ISSN 0975-6299 Vol 2/Issue 1/ Jan-Mar 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

BIO CHEMISTRY

CAESALPINIA BONDUC (L.)ROXB AS A NOVEL DRUG HAVING HYPOGLYCEMIC EFFECT ON ALLOXAN INDUCED DIABETIC RATS

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ABSTRACT

Diabetes mellitus is a major endocrine disorder. Herbal treatments are becoming increasingly popular, as the herbal preparations have no or least side effects than synthetic hypoglycaemic drugs. Hence research has been focused on scientific evaluation of traditional hypoglycaemic drugs of plant origin. In our present study the methanolic extract of hyperglycaemic was investigated for its anti-hyperglycaemic activity at two different doses (100 mg/kg, 200mg/kg body weight hyperglycaemic on blood glucose, lipid profile and antioxidant levels in alloxan induced diabetic rats against standard drug Glibenclamide (600 µg/kg b.w). Results of biochemical estimations were reported as mean ± SD. It was conclude that from these studies the extract prepared from the leaves of *Caesalpinia bonduc (L.)Roxb* possess potential hypoglycaemic effects when compared with standard drug Glibenclamide. Even though both the concentrations showed varying degree of anti-hyperglycaemic activity, 200mg/kg b.w dosage showed better anti-hyperglycaemic activity.

KEYWORDS

Caesalpinia bonduc (L.)Roxb, antihyperglycaemia, antihyperlipidaemia, Diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a major disease characterized by derangement in carbohydrate, fat and protein metabolism. Besides hyperglycaemia several other factors like hyperlipidaemia and enhanced oxidative stress play a major role in diabetic pathogenesis. Although, a number of synthetic drugs are available in market diabetes and its related complications still remain uncontrolled. On the other hand medicinal plants have been used since ancient times to treat diabetes and its related complications[1]. Herbal drugs are prescribed widely because of their effectiveness, lesser side-effects and relative low cost even though their biologically active compounds are unknown[2].

Caesalpinia bonducella is known as Nata Karanja in Hindi and as fever nut, Bonduc Nut in English. The twigs and young leaves of *Caesalpinia bonducella* are traditionally used for the treatment of Diabetes, tumors, inflammation, and liver disorders[3]. In addition, various parts of this plant has been reported to possess multiple therapeutic properties like antidiabetic, antipyretic, antidiuretic, anthelmintic, antibacterial, anticonvulsant, antiviral, antiasthmatic, antiamoebic, and antiestrogenic activities[4]. All parts of the plant have medicinal properties[5].

METHOD AND MATERIALS

(i) *Procurement of animals*:

Male wistar albino rats (140 – 160g) used were purchased from animal house Bangalore, were maintained under standard conditions, fed with a standard diet (Hindustan Lever, India) and water *ad libitum.* The experiments were designed as per guidelines of institutional ethical committee.

(ii) Procurement of diagnostic kits:

Diagnostic kits used for the estimation of Glucose, Cholesterol, Triglyceride and Total Protein were obtained from Agappe Diagnostics, Maharashtra, India.

(iii) *Procurement of Diabetic inducer and induction*:

Alloxan monohydrate was used as the diabetes inducer in rats and was procured from the National chemicals Pvt. Ltd, New Delhi. The solution was made in distilled water and administered as a single dose (150 mg/kg b.w, i.m) [6].

(iv) Preparation of Methanolic Extract of Caesalpinia bonduc (L.) Roxb:

Caesalpinia bonduc (L.) Roxb plant materials were collected from Tiruchirappalli, Tamilnadu, India. The leaves were dried at 45°C for 48 hours, powdered and used for extraction with 50 ml of 99.9% of hot methanol. The methanol mixture were evaporated at 55^{o}C and used for further studies. The extract was administered in different dose (100 & 200mg/kg b.w) by oral gavages to the rats[7].

(v) Procurement of antidiabetic drug:

Glibenclamide was used to treat diabetes and was procured from Aventis Pharma Limited, Goa and was administered with the dosage of 600µg/kg b.w[8]

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(vi) Experimental Design:

The rats were divided into 5 groups (n = 6). Group I served as a control received 0.9% saline. Alloxan was administered as a diabetic inducer except to control (Group I). Group II was alloxan induced diabetic rats. Group III and IV received methanolic extracts of

Caesalpinia bonduc (L.) Roxb. (100mg, and 200mg /kg b.w respectively). Group V received standard drug Glibenclamide.

(vii) Study protocol:

The standard and test formulations were administered for 21 days using oral gavages once in a day. At the end of experiment, rats were sacrificed by cervical decapitation. Blood was collected to separate the serum and plasma. The pancreatic tissue was dissected out, weighed and washed using ice cold saline solution. The resulting supernatant was used for various biochemical assays. The biochemical assays were carried out in semi automated analyzer ERBA CHEM 5.

(viii) Measurement of Blood Glucose levels and Serum Lipids:

The body weight was measured at the beginning and at the end of the experiment. Blood glucose level was determined using a GOD - PAP method[9]. Glycosylated haemoglobin (GHb) was determined[10]. Serum Cholesterol level was determined using the method of Allain CC *et al*.,[11] , HDL - Cholesterol by Steele BW *et al*.,[12] , triglyceride by Bucolo[13]. LDL and VLDL were calculated using the following formulae: LDL cholesterol = Total cholesterol – HDL + (TG/5) and VLDL cholesterol was calculated using the formula (TG/5).

(ix) Estimation of TBARS and Antioxidants:

TBARS in pancreatic tissue was estimated by the method of Nichans and Samualson[14], Superoxide dismutase (SOD) activity by the modified method of Kakkar *et al.,* [15], Catalase (CAT) by Sinha[16] , Reduced glutathione (GSH) by Ellman[17] and Vitamin C (ascorbic acid) by Omaye *et al.*,[18].

(x) Statistical analysis:

All results were expressed as Mean ± S.D. Student 't'test was performed using SPSS soft ware.

RESULTS AND DISCUSSION

Antihyperglycaemic Effect:

Conventional treatment for diabetes poses economic burden and also produce potentially undesirably side effects on long term usage. Management of diabetes mellitus without any side effects is still a challenge to the medical system[19]. In the light of above concept we have selected *Caesalpinia bonduc (L.)Roxb , a* traditional herbal plant to evaluate its hypoglycaemic effects and to compare it with standard drug glibenclamide for its efficacy**.**

The body weight of alloxan-induced diabetic rats was significantly reduced ($p<0.05$). Loss of body weight is one of the symptoms of diabetes due to loss of tissue proteins caused by insulin deficiency[20]. Protein synthesis is decreased in all tissues due to relative deficiency of insulin (an anabolic hormone) [21]. There was significant increase on body weight in *Caesalpinia bonduc(L.)Roxb* treated alloxan-induced diabetic rats ($p<0.05$). The ability of the *Caesalpinia bonduc(L.)Roxb* to protect from maximum body weight loss seems to be due to its ability to reduce hyperglycaemia. Leaf extract of *Caesalpinia bonduc(L.)Roxb* prevented lipolysis and proteolysis by ameliorating the extent of insulin deficiency and thereby caused an increase in body weight[22]. The results of extract of *Caesalpinia bonduc(L.)Roxb* on bodyweight of was comparable with standard drug Glibenclamide and was dose dependent.

Blood glucose level was significantly increased (314.78%) as expected in alloxan-induced diabetic animals ($p<0.001$). Oral administration of *Caesalpinia bonduc(L.)Roxb* (100 & 200mg/kg b.w) (50.52%, 54.43%) and standard drug Glibenclamide (600µg/kg b.w) (46.82%) resulted in a significant reduction of blood glucose ($p<0.001$). The GHb level was also significantly elevated ($p<0.001$) in alloxan-induced diabetic rats showing that the diabetic animals had high blood glucose level. On

administration of *Caesalpinia bonduc(L.)Roxb* the level of GHb was significantly decreased (p<0.001) in dose dependent manner. (TableI)

TABLE I

Effect Of Caesalpinia Bonduc(L.)Roxb On Glucose And Glycosylated Haemoglobin Level

Parameters	Group I	Group II	Group III	Group IV	Group V
Glucose (mg/dl)	86.25 ± 8.03	357.75 ± 10.01* 314.78%	177 ± 3.91** 50.52%	163 ± 8.52** 54.43%	190.25 ± 4.11** 46.82%
G.Hb (g/dl)	5.62 ± 0.25	11.52 ± 0.25* 104.92%	6 ± 0.62** 47.91%	5.8 ± 0.43** 49.65%	6.52 ± 0.35** 43.40%

*Values are means ± S.D n = 6, *P< 0.001 group I Vs group II, ** P<0.001 group II Vs group III,IV,V*

Sharma *et al*.,[23] have reported the hypoglycaemic properties of the *Caesalpinia bonducella* in normal as well as alloxan induced diabetic rats. The leaf juice of *Caesalpinia bonduc(L.)Roxb* have been traditionally used in diabetes. The anti hyperglycaemic action of the extract may be due to blocking of glucose absorption. The drug has potential to act as antidiabetic agent[24].

The antidiabetic effect of *Caesalpinia bonduc (L.) Roxb* extract could be linked to more than one mechanism. According to the studies by Kumar *et al*.,[25] the leaf extract of *Caesalpinia bonduc(L.)Roxb* caused an increase in glycogen concentration of the liver probably by stimulating the enzymes glycogen synthase and hexokinase, both of which contribute to increase glycogen synthesis.

Nikoulina *et al*.,[26] reported that diminished phosphatidylinositol 3-kinase (PI-3K) activation in diabetes which is due insulin deficiency and has been reported to be associated with impaired skeletal muscle glycogen synthase enzyme. Davis[27] observed that the leaf extract of *Caesalpinia bonduc (L.)Roxb* increased PI-3K activation leading to stimulation of muscle glycogen synthase. The increased concentration of glycogen in skeletal and cardiac muscle also might be due to increased expression and translocation of GLUT-4 (glucose transporter) as a result of increased PI-3K activation, leading to increased peripheral uptake of glucose.

The antidiabetic activity of *Caesalpinia bonduc(L.)Roxb* might be attributed to the presence of flavonoids, known to be natural antioxidants, which protect the existing ß -cells (which escaped alloxanization) from dying by their free radical scavenging action[28]. Katbamna *et al.,*[29] reported the presence of many phytoconstituents including saponines in leaf extract of *Caesalpinia bonduc(L.)Roxb.* Thus the saponines present in the *Caesalpinia bonduc(L.)Roxb* might contribute to its anti hyperglycaemic action.

(i) Antilipidaemic effect:

In alloxan-induced diabetes, the increase in blood glucose level is usually accompanied by an increase in plasma cholesterol, triglycerides, LDL and VLDL and decrease in HDL. Excess fatty acids in the plasma produced by the alloxan-induced diabetes promote the conversion of fatty acids into phospholipids and cholesterol in the liver in the form of lipoproteins in blood[30].

In our present study, a significant increase (p<0.001) in cholesterol, triglycerides, LDL, VLDL and decrease in HDL levels were observed in alloxan induced diabetic rats. There was a significant reduction (p<0.001) in the levels of total cholesterol, triglycerides, LDL, VLDL and increase in the level of HDL

cholesterol in *Caesalpinia bonduc(L.)Roxb* treated groups. (Table II)

Table II
Effect Of Caesalpinia Bonduc(L.)Roxb On lipid profile

Parameters	Group I	Group II	Group III	Group IV	Group V
Total Cholesterol (mg/dl)	93.25 ± 3.30	245 ± 4.32* 162.73%	155 .25± 2.5** 36.63%	142.25 ± 2.62** 41.94%	175 ± 3.16** 28.57%
Triglyceride (mg/dl)	113.25 ± 4.57	191.75 ± 4.42* 69.31%	153.5 ± 4.50** 19.94%	145 ± 2.94** 24.38%	175.25 ± 2.5** 8.60%
HDL (mg/dl)	43.25 ± 4.78	24.5 ± 2.28* 43.35%	35 ± 2.16ns 42.85%	38.25 ± 4.27ns 56.12%	32 ± 3.16** 30.61%
LDL (mg/dl)	27.25 ±6.55	182.25 ± 6.18* 568.80%	89.5 ± 3.51 ns 50.89%	75 ± 2.44 ns 58.84%	83 ±48.2 ns 54.45%
VLDL (mg/dl)	64.25 ± 3.30	38.35 ± 0.88* 40.31%	30.7 ± 0.84** 19.94%	29 ± 0.58** 24.38%	35.05 ± 0.5** 8.60%

*Values are means ± S.D n = 6, *P<0.001 group I Vs group II, ** P<0.001 group II Vs group III,IV,V: ns- not significant*

Administration of *Caesalpinia bonduc(L.)Roxb* extract to diabetic animals normalizes blood glucose concentration and reduces triglyceride levels. Oral administration of saponins from some medicinal plants significantly reduced the triglycerides and cholesterol levels in rat. The usage of diet with high saponins contents was also suggested to reduce heart diseases[31]. The observed significant increase in the level of HDL and decrease in other lipoproteins might be due to the saponines present in *Caesalpinia bonduc(L.)Roxb ,* thus showing the cardio protective activity of the herbal plant.

The results demonstrated that the aqueous extracts of *Caesalpinia bonduc(L.)Roxb* induced a significant decrease of plasma cholesterol levels in alloxan induced diabetic rats.

From the study it was interpreted that the *Caesalpinia bonduc(L.)Roxb* has hypolipidaemic activity. Some studies have reported a similar hypolipidaemic activity of medicinal plants[32]. Kannur *et al*.,[24] in his study reported that the seed extracts of *Caesalpinia bonduc (L.)Roxb* has antidiabetic as well as antihyperlipidaemic effect.

(ii) Antioxidant effect:

An imbalance between antioxidants and reactive oxygen species (ROS) results in oxidative stress, leading to cellular damage. Lipid peroxidation, an autocatalytic free radical chain propagating reaction, is known to be associated with pathological conditions and metabolic derangement of the cell[33]. In the present study

the level of TBARS (Table III) in alloxan-induced animals was significantly increased ($p < 0.001$) and the level of SOD,CAT, VIT C, GSH, were decreased ($p < 0.001$) when compared to normal. *Caesalpinia bonduc(L.)Roxb* reduced the level of TBARS in diabetic animals and increased the level of SOD, CAT, VIT C, and GSH when compared to alloxan induced group .

which might be due to its antioxidant and the free radical quenching property of the phytoconstituents of *Caesalpinia bonduc(L.)Roxb.* The results are comparable with the standard drug. The administration of *Caesalpinia bonduc(L.)Roxb* at different doses significantly increased the SOD, CAT, VIT C, and GSH levels in a dose dependent manner

Table-III

Effect Of Caesalpinia Bonduc(L.)Roxb On TBARS and Antioxidants

Parameters	Group I	Group II	Group III	Group IV	Group V
LPO mM/100 g wet tissue	0.75 ± 0.0.03	1.01 ± 0.06* 34.66%	0.84 ± 0.04^{ns} 16.83%	0.79 ± 0.02^{ns} 21.78%	0.90 ± 0.03^{ns} 10.89%
SOD units/mg protein.	47.75 ± 3.5	21.75 ± 2.5^{ns} 54.45%	35.5 ± 2.88^{ns} 63.21%	43 ± 5.16** 97.70%	30.25 ± 4.11^{ns} 39.08%
CAT μM of H_2O_2 consumed / min / mg protein.	35.45 ± 0.28	15.7 ± 0.43* 55.71%	28.42 ± 0.87** 81.01%	31.67 ± 0.46** 101.72%	22.77 ± 0.40** 45.03%
GSH mg/100 g of tissue	55.75 ± 2.98	2.757 ± 3.09* 50.22%	45 ± 3.65** 62.16%	51.5 ± 4.79** 85.58%	40.25 ±1.5** 45.04%
Vitamin C μM/mg tissue.	3.97 ± 0.26	2.6 ± 0.18^{ns} 85.89%	3.2 ± 0.25^{ns} 23.07%	3.6 ± 0.29** 38.46%	2.92 ± 0.17^{ns} 12.30%

*Values are means ± S.D n = 6, * P<0.001 group I Vs group II ; ** P<0.001 group II Vs group III,IV,V:ns- not significant*

Phytochemical analysis of *Caesalpinia bonduc(L.)Roxb* by Gaur *et al.,*[34] has revealed the presence of alkaloids, flavonoids, glycosides, saponins, tannins and triterpenoids. Many flavonoids may help to provide protection against these diseases by scavenging ROS along with antioxidant vitamins and enzymes. The leaf of *Caesalpinia bonduc(L.)Roxb* also contain phenolic compound called Brazilin and Bonducin[35].

Previous studies have reported that triterpenoids (lupeol), present in the *Caesalpinia bonduc(L.)Roxb*, have the ability to protect cells and tissues from oxidative stress by increasing the activity of catalase and superoxide dismutase, etc.[36] Glutathione, a potent inhibitor of the neoplastic process, plays an important role in the endogenous antioxidant system. It is found in high concentration particularly in liver and is known to have a key function in the protective process.[37] The results suggested the antioxidant property of *Caesalpinia bonduc(L.)Roxb.*

(iii) Acute Toxicity Test:

There was no mortality recorded among the rats upto the maximum dose of 500 mg/kg b.w.

CONCLUSION

In present study the results showed that even though both the concentrations of *Caesalpinia bonduc(L.)Roxb* had varying degree of anti-hyperglycemic, Antilipidaemic and antioxidant activity, 200mg/kg b.w showed better results.

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