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Research article

Evaluation of antidiabetic effect of *Epipremnum aureum* on streptozotocin-induced diabetic rats

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ABSTRACT

The present study aimed to examine and compare the antidiabetic effect of different extracts of *Epipremnum aureum* on blood glucose levels, lipid profile, renal and hepatic function of streptozotocin (STZ)-induced diabetic rats. The animals showed a significant increase in the levels of blood glucose, total cholesterol, triglycerides, SGOT, SGPT, ALP, bilirubin, urea, uric acid, creatinine and total protein and a decrease in the HDL and antioxidant (SOD, GSH) levels when compared to the normal animals. The results demonstrated that ethanol extract showed more significant results as compared to acetone and chloroform extracts and also to standard preparation of *Aloe vera*.

INTRODUCTION

Diabetes mellitus is a complex group of metabolic disorders characterized by elevated blood glucose levels due to deficient or ineffective production of insulin by β cells of the pancreas (Harikumar et al., 2014). This disorder causes disturbance in the metabolism of carbohydrates, fats and proteins. The resulting elevated blood glucose level or hyperglycemia may cause acute metabolic complications which also include ketoacidosis and leads to chronic microvascular complication in long term. Long term hyperglycemia associated with diabetes may lead to dysfunction of various organs like kidneys, eyes, nerves, blood vessels and heart. Classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) (Deshmukh and Jain, 2015). According to the WHO, the rate of diabetes is increasing by 35%. Currently, there are more than 150 million patients with diabetes which are expected to be increased to 300 million or more by the year 2025 (Das et al., 2015). From ancient times medicinal plants are being used for the treatment of various ailments and diabetes is one of the major prevailing diseases among all the age groups. Oral hypoglycemic drugs which are used to treat diabetes mellitus are associated with many side effects such as skin reactions, gastrointestinal disturbances, haematological disorders, rise in hepatic enzyme levels, etc. which increase the demand for natural herbs for the treatment purposes. Medicinal plants are cost-effective and have fewer side effects on prolonged use.

The plant *Epipremnum aureum* (Linden & André) G.S.Bunting belongs to the family Araceae. It contains many chemical compounds including alkaloids, steroidal terpenoids, flavonoids, tannins and cardiac glycosides. Flavonoids are hydroxylated phenolics and are potent water-soluble antioxidants that help in free radical scavenging activity and prevention of oxidative cell damage which may contribute to pancreatic β-cell damage.

MATERIAL AND METHODS

Collection of plant material

Epipremnum aureum leaves were collected from the local area of Dehradun, Uttarakhand, India in September 2017. The leaves were cleaned and shade dried for 5 days. The dried plant material was coarsely powdered with the help of a mechanical grinder.

Preparation of extract

Around 500 g of dried coarse powder of leaves was extracted by continuous hot percolation method by soxhlet apparatus as per the polarity of solvents with petroleum ether, chloroform, acetone and finally ethanol.

Selection of animals

Wistar albino rats of either sex, weighing about 150-250 g were used for the study of diabetic activity. The animals were kept in standard polypropylene cages and maintained under controlled environmental conditions such as room temperature (25±2ºC) and humidity (55±5%) with 12 h day and night cycle. All the animals were fed with a standard rat pellet diet and water at *libitum*. The study was performed according to the guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA) and prior permission for conducting animal experimental studies was taken from the institutional animal ethics committee (Approval No. CPCSEA/IAEC/SBS/2017-18/008).

Selection of dose

Dose selection of *E. aureum* leaves was done based on studies performed on the antidiabetic activity of *Epipremnum aureum* (Abhinayani et al., 2013; Adeniyi and Sanusi, 2014).

Induction of diabetes

Intraperitoneal injection of STZ (60 mg/kg) was used to induce diabetes mellitus. Diabetes was induced by a repetitive single dose of STZ for 72 hours. After 2 hours of STZ injection, dextrose 10% was fed to all rats ad *libitum* to prevent hypoglycemia. After 72 hours blood was collected from animals and serum was separated. The severity of the onset of diabetic symptoms depends on the dose. Animals having more than 200 mg/dl of blood glucose levels were used for the study.

Antidiabetic study

Diabetic Wistar rats and normal Wistar rats were grouped into the following six groups. Each group was comprised of 4 rats.

- Group I (Normal control): Normal saline (1 ml/kg) was administered orally for 21 days.
- Group II (Positive control): STZ at a dose of 60 mg/kg was administered intraperitoneally.
- Group III (Standard): Aloe vera juice at a dose of 5 ml/kg bw for 21 days (Sanghi, 2015)
- Group IV (Treatment group 1/ T1): *E. aureum* chloroform extract with a dose of 250 mg/kg was administered orally for 21 days.
- Group V (Treatment group 2/ T2): *E. aureum* acetone extract with a dose of 250 mg/kg was administered orally for 21 days.
- Group VI (Treatment group 3/ T3): *E. aureum* ethanol extract with a dose of 250 mg/dl was administered orally for 21 days.

After completion of the study protocol, blood samples and tissues were collected from each group and were analyzed to estimate their anti-diabetic potential.

Statistical analysis

Values are given as mean ± SEM (n = 4/group). The statistical significance of the difference between means was calculated by ANOVA followed by a t-test for the comparison of groups. P values <0.05 were considered significant.

RESULTS

Effect on serum glucose, HDL cholesterol, total cholesterol and triglycerides levels

The serum glucose level was measured on 0, 7, 14 and 21 days of the treatment. There was an increase in the serum glucose level after the injection of STZ. After 21 days of the treatment, it was found that there was a more significant (P<0.001) decrease in serum glucose level in animals treated with ethanol extract than in animals treated with acetone and chloroform extracts when compared with diabetic control groups (Table 1).

STZ induced diabetic animals produced a significant (P<0.0029) decrease in the HDL level when compared to the normal control group. After 21 days of treatment, it was found that there was a more significant increase in HDL levels in animals treated with ethanol extract of money plant than in animals treated with acetone and chloroform extracts (Table 1).

STZ induced diabetic animals showed a significant (P<0.001) increase in the total cholesterol level when it was compared to the normal control group. After treatment, it was found that there was a more significant decrease in total cholesterol level in animals treated with ethanol extract than with acetone and chloroform extracts when compared to diabetic control groups (Table 1).

STZ induced diabetic animals resulted in a significant (P<0.001) increase in the serum triglyceride level when compared to the normal control group. There was a significant decrease in triglyceride levels in animals treated with ethanol extract than in acetone and chloroform extracts (Table 1).

Table 1. Effect of different extracts on serum glucose, HDL cholesterol, total cholesterol and triglycerides levels

Group	Serum glucose level (mg/dL)			
	0 Day	**7 Day**	**14 Day**	**21 Day**
Normal control (1 ml/kg saline p.o.)	98.5±4.645	97.5±3.378	97.75±3.966	99.75±3.591
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	283.75±13.591	288±14.335	284±14.6	279.25±13.942
STZ + Aloe Vera (5 ml/kg p.o.)	281±15.926	227±11.704**	165.75±4.939**	103.12±2.045***
STZ + Chloroform extract (250 mg/kg p.o.)	289.5±20.641	246±15.556*****	218.5±12.704**	175.75±4.534**
STZ + Acetone extract (250 mg/kg p.o.)	300±112.362	249.25±7.431*	194±8.113**	126±3.35**
STZ + Ethanol extract (250 mg/kg p.o.)	280±8.869	238±12.436**	183.75±11.033**	109±5.115***

	HDL cholesterol (mg/dL)			
Normal control (1 ml/kg saline p.o.)	51.58±2.473	-	-	51.46±2.329
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	33.34±1.745	-	-	35.64±1.79
STZ + Aloe Vera (5 ml/kg p.o.)	31.09±0.907	-	-	46.02±1.059***
STZ + Chloroform extract (250 mg/kg p.o.)	29.73±1.869	-	-	39.49±1.249*
STZ + Acetone extract (250 mg/kg p.o.)	30.08±3.04	-	-	43.38±1.043**
	Total cholesterol (mg/dL)			
Normal control (1 ml/kg saline p.o.)	169.25±6.236	-	-	170.25±4.956
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	315.25±8.066	-	-	320.75±7.597
STZ + Aloe Vera (5 ml/kg p.o.)	314±15.625	-	-	183±3.415***
STZ + Chloroform extract (250 mg/kg p.o.)	330.25±11.578	-	-	208.75±12.828**
STZ + Acetone extract (250 mg/kg p.o)	321.75±19.036	-	-	194.5±8.684**
STZ + Ethanol extract (250 mg/kg p.o)	313.25±17.143	-	-	189±6.123***
	Triglycerides (mg/dL)			
Normal control (1 ml/kg saline p.o)	58.55±5.512	-	-	58.89±6.259
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	289.5±28.489	-	-	302.5±28.225
STZ + Aloe Vera (5 ml/kg p.o)	279.87±9.942	-	-	90.55±3.115***
STZ + Chloroform extract (250 mg/kg p.o)	319.6±26.975	-	-	160.9±10.145*
STZ + Acetone extract (250 mg/kg p.o)	311.3±24.443	-	-	144.02±7.058**
STZ + Ethanol extract (250 mg/kg p.o)	291.27±18.169	-	-	106.42±9.903**

Values are given as mean ± SEM; *P<0.05, **P<0.01, ***P<0.001

Effect on liver functions

STZ induced diabetic animals showed a significant (P<0.0019) increase in the SGOT level when compared to the normal control group. A significant decrease in SGOT level was recorded in animals treated with ethanol extract than in other extracts (Table 2).

STZ induced diabetic animals showed a significant (P<0.001) increase in the SGPT level when compared to the normal control group. After 21 days of treatment, a significant decrease in SGPT level was found in animals treated with ethanol extract than acetone and chloroform extracts when compared to the diabetic control group (Table 2).

STZ induced diabetic animals showed a significant (P<0.001) increase in the total bilirubin level when compared to the normal control group. After 21 days of treatment with *E. aureum* it was found that there was a significant decrease in total bilirubin level in animals treated with ethanol extract of money plant than in animals treated with acetone and chloroform extract when compared to the diabetic control group (Table 2).

Table 2. Effect of different extracts on SGOT, SGPT and total bilirubin levels

Group	**Serum Glutamate Oxaloacetate Transaminase (U/L)**			
	0 Day	**7 Day**	**14 Day**	**21 Day**
Normal control (1 ml/kg saline p.o.)	28.12±1.547	28.1±1.65	28.42±1.855	28.52±1.647
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	50.86±2.132	51.23±2.098	51.68±2.167	52.17±2.192
STZ + Aloe Vera (5 ml/kg p.o.)	53.82±2.982	46.77±2.698**	38.89±1.441**	20.87±0.752***
STZ + Chloroform extract (250 mg/kg p.o.)	48.94±1.649	44.49±1.405**	40.04±0.736**	34.33±0.519**
STZ + Acetone extract (250 mg/kg p.o.)	48.58±12.893	42.34±1.87**	38.76±1.126**	33.63±0.751**
STZ + Ethanol extract (250 mg/kg p.o.)	49.44±1.596	42.66±2.061**	35.84±1.259***	32.46±1.521**
	Serum Glutamate Pyruvate Transaminase (U/L)			
Normal control (1 ml/kg saline p.o.)	29.15±2.57	29.37±2.9	30.02±2.91	29.92±2.514
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	62.61±3.94	63.18±3.757	63.57±3.777	64.05±3.826
STZ + Aloe Vera (5 ml/kg p.o.)	64.09±2.492	53.33±2.003*	40.09±1.912**	32.98±1.681***
STZ + Chloroform extract (250 mg/kg p.o.)	58.64±3.664	53.15±5.037**	44.41±1.561**	38.84±1.387**
STZ + Acetone extract (250 mg/kg p.o.)	58.19±2.311	51.75±1.857**	45.42±1.67**	37.28±1.417**
	Total bilirubin (µmol/L)			
Normal control (1 ml/kg saline p.o.)	0.58±0.071	0.6±0.062	0.60±0.063	0.59±0.071
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	1.42±0.087	1.44±0.091	1.45±0.084	1.49±0.083
STZ + Aloe Vera (5 ml/kg p.o.)	2.08±0.139	1.08±0.128**	0.74±0.043***	0.67±0.038***
STZ + Chloroform extract (250 mg/kg p.o.)	1.85±0.288	1.22±0.197**	0.93±0.069**	0.77±0.034**
STZ + Acetone extract (250 mg/kg p.o.)	1.86±0.053	1.17±0.074**	0.90±0.052**	0.76±0.025**

*P<0.05, **P<0.01, ***P<0.002

Effect on kidney functions

The effect of *E. aureum* on the urea levels of STZ induced diabetic animals shows a significant (P<0.001) increase when compared to the normal control group. After 21 days of treatment, a significant decrease in the urea levels was observed in ethanol extract-treated animals followed by acetone and chloroform extracts treated

groups when compared to the diabetic control group (Table 3).

Similarly, the extracts showed a significant decrease in creatinine levels in diabetic rats in which ethanolic extract was found most effective (Table 3).

STZ caused a significant increase (P<0.0096) in uric acid levels of animals when compared to the normal control group. At the end of the experiment, the ethanol extract showed a significant decrease in uric acid levels followed by acetone and chloroform extracts (Table 3).

In the case of total protein level, the extracts significantly decreased the elevated levels caused by STZ. The ethanol extract was also found most effective in decreasing levels of total proteins (Table 3).

Table 3. Effect of extracts on urea, creatinine, uric acid and total protein levels of experimental rats

Group	Urea (mg/dL)			
	0 Day	**7 Day**	**14 Day**	**21 Day**
Normal control (1 ml/kg saline p.o.)	16.38±0.925	16.24±1.249	16.23±1.32	16.59±1.194
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	56.70±1.596	57.36±1.517	58.19±1.526	58.52±1.487
STZ + Aloe Vera (5 ml/kg p.o.)	57.71±1.749	46.43±1.341**	35.52±0.84***	23.97±1.1***
STZ + Chloroform extract (250 mg/kg p.o.)	55.40±2.34	47.91±2.499**	43.66±2.163**	36.83±1.54**
STZ + Acetone extract (250 mg/kg p.o.)	55.32±3.278	47.57±2.563**	41.43±1.923**	32.63±1.419**
STZ + Ethanol extract (250 mg/kg p.o.)	56.09±2.939	45.49±2.483**	39.40±1.673***	24.8±1.643***
	Creatinine (U/L)			
Normal control (1 ml/kg saline p.o.)	0.90±0.061	0.87±0.049	0.89±0.049	0.91±0.026
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	3.28±0.164	3.43±0.16	3.74±0.197	3.98±0.196
STZ + Aloe Vera (5 ml/kg p.o.)	2.77±0.236	1.94±0.169**	1.53±0.076***	1.04±0.089***
STZ + Chloroform extract (250 mg/kg p.o.)	3.04±0.137	2.35±0.21*	1.95±0.165**	1.20±0.082**
STZ + Acetone extract (250 mg/kg p.o.)	3.08±0.113	2.22±0.171*	1.67±0.069**	1.17±0.083**
	Uric acid (mg/dL)			
Normal control (1 ml/kg saline p.o.)	4.22±0.31	4.49±0.337	4.32±0.452	4.45±0.219
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	10.92±0.072	11.46±0.489	11.65±0.451	11.97±0.491
STZ + Aloe Vera (5 ml/kg p.o.)	11.07±0.58	8.67±0.237**	7.71±0.119***	6.04±0.1***
STZ + Chloroform extract (250 mg/kg p.o.)	10.70±0.836	9.03±0.401*	8.15±0.071**	7.35±0.145***
STZ + Acetone extract (250 mg/kg p.o.)	10.37±0.367	8.73±0.268**	8.11±0.161*8	7.33±0.13***
	Total protein (g/L)			
Normal control (1 ml/kg saline p.o.)	6.93±0.152	-	-	6.99±0.046
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	15.24±0.912	-	-	15.45±0.915
STZ + Aloe Vera (5 ml/kg p.o.)	12.10±0.677	-	-	7.41±0.285***
STZ + Chloroform extract (250 mg/kg p.o.)	11.92±1.041	-	-	7.87±0.406***
STZ + Acetone extract (250 mg/kg p.o.)	12.31±1.032	-	-	7.75±0.348***

*P<0.05, **P<0.01, ***P<0.001

Effect on antioxidant activity

STZ-induced diabetic animals showed a significant (P<0.001) decrease in the Superoxide Dismutase (SOD) level when compared to the normal control group. After 21 days, the extracts of *E. aureum* showed a significant increase in SOD level. The efficacy of ethanol extract was found highest than others. Similar results were observed for Reduced Glutathione (GSH) levels in the experimental rats (Table 4)

Table 4. Effect of extracts on SOD and GSH levels of rats

Group	Levels of SOD and GSH after 21 days	
	SOD (U/mg)	**GSH (U/mg)**
Normal control (1 ml/kg saline p.o.)	30.67±1.65	8.89±0.212
STZ (60 mg/kg, i.p. in citrate buffer pH 4.5)	14.09±0.612	3.49±0.188
STZ + Aloe Vera (5 ml/kg p.o.)	26.98±0.828**	7.61±0.143***
STZ + Chloroform extract (250 mg/kg p.o.)	19.69±0.455*	5.75±0.193**
STZ + Acetone extract (250 mg/kg p.o.)	20.47±0.32*	6.49±0.226**
STZ + Ethanol extract (250 mg/kg p.o.)	24.24±0.569**	7.15±0.135***

*P<0.05, **P<0.01, ***P<0.001

DISCUSSION

The results of the present study showed that the elevated level of serum glucose, total cholesterol, triglycerides, SGOT, SGPT, ALP, bilirubin, urea, uric acid, creatinine and total protein in STZ-induced diabetic rats were significantly reduced and antioxidant levels (SOD and GSH) were significantly increased after treatment. Overall results showed that the ethanolic extract was most effective as compared to chloroform and acetone extracts of *E. aureum.*

In diabetes mellitus, increased glucose levels can inactivate antioxidant enzymes such as SOD, GSH, etc. and hyperglycemia-induced oxidative stress can lead to lipid peroxidation. *Epipremnum aureum* extracts increased the reduced level of antioxidant enzymes and decreased lipid peroxidation which indicates the antioxidant activity of plant extract. The extracts showed restoration of reduced glutathione which can help in the prevention of diabetic complications.

In diabetes, the level of serum lipids is mostly increased which indicates side effects for coronary heart disease (Miller et al., 1977). In diabetes, lipoprotein lipase is not activated due to insulin deficiency which results in hypertriglyceridemia. The plant extracts significantly reduced serum triglyceride, total cholesterol levels and increased HDL levels in diabetic rats which restored delayed insulin response and reduces serum glucose levels. The constituents of plant extract may act as inhibitors of enzymes such as hydroxyl methyl glutaryl CoA reductase which contributes to cholesterol synthesis, which in turn shows anti-diabetic action.

Increased serum creatinine, urea and uric acid level is a sign of impaired renal functions. The treatment with *E. aureum* extracts significantly reduced the increased level of creatinine, urea and uric acid (Trinder, 1949). The plant extracts ameliorate impaired renal function and inhibit liver damage in STZ induced diabetes.

Hepatotoxicity is another risk which is associated with diabetes mellitus (Moron et al., 1979). Oral hypoglycaemic drugs on prolonged use lead to side effects such as liver damage. Increased levels of SGOT, SGPT and total bilirubin levels contribute to damaged structural integrity of the liver (Pearlman and Lee, 1974). Switching allopathic drugs with medicinal plants reduces the side effects of prolonged use.

The active constituents of *E. aureum* extract show a reduction in the levels of malondialdehyde, hydroperoxide and conjugated dienes. The plant extract has a stimulating effect on glucose utilization and the level of antioxidant enzymes such as superoxide dismutase and reduced glutathione. The antidiabetic action might be based on the antioxidant action of plant extract. The results of this study might be helpful for further clinical research on human beings.

CONCLUSION

The present study concluded that the leaves of *Epipremnum aureum* possess a significant and consistent hypoglycemic effect along with improved lipid profile, hepatic and renal function in diabetic rats. Plant extracts have proved in improving diabetic complications and may have beneficial effects in the treatment of type 2 diabetes mellitus. It holds the hope for a new generation of oral hypoglycaemic drugs. The study was an effort to reduce the risk factors which are associated with diabetes mellitus by switching from oral hypoglycaemic drugs to natural herbs.

CONFLICTS OF INTEREST

The author(s) declare(s) no conflicts of interest.

DECLARATION

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