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Antihyperlipidemic and hypoglycemic potential of *Barleria buxifolia* leaves in STZ induced diabetic rats.

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Abstract

Number of plants and their by-products have been used as antidiabetic agents and many new drugs have evolved after scientifically validating the traditional uses,there are many more herbal/medicinal plants that have to be explored and validated.The purpose of this study was examine the metanolic and aqueous extract leaves in *Barleria buxifolia* leaves in Streptozotocin (STZ) induced hypoglycemic activity.STZ (60 mg/kg) was used to induce diabetes in rats. Methanolic and aqueous extract of *Barleria buxifolia* was given orally at dose of 200/400 (mg/kg) to diabetic rats initiate from 0 to 28th days.Blood collection for estimation of blood glucose level, triglyceride and cholesterol level were estimated.The oxidative parameters like superoxide dismutase activity(SOD),Catalase activity and reduced glutathione activity were estimated. Present study reveals that Barleria buxifolia is effective in the treatment of diabetic rats.The methanolic and aqueous extract of *Barleria buxifolia* at high (400mg/kg) and low dose (200 mg/kg) lowers increased blood glucose level and it also lowers increased triglyceride and cholesterol levels.The methanolic and aqueous extract of *Barleria buxifolia* at high (400mg/kg) and low dose (200 mg/kg) elevates decreased superoxide dismutase activity,catalse activity and reduced glutathione activity. The findings of research shows that the methanolic and aqueous extract of *Barleria buxifolia* have anti-diabetic potential which may be used for the treatment of diabetes mellitus.

Keywords: *Barleria buxifolia*, Streptozotocin, Diabetes mellitus,Diabetic complications

Introduction

Diabetes mellitus(DM) is a metabolic disorder characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[1]

The level of hyperglycaemia associated diabetes increases the risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to the related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life.[2]

There are mainly two major types of diabetes mellitus.Type 1is also called as Insulin dependant Diabetes Mellitus (IDDM).It is due to failure of body for insulin production.[3]Type 2 is also called as Non – Insulin Dependant diabetes Mellitus (NIDDM) .In this type of cells are unable for insulin usage.[4]Plants have always been a source of drugs for humans since ancient time.

According to World Health Organization, upto 90%of population in developing countries use plants and its products as traditional medicine for primary healthcare.[5]The most common and effective antidiabetic medicinal plants of Indian origin are Babul (*Acasia arabica*),bael(*Aegle marmelose*),church steeples (*Agrimonia eupatorium*),onion (*Allium cepa*),garlic (*Allium sativum*),ghrita kumara (*Azardichta indica*) etc.[5]The present chosen herb bearing a name *Barleria buxifolia* grown in wasteplace, India.Pharmacological studies on Barleria buxifolia leaves were proven its antioxidant,hepatoprotective, antidepressants and anti-inflammatory activities in experimental animals due to presence of various phytochemicals like flavonoids,amino acid,alkaloids,phenol,saponin,terpenoids and anthroquinone have proven capacity to cure and control disease prognosis.[6]

Materials & Methods

Plant Materials

Procurement and Authentication of plant materials

Barleria buxifolia plantswere collected from Thiruvalla, Kerala. The plant was diagnosed and authenticated by Mrs. A. M. Gaharwar, Assistant Professor of Vasantrao Naik College of Agricultural Biotechnology , Yavatmal with No. VNCABT/Ytl/Hort/900/2022.

Method of extraction

Extraction of *Barleria buxifolia* leaves

Leaves of *Barleria buxifolia* plant were collected,dried in shade and coarsely powdered.The powdered leaves were subjected to maceration with the use of methanol and thereafter water to get methanolic & aqueous extract respectively.

Drug and chemical substances

streptozotocin (STZ) used for the induction of diabetes & glibenclamide used as standard drug

All distinctive chemical substances and reagents used were of analytical grade.

Procurement of animals

Healthy sprague dawley male rats approximately 8 weeks of age weighing about 200-210 gm were purchased from NIN Hyderabad,India and used for the pharmacological screening. The animals were housed in polypropylene cages with cord mesh top and husk bedding and maintained beneath widespread environmental conditions (22+20C), relative humidity 55-60%,moderate dark cycle of 12 hours each and fed with widespread pellet diet and water. The protocols for all the animal studies was approved by Institutional Animal Ethical Committee(IAEC),P.Wadhwani college of pharmacy,Yavatmal with research no. 650/PO/Re/S/2002/CPCSEA/2022/09.

Methodology

Experimental Designs

The animals were grouped into seven following groups as follows. (n=6)

- Group-I :- Normal Control Group

Animals were treated with saline solution

- Group-II :- Diabetic control group (Negative Control)

Animals were treated with STZ (60 mg/kg)

- Group-III :- STZ + High dose of MEBB

Diabetes rats were treated with high dose of methanolic extract of *Barleria buxifolia*(400mg/kg)

- Group-IV :- STZ + Low dose of MEBB

Diabetes rats were treated with low dose of methanolic extract of *Barleria buxifolia*(200mg/kg)

- Group V :- STZ + High dose of AEBB

Diabetes rats were treated with high dose of aqueous extract of *Barleria buxifolia*(400mg/kg)

- Group VI :- STZ + Low dose of AEBB

Diabetes rats were treated with low dose of aqueous extract of *Barleria buxifolia* (200mg/kg)

- Group VII :- STZ + Glibenclamide

Diabetes rats were treated with standard drug Glibenclamide (5mg/kg)

Induction of Diabetes

Diabetes was induced in rat with the use of single i.p. injection of STZ 60mg.kg–1b.w. (procured from NIN hyderabad) in freshly prepared cold citrate buffer (pH 4.5). In order to prevent lethal hypoglycemia due to huge pancreatic insulin release, rats were treated with 5 % dextrose glucose solution bottles in their cagesto a period of 24h. After 72h, the animals showed blood glucose level 200 (mg/dl) considered diabetic and were used for the study . Diabetic rats were kept under standard laboratory condition for the stabilization of blood glucose level during the period of study.[7]

Parameter evaluated

Bio-chemical parameters

The blood sample withdrawn from rats by retro orbital plexus puncture method under mild ether anaesthesia was centrifuged at 3000 rpm for 20 min.Blood glucose, serum triglyceride and serum cholesterol were estimated by using kit.The oxidative parameters superoxide dismutase activity,catalase activity and reduced glutathione activity were estimated.

Statistical Analysis

The data was statistically analyzed by one-way analysis of variance (ANOVA) followed by Dunnets comparison test with equal sample size and student t-test was compared with unpaired groups.The difference was considered significant when **p<0.01. All the values were expressed as mean ± standard deviation (S.D.)

RESULTS

Table No.1 Presence of Phytochemical constituents in Methanolic and Aqueous Extract of *Barleria buxifolia*.

Sr.No	Phytoconstituents	Tests	BB MethanolicExtract	BB AqueousExtract
1.	Test for Alkaloids	Hager's Reagent	+	+
2.	Test for Carbohydrates	Molisch Test	+	+
3.	Test for Glycosides	Killer Killani Test	+	+
4.	Test for Amino acid	Ninhydrin Test	_	_
5.	Test for Tannins	Ferric chloride Test Lead acetate Test	+ +	+ -
6.	Test for Steroids	Salkowski Test	+	+
7.	Test for Phenols	Ferric Chloride Test	+	+
8.	Test for Flavonoids	Ferric Chloride Test Lead Acetate Test	+ +	+ _
9.	Test for Terpenoids	Salkowski Test	+	+
10.	Test for Saponins	Foam Test	+	+
11.	Test for Anthraquinone	_	_	_

+ Present , - Absent

The preliminaryphytochemical studies revealed the presence of alkaloids, carbohydrates,glycosides,tannin,steroid,phenol,terpenoid,saponin and flavonoids were noticed in *Barleria buxifolia* leaves extract as given in Table 1.

Table No.2 Effect of *Barleria buxifolia* on serum blood glucose level in streptozotocin induced diabetic rats

The results were expressed as mean ± SD (n=6)

$^{ns}p>0.05$,**$p<0.01$ when compared to STZ treated negative control group.

Groups	Blood glucose (mg/dl)			
	Days			
	Before induction of Diabetes	Day 0	Day 14	Day 28
Normal control	97.37±3.6	97.28±2.22	98.54±5.7	96.11±2.8
Negative control	96.67±3.34	256.91±7.67^{ns}	265.35±7.36**	275.67±7.84**
STZ + High dose of MEBB	97.28±2.22	258.67±4.26^{ns}	196.04±1.34**	191.23±2.39**
STZ + Low dose of MEBB	98.54±5.7	260.92±8.21^{ns}	213.49±10.31**	214.69±3.52**
STZ + High dose of AEBB	99.38±4.32	249.77±5.82^{ns}	194.84±1.2**	197.21±1.27**
STZ + Low dose of AEBB	96.63±2.74	255.67±4.81^{ns}	212.68±12.66**	215.6±2.92**
STZ + Glibenclamide	96.25±4.57	260.94±7.54^{ns}	146.31±10.33**	105.6±7.76**

Table 2 reveals the effect of STZ on blood glucose level of the rats on day 0 ,14th and 28th .There was significant increase ($p<0.01$) in the blood glucose level in negative control group compared to normal control rats on 0,14th,28thday.Group III (High dose of MEBB),Group IV (Low dose of MEBB),Group V (High dose of AEBB),Group VI (Low dose of AEBB) showed significant decrease in ($p<0.01$) in the blood glucose level compared to negative control group.

Table No.3 Effect of *Barleria buxifolia* on serum triglyceride level in streptozotocin induced diabetic rats

Groups	Serum Triglyceride (mg/dl)			
	Days			
	Before induction of Diabetes	Day 0	Day 14	Day 28
Normal control	56.54±1.6	57.13±1.84	55.72±1.26	56.41±1.27
Negative control	60.6±3.95	63.22±2.33^{ns}	111.25±2.27**	129.15±2.17**
STZ + High dose of MEBB	59.57±4.26	62.69±2.6^{ns}	70.25±1.55**	77.2±1.62**
STZ + Low dose of MEBB	56.42±2.16	62.42±1.92^{ns}	88.05±1.49**	94.42±1.17**
STZ + High dose of AEBB	58.61±2.28	61.63±3.67^{ns}	69.76±3.4**	74.13±1.02**
STZ + Low dose of AEBB	57.22±1.81	60.28±1.9^{ns}	91.94±1.12**	98.24±2.2**
STZ + Glibenclamide	58.56±2.67	61.42±1.5^{ns}	59.56±1.09**	65.32±1.73**

The results were expressed as mean ± SD (n=6)
$^{ns}p>0.05$,**$p<0.01$ when compared to STZ treated negative control group.
Table 3 reveals the effect of STZ on triglyceride level of the rats on day 0 ,14th and 28th .There was significant increase ($p<0.01$) in the triglyceride level in negative control group compared to normal control rats on 0,14th,28th day.Group III (High dose of MEBB),Group IV (Low dose of MEBB),Group V (High dose of AEBB),Group VI (Low dose of AEBB) showed significant decrease in the triglyceride level compared to negative control group.

Table No.4 Effect of *Barleria buxifolia* on serum cholesterol level in streptozotocin induced diabetic rats

Groups	Serum Cholesterol (mg/dl)			
	Days			
	Before induction of Diabetes	Day 0	Day 14	Day 28
Normal control	152.48±3.75	153.04±2.14	154.99±3.63	155.64±2.1
Negative control	149.59±1.23	151.41±1.44^{ns}	201.41±1.81**	252.1±4.29**
STZ + High dose of MEBB	148.77±1.09	150.37±1.91^{ns}	179.08±2.03**	194.89±1.04**
STZ + Low dose of MEBB	147.14±1.57	151.05±2.05^{ns}	191.95±3.69**	219.84±1.13**
STZ + High dose of AEBB	150.4±1.51	150.82±1.98^{ns}	176.51±1.44**	198.13±2.11**
STZ + Low dose of AEBB	149.79±1.89	152.14±2.85^{ns}	186.62±2.47**	225.83±1.89**
STZ + Glibenclamide	148.41±2.49	149.75±3.97^{ns}	159.47±2.94**	162.69±1.98**

The results were expressed as mean ± SD (n=6)
$^{ns}p>0.05$,**$p<0.01$ when compared to STZ treated negative control group.
Table 4 reveals the effect of STZ on cholesterol level of the rats on day 0 ,14th and 28th .There was significant increase ($p<0.01$) in the cholesterol level in negative control group compared to normal control rats on 0,14th,28th day. Group III (High dose of MEBB),Group IV (Low dose of MEBB),Group V (High dose of AEBB),Group VI (Low dose of AEBB) showed significant decrease in the cholesterol level compared to negative control group.

Table No. 5 Superoxide dismutase activity (units/mg of protein) in normal and diabetic rat treated and untrated with *Barleria buxifolia*

Groups	SOD
Normal control	171.42±1.88
Negative control	111.99±2.04**
STZ + High dose of MEBB	147.27±1.7**
STZ + Low dose of MEBB	141.23±2.41**
STZ + High dose of AEBB	152.73±2.92**
STZ + Low dose of AEBB	145.9±1.4**
STZ + Glibenclamide	157.76±2.58**

The results were expressed as mean ± SD (n=6)
$^{ns}p>0.05$,**$p<0.01$ when compared to STZ treated negative control group.

Table 5 and Figure 4 shows the superoxide dismutase activity in normal and diabetic rats.It shows that the superoxide dismutase activity in diabetic rat was significantly decreased as compared to normal rats. Group III (High dose of MEBB),Group IV (Low dose of MEBB),Group V (High dose of AEBB),Group VI (Low dose of AEBB) showed significant increase in the superoxide dismutase activity as compared to negative control group.

Table No. 6 Catalase activity (units/mg protein) in normal and diabetic rat, treated and untreated with *Barleria buxifolia*

Groups	CAT
Normal control	183.93±3.7
Negative control	119.94±1.9**
STZ + High dose of MEBB	166.2±1.61**
STZ + Low dose of MEBB	153.85±1.47**
STZ + High dose of AEBB	160.31±1.34**
STZ + Low dose of AEBB	151.3±2.1**
STZ + Glibenclamide	173.69±1.57**

The results were expressed as mean ± SD (n=6)
$^{ns}p>0.05$,**$p<0.01$ when compared to STZ treated negative control group.

Table 6 shows the Catalase activity in normal and diabetic rats.It shows that the catalase activity in diabetic rat was significantly decreased as compared to normal rats. Group III (High dose of MEBB),Group IV (Low dose of MEBB),Group V (High dose of AEBB),Group VI (Low dose of AEBB) showed significant increase in the catalase activity as compared to negative control group.

Table No.7 Glutathione contents (units/ mg protein) in rats with *Barleria buxifolia*

Groups	GSH
Normal control	240.48±2.57
Negative control	149.89±1.39**
STZ + High dose of MEBB	221.35±3.51**
STZ + Low dose of MEBB	197.08±1.63**
STZ + High dose of AEBB	217.61±1.1**
STZ + Low dose of AEBB	191.77±2.54**
STZ + Glibenclamide	228.31±1.17**

The results were expressed as mean ± SD (n=6)
$^{ns}p>0.05$,**$p<0.01$ when compared to STZ treated negative control group.

Table 7 shows the reduced glutathione activity in normal and diabetic rats.It shows that the reduced glutathione activity in diabetic rat was significantly decreased as compared to normal rats. Group III (High dose of MEBB),Group IV (Low dose of MEBB),Group V (

High dose of AEBB),Group VI (Low dose of AEBB) showed significant increase in the reduced glutathione activity as compared to negative control group.

DISCUSSION

Diabetes mellitus is a group of metabolic disorder in which person has high blood glucose ,either because the body does not produce enough insulin , or because cells do not respond to the insulin thai is produced. This high blood glucose produces the classical symptoms of polyphagia(increased hunger), polyuria (increased urination), polydipsia (increased thirst). There are three main types of to produce insulin, and presently requires the person to inject insulin or wear an insulin pump.[8] Type 1 diabetes is also called as " Insulin Dependant Diabetes Mellitus" (IDDM) or "Juvenile Diabetes". Type 2 DM results from insulin resistance , a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. Type 2 diabetes is also called as "Non Insulin Dependant Diabetes mellitus"(NIDDM) or "Adult- Onset Diabetes". The third main form, gestational diabetes occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level. [8]

Streptozotocin (STZ) and Alloxan (ALX) are the most frequently used drugs and this model has been useful for the study of multiple aspects of disease. Both drugs exert their diabetogenic action when they are administred parenterally(intravenously, intraperitoneally or subcutaneously). STZ has longer half-life (15 min against 1.5 min of alloxan).[9] This makes it more stable in solution before and after injection into animals. STZ-induced hyperglycemia is relatively more stable and for a longer duration (as much as three months compared to alloxan-induced hyperglycemia that can only be sustained for less than a month). Moreover, the mechanism of STZ diabetogenicity is less associated with cellular toxicity, hence, lesser animal mortality. Alloxan on the contrary, induces diabetes by a mechanism characterized by incidences of ketosis, ROS toxicity, and high mortality rate which is particularly a major setback in experimental diabetes studies.[10]

One reason for this is that STZ is more selective to islet beta cells than alloxan which causes severe damage to other cell types which express GLUT2 (systemic toxicity).[11]In addition, compared to alloxan, STZ diabetogenicity is not severely interfered with by blood glucose level. Overall, STZ diabetogenicity is more effective and with lesser variation with animal species.[12] So STZ induced diabetic model is preferred for the induction of diabetes in rat which is given intraperitoneally having dose 60 mg/kg.

Herbal medicine is one of the ancient therapies used by humanity.[13]During the recent years,people are eager to use herbal medicines due to their lower complications and fewer side effects than synthetic drugs.[14]The most common and effective antidiabetic medicinal plants of Indian origin are Babul (*Acasia arabica*),bael(*Aegle marmelose*),church steeples (*Agrimonia eupatorium*),onion(*Allium cepa*),garlic(*Allium sativum*),ghrita kumara (*Azardichta indica*) etc.[6]

Barleria buxifolia contains amino acid, alkaloids, anthroquinone, Phenol, Saponin, Terpenoids and Flavonoids.Hence this plant was selected for screening of Diabetes mellitus.[5]*Barleria buxifolia* minimised the increased blood glucose level, triglyceride and cholesterol level.

After treatment with Streptozotocin, there was significant increase in blood glucose level as compared to normal control groups. Treatment with *Barleria buxifolia* leaves shows significant reduction in blood glucose levels in dose dependant manner.
There was significant($p<0.01$) increase in the the level of serum triglyceride and cholesterol in the diabetic control rats compared to normal control rats. This study also reveals that *Barleria buxifolia* leaves extract decreases the level of Triglyceride and Cholesterol significantly when compared to negative control rats.

The results of the present study demonstrate that diabetic condition caused due to streptozotocin induce diabetes is associated with significant decrease of superoxide dismutase activity (SOD),Catalase and reduced glutathione indicating that free radicals are effectively involved in the development of diabetes.This study reveals that *Barleria buxifolia* leaves extract increase the level of superoxide dismutase activity (SOD),Catalase and reduced glutathione significantly when compared to negative control rats[15-22].
Hence,the results obtained in the present study indicated that *Barleria buxifolia* has potential to treat diabetes.

CONCLUSION

The present study was designed to evaluate the anti-diabetic potential of *Barleria buxifolia* based on its chemical constituent and its used as medicine for the control of diabetes.
The findings of research shows that the methanolic and aqueous extract of *Barleria buxifolia* may contains bioactive constituents with anti- diabetic potential which can be used for the treatment of diabetes mellitus

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