ANTIDIABETIC AND HYPOLIPIDEMIC ACTIVITY OF METHANOLIC EXTRACT OF SPHAERANTHUS INDICUS IN ALLOXAN INDUCED DIABETIC RATS

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ABSTRACT
Diabetes mellitus is a complex and a multifarious group of disorders that disturbs the metabolism of carbohydrates, fat and protein. In the present study methanolic extract of whole plant of Sphaeranthus indicus was screened for hypoglycemic, antidiabetic and hypolipidemic activities. Fasting normal rats treated with the methanolic extract of Sphaeranthus indicus showed significant improvement in oral glucose tolerance test. Sphaeranthus indicus was administered to alloxan (150 mg/kg b. w) induced diabetic Wistar rats at 300 mg/kg b.w for 21 days. The methanolic extract of Sphaeranthus indicus showed significant antidiabetic activity (p<0.01) when compared to diabetic rats and in addition, oral administration of Sphaeranthus indicus 300 mg/kg b. w significantly decreased glycosylated hemoglobin (HbA1c), serum total cholesterol, triglyceride and at the same time markedly increased HDL-cholesterol and magnesium levels. Sphaeranthus indicus also restored the altered body weight to near normal. Glipizide (5 mg/kg b.w) was used as a reference standard. Results of this experimental study indicated that Sphaeranthus indicus possess hypoglycemic, antidiabetic and hypolipidemic activities and hence it could be used as a drug for treating diabetes.

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INTRODUCTION

Diabetes is a serious illness with multiple complications and premature mortality, accounting for at least 10% of total health care expenditure in many countries\(^1\). The prevalence of diabetes for all age-groups worldwide is projected to rise from 382 million in 2013 to 592 million in 2035\(^2\). According to a recent report in India more than 62 million people have diabetes in the year 2011, representing 30% of the Indian population. By 2030, it is expected to cross the 100 million mark. Persons with undiagnosed diabetes or IGT are known at high risk of cardiovascular disease\(^3\).

Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides, glucosidase inhibitors which are used as monotherapy or in combination to achieve better glycaemic regulation. Many of these oral antidiabetic agents have a number of serious adverse effects\(^3\). Thus, the management of diabetes without any side effects is still a challenge. There is a growing interest in herbal remedies, the use of medicinal plants for the treatment of diabetes mellitus dates back from the Ebers papyrus of about 1550 B.C. A multitude of herbs, spices and other plant materials have been described for the treatment of diabetes throughout the world\(^4\). Because of perceived effectiveness, minimal side effects in clinical experience and relatively low cost, herbal drugs are widely prescribed even when their biologically active compounds are unknown.

In the present study, \textit{Sphaeranthus indicus} was selected. \textit{Sphaeranthus indicus} Linn belongs to family \textit{Asteraceae}. The plant is commonly known as \textit{Gorakhmundi} in Hindi. It is an annual spreading herb, which grows approximately 15-30 cm in height. The plant is distributed throughout the plains and wet lands in India, Sri Lanka and Australia\(^5\). All the parts of the plant have medicinal uses. The plant is known to possess varied medicinal properties and is reportedly used in ayurvedic preparations for treating epileptic convulsions, mental illnesses and hemicranias. It is used to treat vitiated conditions of jaundice, diabetes, leprosy, fever, pectoralgia, cough, gastropathy, hernia, haemorrhoids, helminthiasis, dyspepsia, skin diseases and as a nerve tonic\(^6\). The oil prepared from the plant root is reported to be useful in treating scrofula and as an aphrodisiac, while the external application of the herb paste is reported to be beneficial in treating pruritus, oedema, arthritis, filariasis, gout and cervical adenopathy\(^7\). A large number of constituents have been isolated from extracts of the whole herb, flowers and leaves. The essential oil, obtained by steam distillation of the whole herb, contains ocimene, \textit{a}-terpinene, methyl-chavicol, \textit{a}-citral, geraniol, \textit{a}-ionone, \textit{b}-ionone, \textit{d}-cadinene, \textit{p}-methoxy-cinnamaldehyde and an alkaloid sphaeranthine\(^8\). The alcoholic extract of powdered capitulum contains stigmastanol, \textit{b}-sitosterol, hentriacontane, sesquiterpene lactone, sesquiterpine glycoside, sphaeranthanolide\(^9\), flavone and isoflavone glycosides\(^10\). Many medicinal properties have been attributed to the extracts, fractions and isolated constituents of \textit{S. indicus}, including hypotensive, peripheral vasodilatory and cathartic, antimicrobial activity. Essential oil obtained from leaves possesses antifungal properties. Herbal cosmetic creams containing the extract of \textit{S. indicus} have been used for the treatment of dermal wounds\(^11\).

Meanwhile, in diabetics, oxidative stress has been found to be mainly due to an increased production of oxygen free radicals and a sharp reduction of antioxidants defenses and the tissue antioxidant status were an important factor in the development of diabetic complications. On the other hand, a variety of antioxidants scavenges free radicals and prevents oxidative damage to biological structures.

In the present study, methanolic extract of whole plant of \textit{Sphaeranthus indicus} was screened for \textit{in-vitro} antioxidant assay, antidiabetic assay, hypoglycemic, antihyperglycemic, hypolipidemic activities and effect on magnesium and change in body weights were also measured.

MATERIALS AND METHODS

Plant material and preparation of extract

The whole plant of \textit{Sphaeranthus indicus} (\textit{Asteraceae}) was collected from Vechareni, Warangal district, Telangana (India) in the month of January, 2014 and was identified and authenticated from Botany department of Osmania University Hyderabad. The plant material was cleaned, made into small pieces, dried in shade and coarsely powdered and stored. The coarsely powdered plant material (500g) was subjected to extraction with methanol using simple distillation. The extract was concentrated to semisolid mass and stored in air tight containers.

Acute toxicity testing

Studies were carried out in order to check the toxic effects of the extracts. The study was performed as per Organization for Economic Cooperation and Development (OECD) guidelines no 425. Mice were used for this purpose. The animals were fasted overnight, providing only water, after which the extract was administered to the respective groups orally at the dose level of 2000 mg/kg b. w. by gastric intubation and the groups were observed continuously for 24 h for behavioral, neurological and autonomic profiles, and then at 24 h and 72 h for any lethality. The animals were further observed for toxic symptoms for 14 days. According to the guidelines if mortality is observed in 2 or 3 animals, then the dose administered is assigned as a toxic dose. If mortality is observed in one animal, then the same dose is repeated again to confirm the toxic dose. If mortality is not observed at all, the plant extract is considered as non-toxic. Alternatively, the toxicity test is started with a dose of 1000 mg/kg b. w. and repeated for further other doses such as 1500, 2000 and finally 3000 mg/kg b.w.\(^12\).

Dose selection studies

Dose selection studies were performed at hourly basis for 12 hours to determine the optimum dose which reduces the percentage blood glucose levels by 30-40 %\(^13\).
In-vitro antioxidant assays for methanolic extract of Sphaeranthus indicus

DPPH radical scavenging activity

The hydrogen donating ability of extracts was examined in the presence of DPPH stable radical. One milliliter of 0.3 mM DPPH methanolic solution was added to 2.5 mL of test solution of different concentrations and allowed to react at room temperature. After 30 minutes, the absorbance values were measured at 517 nm. Methanol (1.0 mL) and plant extract solution (2.5 mL) was used as blank, DPPH solution (1.0 mL, 0.3 mM) and methanol (2.5 mL) served as negative control. Ascorbic acid was used as standard. Ascorbic acid was used as standard. The results were expressed as the percentage inhibition of NBT.

NBT reduction assay

A reaction mixture (3 mL) per tube was prepared with 1.4 mL of 50 mM KH₂PO₄-KOH pH 7.4 containing 1 mM EDTA, 0.5 mL of 100 µM hypoxanthine, 0.5 mL of 100 µM NBT. The reaction was started by adding 0.066 units per tube of xanthine oxidase freshly diluted in 100 µL of phosphate buffer and 0.5 mL of test extract in saline. The subsequent rate of NBT reduction was determined by spectrophotometric method at 560 nm. Gallic acid was used as standard. The results were expressed as the percentage inhibition of NBT.

In-vitro antidiabetic assays of methanolic extract of Sphaeranthus indicus

In-vitro Alphaamylose inhibitory activity

The Alpha-amylase inhibitory assay was carried out by following the standard protocol. In a tube containing 0.2 mL of 0.5 M Tris-HCl buffer (pH 6.9) and 0.01 M calcium chloride (substrate), starch azure (2 mg) was suspended. Then tube was boiled for 5 minutes and pre incubated at 37°C for 5 minutes. 1 mL of 0.1% of gum acacia was used to dissolve 1 mg of dried plant extracts in order to obtain different concentrations of extract from which 0.2 mL of plant extracts of a particular concentration was added in the tube containing the substrate solution. Then in above solution 0.1 mL of porcine pancreatic amylase in Tris-HCl buffer (2 units/mL) was added. The process was carried out at 37°C for 10 minutes. The reaction was stopped by adding 0.5 mL of 50% acetic acid in each tube and the reaction mixture was then centrifuged at 3000 rpm for 5 minutes at 4°C. The absorbance of resulting supernatant was measured at 595 nm using UV spectrophotometer.

In-vitro Alpha-glucosidase inhibitory activity

The enzyme α-glucosidase inhibitory activity of Sphaeranthus indicus was determined by incubating solution (0.1 mL) of an enzyme preparation with 0.2 M Tris buffer, pH 8.0 (1.0 mL) containing different concentrations of methanolic extract at 37°C for 60 minutes by using glucose as working standard. The reaction mixture was heated for two minutes in boiling water bath to stop the reaction. The amount of liberated glucose was measured by glucose oxidation method. (Assay condition 37°C±0.1°C, pH-8.0; O.D at 540 nm). Same protocol was repeated thrice.

Animals

Healthy adult Wistar Albino rats of 180-250 g of either sex were selected for the study. The animals were obtained from Gentox laboratories, Hyderabad. The animals were housed in standard cages and kept under standard condition according to CPCSEA guidelines. They were given a standard diet and water ad libitum. The ethical clearance was obtained from Institutional Animal Ethics Committee (IAEC) before the experiment.

Evaluation of antidiabetic activity of Sphaeranthus indicus

Effect of Methanolic extract of Sphaeranthus indicus on glucose tolerance in rats

Healthy Wistar Albino rats were selected and randomly divided into two groups (n=6). Group ‘I’ serves as normal control receiving distilled water, Groups ‘II’, serves as test groups receiving methanolic extract at 300 mg/kg b.w. After an hour of extract administration, glucose (2.0 g/kg b.w. p.o.) was administered to group-II. Blood was withdrawn from the retro orbital plexus at 60, 90, 120 and 150 minutes. The blood glucose level was estimated using GOD-POD method.

Effect of Methanolic extract of Sphaeranthus indicus in diabetic rats

Diabetes was induced with alloxan (150 mg/kg b.w. i.p. given on two consecutive days) in healthy wistar albino rats. After the injection animals had free access of food and 0.5% glucose solution overnight to prevent from hypoglycemic shock. Diabetes was induced within 48 hours of administration of alloxan. The animals were kept for a stabilization period of 7 days and the animals with blood glucose levels above 350 mg/dL were selected for present the study.

Healthy Wistar Albino rats were selected and randomly divided into four groups (n=6). Group ‘I’ serves as normal control receiving distilled water, group ‘II’ serves as diabetic control which also receives distilled water, groups ‘III’ serves as test group receiving 300 mg/kg b.w. of the extract and group ‘IV’ serves as standard group receiving glipizide (5 mg/kg b.w.) The extract was administered orally for 21 days, once daily. Blood samples were withdrawn from retro orbital plexus on 0th, 7th, 14th and 21st day of extract administration. The blood glucose levels were estimated.

Effect of Methanolic extract of Sphaeranthus indicus on serum lipid profile

All the rats were bled after 21 days of treatment. Blood was collected into tubes and the serum was separated by centrifugation. Lipid levels like cholesterol, triglycerides and HDL levels were estimated by using semi auto analyser.
Estimation of body weights

Body weights of all the animals were measured on the initial day of the study and after 21 days of treatment final body weights were measured and effect of S. indicus was determined[18].

Determination of serum magnesium levels and glycosylated haemoglobin

Serum magnesium levels were estimated by the method of Garfinkel[19] and glycosylated haemoglobin was estimated by the method of Shirwaikar[20].

Statistical analysis

All the data are expressed as mean±SEM. Statistical data was evaluated by one-way analysis of variance, followed by Dunnett’s t-test for multiple comparisons. p<0.01 was considered as highly significant[18].

RESULTS AND DISCUSSION

Effect of methanolic extract of Sphaeranthus indicus on in-vitro antioxidant assays

Methanolic extract of Sphaeranthus indicus showed DPPH radical scavenging and NBT activity with IC_{50} value 7.2 and 60 when results were compared with standard ascorbic acid (IC_{50} value 4.15) and gallic acid (IC_{50} value 3) respectively (Table no. 1).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>DPPH radical scavenging assay IC_{50} (µg/mL)</th>
<th>NBT inhibition assay IC_{50} (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanolic extract of S. indicus</td>
<td>7.2</td>
<td>60</td>
</tr>
<tr>
<td>Ascorbic acid (standard)</td>
<td>4.15</td>
<td>-</td>
</tr>
<tr>
<td>Gallic acid (standard)</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

Effect of methanolic extract of Sphaeranthus indicus for in-vitro antidiabetic assays

The crude methanolic extract of Sphaeranthus indicus also showed good inhibitory activity for alpha-amylase and alpha-glucosidase with the IC_{50} value of 50 and 8 as compared to standard acarbose having IC_{50} value 3 (Table no. 2).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Alpha amylase inhibitory assay IC_{50} (µg/mL)</th>
<th>Alpha glucosidase inhibitory assay IC_{50} (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanolic extract of S. indicus</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>Acarbose (standard)</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Acute toxicity studies

The oral administration of methanolic extract of Sphaeranthus indicus did not exhibit any signs of toxicity and mortality even upto 3000 mg/kg b. w. of extract.

Dose selection studies in normal rats

In dose selection studies, 300 mg/kg b. w. was found to reduce the percentage blood glucose levels by 37% after 3^rd^ h, which is in between 30-40% and serves the criteria. Hence, 300 mg/kg b. w. has been selected for the chronic study (Table no. 3).

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Percentage glucose reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SEM (100 mg/kg)</td>
</tr>
<tr>
<td>0</td>
<td>0.00±0.00</td>
</tr>
<tr>
<td>1</td>
<td>04.26±1.2</td>
</tr>
<tr>
<td>2</td>
<td>14.22±1.14</td>
</tr>
<tr>
<td>3</td>
<td>22.25±1.56</td>
</tr>
<tr>
<td>4</td>
<td>18.83±1.83</td>
</tr>
<tr>
<td>6</td>
<td>15.44±1.72</td>
</tr>
<tr>
<td>8</td>
<td>12.18±1.68</td>
</tr>
<tr>
<td>10</td>
<td>08.06±0.87</td>
</tr>
<tr>
<td>12</td>
<td>05.8±0.96</td>
</tr>
</tbody>
</table>
Hypoglycemic effect of methanolic extract of Sphaeranthus indicus on oral glucose tolerance in normal rats

Methanolic extract of Sphaeranthus indicus has shown significant hypoglycemic activity (p<0.01, p<0.05) in glucose loaded animals at the dose of 300 mg/kg b.w. Blood glucose level was reduced to 70 mg/dL from 95 mg/dL at 3 h. When results were compared to normal control rats over the 5-h period (Table no. 4).

Table 4: Effect of methanolic extract of Sphaeranthus indicus 300 mg/kg b. w. on oral glucose tolerance in normal rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Blood glucose levels (mg/dL)</th>
<th>0 h</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
<th>5 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Control</td>
<td>96±1.14</td>
<td>95±1.12</td>
<td>93±0.62</td>
<td>94±1.41</td>
<td>97±1.25</td>
<td>99±1.33</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>S. indicus</td>
<td>95±1.43&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90±0.54&lt;sup&gt;b&lt;/sup&gt;</td>
<td>86±1.23&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70±1.61&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75±0.95&lt;sup&gt;a&lt;/sup&gt;</td>
<td>87±2.32&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM, (n=6). Test group was compared with vehicle control. Significant values are expressed as a=p<0.01, b=p<0.05 and ns=non significant.

Evaluation of antidiabetic effect of methanolic extract of Sphaeranthus indicus in alloxan induced diabetic rats

The methanolic extract of S. indicus at a dose of 300 mg/kg b. w. has the capacity to significantly (p<0.01) lower the elevated blood glucose levels when compared to diabetic control rats (Table no. 5). There are two possible reasons for hypoglycemic and antidiabetic effect of S. indicus. Firstly in vitro studies indicated that, the extract possess significant antidiabetic activity by inhibiting α-amylase and α-glucosidase enzymes. Further the phytochemical studies of S. indicus have revealed the presence of sterols, phenols and flavonoids of which flavonoids were reported to have a major role in reducing oxidative stress associated with diabetes, which in turn helps in the regulation of plasma glucose concentration <sup>[20]</sup> (Table no. 5).
Table 5: Effect of methanolic extract of *Sphaeranthus indicus* 300 mg/kg b. w in alloxan induced diabetic rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Blood glucose levels (mg/dL)</th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Vehicle control</td>
<td></td>
<td>89±1.25</td>
<td>87±1.48</td>
<td>87±2.01</td>
<td>89±1.25</td>
</tr>
<tr>
<td>II</td>
<td>Diabetic control</td>
<td></td>
<td>254±2.27</td>
<td>256±2.55</td>
<td>257±3.18</td>
<td>259±2.08</td>
</tr>
<tr>
<td>III</td>
<td><em>Sphaeranthus indicus</em></td>
<td></td>
<td>230±8.82</td>
<td>199±7.81</td>
<td>174±7.50</td>
<td>109±2.52</td>
</tr>
<tr>
<td>IV</td>
<td>Glipizide</td>
<td></td>
<td>223±2.54</td>
<td>175±3.34</td>
<td>156±2.63</td>
<td>97±0.58</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM (n=6). Test group was compared with all the other groups. Significant values are expressed as (a=p<0.01, when compared with vehicle control) (**=p<0.01, when compared with diabetic control) (#=p<0.05 and ns=non significant, when compared with standard).

Figure 3: Effect of methanolic extract of *Sphaeranthus indicus* 300 mg/kg b. w in alloxan induced diabetic rats.

**Effect of methanolic extract of *Sphaeranthus indicus* on serum lipid levels in alloxan induced diabetic rats**

The methanolic extract of *Sphaeranthus indicus* was tested for lipid lowering properties and results were reported in Table 6. The administration of the extract to the alloxan induced diabetic rats significantly (p<0.01) improved the above parameters. The observed hypolipidemic effect may be because of decreased cholesterogenesis and fatty acid synthesis (Table no. 6).

Table 6: Effect of *Sphaeranthus indicus* on lipid levels in diabetic rats after 21 days.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total cholesterol (mgdL⁻¹)</th>
<th>HDL cholesterol (mgdL⁻¹)</th>
<th>Triglycerides (mgdL⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle control</td>
<td>109±6.71</td>
<td>46±1.63</td>
<td>85±1.98</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>147±4.99</td>
<td>30±0.92</td>
<td>118±4.06</td>
</tr>
<tr>
<td><em>Sphaeranthus indicus</em></td>
<td>125±1.83</td>
<td>38±2.56</td>
<td>103±2.70</td>
</tr>
<tr>
<td>Glipizide</td>
<td>109±2.32</td>
<td>40±1.94</td>
<td>90±1.48</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM (n=6). Test group was compared with all the other groups. Significant values are expressed as (a=p<0.01 and b=p<0.05, when compared with vehicle control) (**=p<0.01 and *=p<0.05, when compared with diabetic control) (#=p<0.05 and ns=non significant, when compared with standard).

**Effect of *S. indicus* on glycosylated haemoglobin (HbA1c), magnesium levels and body weight in alloxan induced diabetic rats**

Glycosylated haemoglobin increases in patients with diabetes mellitus. In diabetes, protein synthesis is decreased in all tissues because of the relative insulin deficiency and thus the synthesis of haemoglobin is also suppressed[21]. The administration of the extract to the alloxan induced diabetic rats significantly (p<0.01) lowered the glycosylated haemoglobin when compared with diabetic control (Table no. 7).

Magnesium is an important component of many unprocessed foods, such as whole grains, nuts and green leafy vegetables and it is largely lost during the processing of some foods. Hypomagnesaemia is common in patients with type 2 diabetes. Although diabetes can induce hypomagnesaemia, magnesium deficiency has also been proposed as a risk factor for type 2 diabetes.
Table 7: Effect of *Sphaeranthus indicus* on glycosylated haemoglobin (HbA1c), magnesium levels and body weight in diabetic rats after 21 days.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glycosylated haemoglobin(%)</th>
<th>Magnesium levels(mEq/L)</th>
<th>Body weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial day</td>
<td>Final day</td>
</tr>
<tr>
<td>Vehicle control</td>
<td>3.36±0.08</td>
<td>≥80.09</td>
<td>203±7.61</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>6.78±0.22</td>
<td>≥2.0.13</td>
<td>206±5.39</td>
</tr>
<tr>
<td><em>Sphaeranthus indicus</em></td>
<td>4.46±0.10</td>
<td>≥2.0.11</td>
<td>200±7.53</td>
</tr>
<tr>
<td>Glipizide</td>
<td>3.88±0.17</td>
<td>≥2.0.07</td>
<td>203±9.01</td>
</tr>
</tbody>
</table>

Magnesium is a necessary cofactor for several enzymes that play important roles in glucose metabolism. Animal studies have shown that magnesium deficiency has a negative effect on the post-receptor signalling of insulin. Some short-term metabolic studies suggest that magnesium supplementation has a beneficial effect on insulin action and glucose metabolism. Animals treated with the test extracts and glipizide showed a good improvement in serum magnesium levels (Table no. 7).

At the end of 21 days treatment, the body weight of normal rats, methanolic extract and standard drug treated group, increased significantly (P<0.01) whereas the body weight of diabetic control group has been decreased (Table no. 7).

**CONCLUSIONS**

The present investigation revealed that methanolic extract of *Sphaeranthus indicus* have shown potent antioxidant, hypoglycemic and antihyperglycemic activity. Methanolic extract of *Sphaeranthus indicus* at dose of 300mg/kg b.w. can be used in the treatment of Diabetes Mellitus. Further studies are being carried out to isolate the pure active constituents responsible for activity and to elucidate the exact mechanism of action for hypoglycemic and antihyperglycemic activity.

**REFERENCES**


