with GLB (0.5 mg/kg) registered a less gradual decrease in body weights till the end of the third week. The

observed decrease was 1.70%, 2.90% and 3.80% by the 7th, 14th and 21st day respectively. The methanol (90%) extract treated group also registered significant ($P < 0.05$) check on the loss in body weight as compared to diabetic control group and the reduction by the 7th, 14th and 21st day was 1.53%, 4.48% and 5.56% respectively.

Table 4: Effect of the methanol extract treated rats at the dose of 500 mg/kg on body weight in STZ induced diabetic rats

Groups	0 day	7 day	14 day	21 day
Normal Control	188.35±7.94	185.18±7.17	185.83±7.95	187.28±8.54
Diabetic Control	189.90±8.24	157.75±5.49 ^a (↓ 20.38%)	126.97±4.99 ^a (↓ 49.56%)	104.07±4.39 ^a (↓ 82.47%)
Test IIC (GLB 500 mg/kg)	179.73±7.68	176.71±6.77 ^b (↓ 1.70%)	174.60±6.40 ^b (↓ 2.90%)	173.10±5.71 ^b (↓ 3.80%)
Test IC (AME 500 mg/kg)	189.33±9.14	186.47±11.5 ^b (↓ 1.53%)	181.20±12.79 ^b (↓ 4.48%)	179.35±4.02 ^b (↓ 5.56%)

All values represent means ±S.D. of the mean (n=6)

a = $P < 0.05$ vs normal group; b = $P < 0.05$ vs diabetic control group.

Table 5 shows the effect of the 21 days treatment of diabetic rats with methanol extract of the leaves at 500 mg/kg and of glibenclamide at 0.5 mg/kg on serum cholesterol, triglycerides, HDL, VLDL, LDL levels and tissue glycogen level.

Table 5: Effect of 21 days treatment of *Momordica balsamina* AME (500 mg/kg) on lipid profile and tissue glycogen content on STZ induced diabetic rats

Groups	Total Cholesterol level (mg/dl)	Triglycerides level (mg/dl)	HDL-C level (mg/dl)	LDL-C level (mg/dl)	VLDL-C level (mg/dl)	Tissue glycogen level (mg/g of tissue)
Normal Control	93.64±3.99	66.28±2.54	34.35±3.33	46.03±3.90	13.26±0.51	9.92±0.98
Diabetic Control	236.67±10.99 ^a	149.27±5.40 ^a	25.96±3.06 ^a	180.80±11.63 ^a	29.86±1.07 ^a	2.93±0.79 ^a
Test IC (AME 400 mg/kg)	159.28±5.84 ^b	122.55±2.51 ^b	30.36±1.98 ^b	114.70±4.07 ^b	25.61±0.92 ^b	5.89±1.03 ^b
Test IIC (GLB 500 mg/kg)	112.98±4.50 ^b	94.21±4.89 ^b	32.37±1.69 ^b	61.77±5.07 ^b	18.84±0.98 ^b	8.05±0.29 ^b

All values represent mean ±S.D. (n=6)

a = $P < 0.05$ vs normal group; b = $P < 0.05$ vs diabetic control group

Animals of the STZ-induced diabetic control group showed a significant ($P < 0.05$) rise in serum total cholesterol (236.67 ± 10.99 mg/dl), triglycerides (149.27 ± 5.40 mg/dl), LDL-C (180.80 ± 11.63 mg/dl) and VLDL-C (29.86 ± 1.07 mg/dl) levels (table 5) and significant ($P < 0.05$) reduction in serum HDL-C (25.96 ± 3.06 mg/dl) and liver glycogen (2.93 ± 0.79 mg/g) level in comparison to normal group.

After 21 days treatment, the methanol extract (500 mg/kg) treated group showed significant ($P < 0.05$) reduction in serum total cholesterol (158.28 ± 5.84 mg/dl), triglycerides (122.55 ± 2.51 mg/dl), LDL-C (114.70 ± 4.07 mg/dl) and VLDL-C (25.61 ± 1.07 mg/dl) levels and significantly ($P < 0.05$) elevated serum HDL-C (30.36 ± 1.98 mg/dl) and liver glycogen (5.89 ± 1.03 mg/g) levels. GLB (0.5 mg/kg) treated group showed significant ($P < 0.05$) reduction in total serum cholesterol (112.98 ± 4.50 mg/dl), triglycerides (94.21 ± 4.89 mg/dl), LDL-C (61.77 ± 5.07 mg/dl) and VLDL-C (18.84 ± 0.98 mg/dl) levels and elevated serum HDL-C (32.37 ± 1.69 mg/dl) and liver glycogen (8.05 ± 0.29 mg/g) levels as compared to diabetic control group (table 5).

Discussion

The present study of antihyperglycemic effect of MB was taken into consideration due to its ethno pharmacological claim that fruits are beneficial in the management of diabetes. The study was performed on the fruit powder and its ME because the extract had shown maximum extractable (15.8% w/w). Phytochemical screening of the extract revealed the presence of alkaloids, phenolic compounds, flavonoids and steroids.

The results as shown in table 1 revealed no significant effect of the extract in serum glucose level in normal healthy rats, suggesting drug does not have *per-se* hypoglycemic effect, which is generally reported with oral synthetic anti-diabetic drugs. Thus, it seems to be safe to use this drug as an oral anti-hyperglycemic agent like metformin (29).

In OGTT model a significant check was observed in the serum glucose rise in animals treated with the FPP, in comparison to normal group and was dose dependent. Similar but more significant effect and dose dependent was seen in animals treated with ME in comparison to the normal untreated group. Animals treated with glibenclamide also showed a significant inhibition of serum glucose rise (table 2).

This effect of ME in normal rats in OGTT model may be attributed to the inhibition of α -glucosidase enzymes which reduce intestinal absorption of glucose (30) or it may have stimulated the release of more insulin from pancreas. Insulin stimulates muscle and fat cells to remove glucose from the blood and also stimulate the liver to metabolize glucose (31).

The methanol extract of the fruit pulp at dose of 500 mg/kg caused a significant ($P < 0.05$) fall in serum glucose of diabetic rats in comparison to 0 day (table 3). The results were comparable with those of the standard drug GLB. The antihyperglycemic activity of the leaves may be due to a stimulating effect on the remnant β -cells or improvement in insulin action at the cellular level. Moreover, the methanol extract showed the presence of flavonoids (antioxidant compound), with potential to treat diabetes by rejuvenating the pancreatic cells (30-32). This supports our proposed mechanism of action in the treatment of diabetes.

Treatment with the methanol extract for 21 days significantly ($P < 0.05$) reduced serum total cholesterol, triglycerides, VLDL-C and LDL-C levels and significantly ($P < 0.05$) raised HDL-C level in comparison to diabetic control group (table 5). Lipid lowering effect may be either due to up-regulation of peroxisome proliferator activator receptors (PPAR) activity or due to increased insulin secretion (33, 34). This suggests that methanol extract of the leaves may inhibit the cholesterol synthesis pathway by inhibiting HMG-CoA reductase (35, 36) or by reducing the NADPH required for fatty acids and cholesterol synthesis (37). Such a lipid lowering activity of this drug in STZ-induced diabetic rats may also help in preventing associated atherogenesis and other secondary complications of diabetes mellitus (8). The results of lipid profile warrant more detailed study of treatment at 500 mg/kg, p.o. twice a day.

After 21-days treatment with the methanol extract, the liver glycogen level was significantly ($P < 0.05$) elevated. Improvement of glycogen level in liver may occur by two possible ways, one due to increased insulin level and the second due to up-regulation of GLUT - 4 and PPAR - γ activity which facilitates uptake of glucose by the peripheral tissues (38, 39).

In diabetic control group, loss in body weight may be attributed to some abnormality in carbohydrate metabolism such as lipolysis, glycogenolysis and acidosis, or it could be caused by disturbances in some metabolic pathways and results in protein deficiency (40-42). However, diabetic rats treated with GLB and ME showed no significant loss in body weight which may be possible due to increased insulin secretion and food consumption (43, 44).

In conclusion, *Momordica balsamina* plant commonly used as a vegetable, showed a significant antihyperglycemic effect, and lipid profile and arrest loss in body weight in STZ-induced diabetic rats. All these results point to the antidiabetic potential of this plant.

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Abbreviation

AE – Aqueous extract, CMC – Carboxymethylcellulose, DM – Diabetes mellitus, GLB – Glibenclamide, HDL-C – High Density Lipoprotein Cholesterol, i.p. – Intraperitoneal, LDL-C – Low Density Lipoprotein Cholesterol, FPP – Fruit pulp powder, ME – Methanol extract, OGTT – Oral Glucose Tolerance Test, p.o. – Per oral, PEG – Polyethyleneglycol, PPAR - Peroxisome Proliferator Activator Receptors, STZ– Streptozotocin, VLDL-C – Very Low Density Lipoprotein Cholesterol.

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