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The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(3): 46-50

www.thepharmajournal.com
Received: 13-01-2023
Accepted: 18-02-2023

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Antidiabetic efficacy of *Swertia chirayita* extract in streptozotocin induced diabetic wistar rats

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DOI: https://doi.org/10.22271/tpi.2023.v12.i3a.19611

Abstract
The alcoholic extract of *Swertia chirayita* extract was tested for its biochemical and pathomorphological effects in streptozotocin induced diabetes in rats. Streptozotocin produced diabetes effectively in all the animals at 45 mg/kg b.w. intraperitonially. The diabetic animals showed significant increase in serum levels of glucose, cholesterol, triglycerides, ALT and AST and a significant reduction in serum insulin levels. *Swertia chirayita* treated rats at the dose of 500 mg/kg b.w showed significant reduction in the serum levels of glucose, cholesterol, triglycerides, ALT and AST with significant improvement in serum insulin levels compared to diabetic animals from day 3 post treatments till the end of the study. *Swertia chirayita* also improved the damage caused by streptozotocin morphologically in pancreas by promoting the regeneration of beta cells of islets of Langerhans.

Keywords: Diabetes, *Swertia chirayita*, streptozotocin

1. Introduction
Diabetes mellitus is a metabolic disorder characterized by high blood glucose levels and disturbances in carbohydrate, fat and protein metabolism affecting both humans and animals. It is one of the most frequently diagnosed endocrinopathies in cats and dogs and the incidence is increasing due to an increase in the frequency of predisposing factors such as obesity and physical inactivity in these animals (Hoenig, 2002) [8].
Oral hypoglycemic agents such as biguanides, sulphonylureas and thiozolidinediones or insulin therapy are the mainstay of treatment of diabetes. They are effectively used in controlling hyperglycemia, but they fail to significantly alter the course of complications and side effects caused by them.
Many studies have confirmed the benefits of medicinal plants with hypoglycemic effects in management of diabetes. Medicinal plants and their formulations are being used for treating diabetes in Ayurvedic medicine system as well as in ethnomedicinal practices. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. The ethnobotanical information reports about 800 plants that may possess anti-diabetic potential (Alarcon-Aguilara *et al.*, 1998) [2].
The new bioactive drugs isolated from hypoglycemic plants have showed antidiabetic activity with more efficacy than oral hypoglycemic agents (Joseph and Jin, 2011) [9]. In view of this present study was taken up to evaluate the antidiabetic efficacy of *Swertia chirayita* and also to compare hypoglycemic effect with oral hypoglycemic agent glibenclamide.
Swertia chirayita belongs to the family of Gentianaceae and genus *Swertia* L, commonly called as Indian Gentian or Bitter stick. It is known for the treatment of diabetes since long time. Significant blood sugar lowering effect was observed when ethanol extract of *Swertia chirayita* was fed (Sekar *et al.*, 1987; Saxena *et al.*, 2007 and Renu *et al.*, 2011) [18, 17, 16].

2. Materials and Methods
2.1 Experimental animals: Normal adult female Wistar albino rats weighing 170-180 g were procured from M/s RRL Instruments and Animals supplier, Bengaluru for the study purpose. They were maintained under standard laboratory conditions and offered ad libitum of standard commercial rat feed (M/s Amruth Feeds, Bengaluru) and clean drinking water.

2.2 Streptozotocin: To induce diabetes in rats, streptozotocin (M/s Sigma Chemicals, St. Louis, USA) was used intraperitonially in ice-cold citrate buffer (pH 3.5-4.5) at the dose of 45 mg/kg.

2.3 Glibenclamide solution: Glibenclamide (Daonil ®, 5 mg) an oral hypoglycaemic drug was administered orally at a dose of 600 µg/ kg b.w (Babu and Prince, 2004) [3].

2.4 Plant extract: The alcoholic plant extract of *Swertia chirayita* used in the present study was obtained from Katyani Exports, Pitampura, New Delhi, India. The powdered extract was weighed according to body weight and dissolved in water to make the final concentration and administered to the experimental animals.

2.5 Biochemical kits: The serum samples collected at various intervals were subjected to biochemical estimation of glucose, cholesterol, triglycerides, ALT and AST using Semi-Automatic biochemical analyzer with commercial biochemical kits (M/s Span diagnostics, Bengaluru). For the estimation of serum insulin concentrations, radio-immunoassay was performed using iodine labelled insulin assay kit (RIAK-1) obtained from Board of Radiation and Isotope Technology (BRIT), BARC, Mumbai, India.

2.6 Experimental design: The rats were weighed and randomly divided into four different groups of 12 animals each based on body weight. Group I served as the normal control, Group II was diabetic control, Group III was diabetic animals treated with standard oral hypoglycemic drug glibenclamide at a dose of 600 µg/kg b.w and Group IV was diabetic rats supplemented with alcoholic extract of *Swertia chirayita* at a dose of 500 mg/kg b.w.
The experiment was conducted for the period of 45 days and at regular intervals on days 15, 30 and 45 about 2 ml of blood was collected and subjected for estimation of glucose, cholesterol, triglycerides, AST, ALT and insulin levels. To study the progressive effects of the treatments given to different groups, two rats from each group were sacrificed on 15th and 30th day and the remaining rats on 45th day of experimentation. Sacrificed animals were subjected for detailed post mortem examination and gross change if any, were recorded. Further, representative tissue samples were collected in 10 percent Neutral buffered formalin (NBF) for the pathomorphological evaluation.

2.7 Experimental induction of diabetes: The animals were fasted overnight and diabetes was induced by freshly prepared streptozotocin at the dose of 45 mg/kg intraperitonially in 0.1 M citrate buffer (pH 3.5-4.5). The normal control animals received citrate buffer alone. The diabetic state was confirmed by estimating the serum glucose level at 72 hours post streptozotocin injection using Span Diagnostic kit with Semi-Automatic Biochemical Analyzer (ARTOS, Bengaluru).

2.8 Statistical analysis: Statistical analysis was performed using the statistical software Graph pad Prism. Mean values and standard error of mean were calculated and all values were expressed as Mean (± SE). The data were analyzed by Two Way ANOVA.

3. Results and Discussion

Diabetes was induced effectively by Streptozotocin in all the animals. All the rats from Group II to IV became diabetic and showed hyperglycaemia with an increase in mean serum glucose levels ranging from 609.66±50.59 mg/dl to 659.75±41.08 mg/dl by 72 hrs after STZ administration. Induction of diabetes with hyperglycaemia by STZ has been attributed to its selective beta cell cytotoxicity (Mir *et al.*, 2008) [12]. It is taken up by pancreatic beta cells via glucose transporter GLUT2 and the cytotoxic effect has been attributed to alkylation of DNA leading to DNA damage (Delaney *et al.*, 1995 and Elsner *et al.*, 2000) [6, 7].
Clinically the animals exhibited the signs of polyurea, polydypsia, polyphagia, restlessness and poor body condition. The diabetic animals (Group II) showed hyperglycaemia, hyperlipidemia, increased levels of serum ALT, AST and decreased levels of serum insulin which persisted till the end of the experiment. Clinically, *Swertia chirayita* treatment reduced the severity of the diabetic manifestation from 15th day post treatment onwards which could be directly attributed to the improvement on hyperglycaemia and hypoinsulinaemia.
The mean serum glucose levels in the diabetic control rats were significantly higher ($p \leq 0.001$) on all the intervals of study in comparison with those of normal control group (Table 1). Present study observed that the mean serum glucose levels were progressively reduced on *Swertia chirayita* extract treatment compared to those of diabetic control group. The decrease in glucose values was comparable to those of glibenclamide on all the days of observation.

Table 1: Effect of *Swertia chirayita* on serum glucose (mg/dL) values in streptozotocin induced diabetic rats

Groups	Days Post Treatment			
	3	15	30	45
Group I (NC)	89.25±2.86	86.00±4.21	84.20±5.67	85.87±4.22
Group II (DC)	658.58±40.52^{a}	526.00±21.74^{ac}	483.80±48.80^{ac}	565.37±45.65^{ac}
Group III (GC)	609.66±50.59^{a}	327.75±30.35^{ab}	304.10±28.30^{ab}	198.62±18.04^{b}
Group IV (SC)	659.75±41.08^{a}	392.33±25.81^{ab}	313.50±27.63^{ab}	238.50±17.43^{ab}

Mean values with different superscript differ significantly
^{a}Comparison with Group I, ^{b}Comparison with Group II, ^{c}Comparison with Group III
Values are statistically significant at $p \leq 0.05$

Hypoglycemic effect of alcoholic extracts of *Swertia chirayita* in diabetic rats models were demonstrated by various earlier workers (Kar *et al.*, 2003 and Renu *et al.*, 2011) [10, 16]. Various crude extracts of *Swertia chirayita* and its isolated fractions have shown hypoglycemic activity. Oral administration of 95 % ethnolic extract and hexane fraction of *Swertia chirayita* to normal, glucose fed and STZ induced diabetic rats significantly lowered blood glucose levels (Sekar *et al.*, 1987) [18]. Hexane fraction of the plant showed lowered blood glucose levels and insulin release from pancreatic β-cells (Chandrasekhar *et al.*, 1990) [5]. Swercherin isolated from hexane fraction of the plant exerted potent hypoglycemic activity in STZ induced diabetic rats (Saxena *et al.*, 2007) [17]. Xanthone isolated from hexane fraction of

Swertia chirayita was identified as swerchirin and it lowered the blood glucose by stimulating the insulin release by beta cells by degranulation (Saxena *et al.*, 2007) [17]. Phoboo *et al.* (2013) [13] showed that crude extract of this plant contained three main phytochemicals such as mangiferin, swertiamarin and amarogentin. Among these they attributed mangeferin to α-glucosidase and 2,2-diphenyl-1-picrylhydrazyl radical inhibitory activity indicating antihyperglycemia potential of *Swertia chirayita* by *in vitro* biochemical assays.

The mean (± SE) values of serum cholesterol and triglyceride levels in the diabetic control group were found to be significantly higher ($p \leq 0.001$) compared to normal control group indicating hyperlipidemia (Table 2 and 3). Serum cholesterol and triglycerides values of *Swertia chirayita* treated animals showed a decreasing trend compared to diabetic control animals. Similar findings in lipid profile was also observed by Renu *et al.* (2011) [16] by oral administration of *Swertia chirayita* in STZ-NAD induced diabetic mice. The decrease in the cholesterol and triglyceride levels in serum has been attributed to the bellidifolin and swerchirin, the xanthenoids isolated from swertia species (Basnet *et al.*, 1994 and Tian *et al.*, 2008) [4, 20]. Further, in the present study the administration of *Swertia chirayita* lowered blood glucose and increased plasma insulin levels thereby preventing lipolysis.

Table 2: Effect of *Swertia chirayita* on serum cholesterol (mg/dL) values in streptozotocin induced diabetic rats

Groups	Days Post Treatment			
	3	15	30	45
Group I (NC)	80.88±3.58	81.15±3.63	84.65±5.52	81.68±3.07
Group II (DC)	136.21±7.61[a]	155.96±5.28[ac]	178.29±6.69[ac]	194.67±6.64[ac]
Group III (GC)	136.16±7.65[a]	125.74±5.36[ab]	114.61±4.01[ab]	105.03±4.88[b]
Group IV (SC)	137.69±7.64[a]	129.00±5.02[ab]	116.14±4.05[ab]	109.71±3.92[ab]

Mean values with different superscript differ significantly
[a]Comparison with Group I, [b]Comparison with Group II, [c]Comparison with Group III
Values are statistically significant at $p \leq 0.05$

Table 3: Effect of *Swertia chirayita* on serum triglycerides (mg/dL) values in streptozotocin induced diabetic rats

Groups	Days Post Treatment			
	3	15	30	45
Group I (NC)	94.28±3.240	95.04±2.38	93.03±2.33	98.70±6.26
Group II (DC)	206.26±6.08[a]	239.47±7.20[ac]	281.59±15.59[ac]	312.85±17.97[ac]
Group III (GC)	205.80±10.82[a]	171.24±10.05[ab]	141.33±12.87[ab]	111.61±9.05[b]
Group IV (SC)	210.95±9.30[a]	187.21±9.04[ab]	144.12±9.90[ab]	115.75±5.22[b]

Mean values with different superscript differ significantly
[a]Comparison with Group I, [b]Comparison with Group II, [c]Comparison with Group III
Values are statistically significant at $p \leq 0.05$

The mean (± SE) values of serum ALT and AST levels in the diabetic control group also showed significantly higher ($p \leq 0.001$) values compared to normal control group (Table 4 and 5). The mean serum ALT and AST values in *Swertia chirayita* treated group revealed a progressive and significant decrease when compared to diabetic control rats (Group II) and were almost comparable to those of glibenclamide treated group and with normal control on 45th day.

Table 4: Effect of *Swertia chirayita* on serum alanine aminotransferace (ALT) (IU/L) values in streptozotocin induced diabetic rats

Groups	Days Post Treatment			
	3	15	30	45
Group I (NC)	53.07±1.64	51.81±1.70	51.52±1.90	52.61±1.83
Group II (DC)	130.33±7.34[a]	163.02±8.74[ac]	206.58±13.60[ac]	254.81±27.62[ac]
Group III (GC)	125.41±5.66[a]	122.50±3.23[abc]	100.37±2.08[ab]	88.87±3.98[ab]
Group IV (SC)	124.89±7.31[a]	109.60±4.95[ab]	82.03±5.15[ab]	77.95±5.22[b]

Mean values with different superscript differ significantly
[a]Comparison with Group I, [b]Comparison with Group II, [c]Comparison with Group III
Values are statistically significant at $p \leq 0.05$

Table 5: Effect of *Swertia chirayita* on serum aspartate aminotransferace (AST) (IU/L) values in streptozotocin induced diabetic rats

Groups	Days Post Treatment			
	3	15	30	45
Group I (NC)	61.40±2.05	63.84±2.09	65.58±1.81	67.27±2.87
Group II (DC)	170.10±10.20[a]	208.01±9.23[ac]	247.82±21.23[ac]	286.87±23.35[ac]
Group III (GC)	169.65±10.70[a]	154.55±7.89[ab]	130.17±10.92[ab]	113.12±10.17[ab]
Group IV (SC)	171.81±9.27[a]	144.42±9.48[ab]	105.86±9.81[ab]	91.02±7.39[b]

Mean values with different superscript differ significantly
[a]Comparison with Group I, [b]Comparison with Group II, [c]Comparison with Group III
Values are statistically significant at $p \leq 0.05$

The improvement noticed in the level of enzymes may be due to improvement in the carbohydrate, fat and protein metabolism. Also, the constituents derived from swertia species like gentiopicroside, sweroside and 1, 4, 5, 8-tetrahydroswertianolin exhibited hepatoprotective activities. Similar type of hepatoprotective activities of *Swertia chirayita* has been evaluated by many earlier workers (Karan *et al.*, 1999 and Reen *et al.*, 2001) [11, 15].

The serum insulin values in the present study were estimated by RIA method and the mean insulin values were significantly lowered ($p \leq 0.001$) in diabetic control groups compared to normal control animals (Table 6). The serum insulin levels in *Swertia chirayita* treatment group showed a gradual and progressive improvement compared to diabetic control (Group II). Though there was an increase in the mean values, they failed to reach the normal values and were significantly lower when compared to those of normal treatment group.

Table 6: Effect of *Swertia chirayita* on serum insulin (µU/ml) values in streptozotocin induced diabetic rats

Groups	Days Post Treatment			
	3	15	30	45
Group I (NC)	53.85±3.21	52.85±3.16	54.15±2.78	52.08±5.35
Group II (DC)	17.58±1.70[a]	15.66±0.87[a]	13.61±1.37[ac]	14.05±1.81[ac]
Group III (GC)	15.42±2.06[a]	18.44±2.41[a]	25.73±2.07[ab]	31.01±2.91[ab]
Group IV (SC)	17.96±1.36[a]	19.87±1.99[a]	21.76±2.60[ab]	25.04±2.53[ab]

Mean values with different superscript differ significantly
[a]Comparison with Group I, [b]Comparison with Group II, [c]Comparison with Group III
Values are statistically significant at $p \leq 0.05$

Improved insulin level in *Swertia chirayita* treatment could be due to regeneration or repair of damaged beta cells by *Swertia chirayita*. A similar observation has also been made by earlier workers who noticed increase in serum insulin after treatment with *Swertia chirayita* extract. The swerchirin of *Swertia chirayita* has been reported to have direct action on pancreatic beta cells by degranulation thereby leading to increase in serum insulin levels. Saxena *et al.* (2007) [17] showed the degranulation of beta cells following administration of swerchirin isolated from hexane fraction of *Swertia chirayita.* Improvement of architecture of Islets of Langerhans in the present study, a finding observed microscopically also strengthens the insulinotropic role of *Swertia chirayita* by regenerating insulin producing cells.

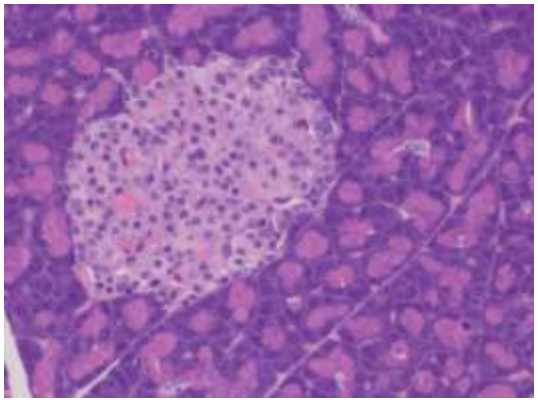

Fig 1: Pancreas of normal control animal showing normal islet of Langerhans architecture.

The pancreas of diabetic control rats in the present study revealed the numerous lobules with loss of architecture microscopically. Islets of Langerhans were reduced in number per lobule. The normal distribution of alpha and beta cells appeared altered with considerable reduction in the number of beta cells that were either necrotic or highly swollen with vacuolated cytoplasm (Figure 2). By the end of the study, islets revealed a mild fibrotic change and infiltration of a few inflammatory cells. In the present study, the decrease in the number of islets and cellularity in the islets could be due to the cytotoxic effect of streptozotocin which is specific for beta cells of islets as indicated by earlier workers (West *et al.*, 1996; Szkudelski, 2001; Akbarzadeh *et al.*, 2007 and Zafar *et al.*, 2009) [21, 19, 1, 22].

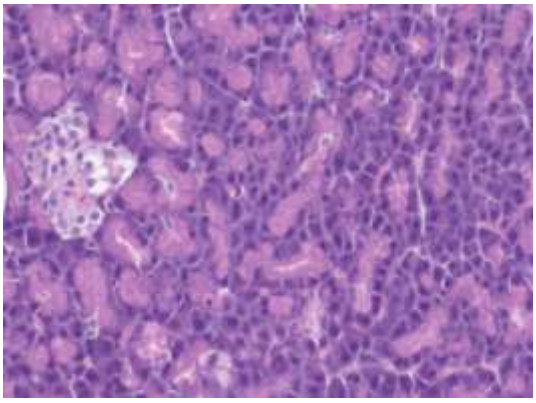

Fig 2: Pancreas of diabetic control animal showing loss of normal architecture with vacuolated and degenerating islet cells.

The improvement in architecture of pancreatic islets in the present study could be attributed to the effect of *Swertia chirayita* on pancreas resulting in promotion of regeneration of beta cell subsets or repair of damaged cells. The islets revealed hypercellularity with advancement of time on treatment (Figure 3).

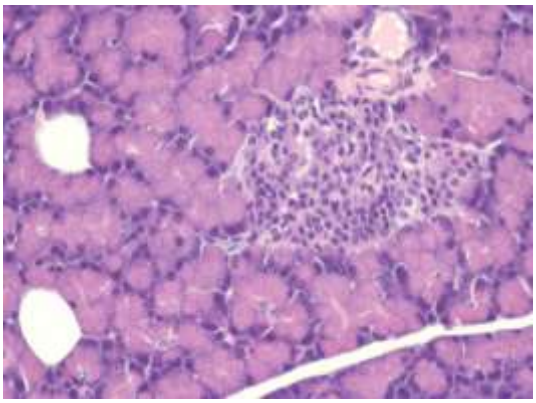

Fig 3: Pancreas from a diabetic rat treated with *Swertia chirayita* showing an improvement in the architecture of islet cells.

The insulinomimetic property by *Swertia chirayita* on pancreas is well recorded by earlier workers (Saxena *et al.*, 2007) [17]. Short pulse of glucose metabolism, as would happen after a meal, will trigger secretion of insulin by beta cells but not replication, while more persistent activation of the pathway will trigger replication indicating an organism's need for more beta cells (Porat *et al.*, 2011) [14]. Probably the more persistent activation of *Swertia chirayita* by insulinomimetric property may be responsible for beta cells regeneration in the present study.

4. Conclusion

The present study was focused on evaluation of antidiabetic effect of *Swertia chirayita* in induced diabetes in rats. Diabetes mellitus can be effectively induced by using streptozotocin at the dose rate of 45 mg/kg intraperitonially in laboratory rats. The alcoholic extract of *Swertia chirayita* at a dose of 500 mg/kg body weight was effective in alleviating streptozotocin induced diabetes and its associated metabolic alterations and was almost comparable to those of oral hypoglycemic agent glibenclamide. There was also a progressive reconstruction of normal architecture of islets with increase in beta cells in pancreas in the present study.

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