Introduction

Diabetes mellitus is a disease characterized by disordered metabolism and abnormally high blood sugar levels resulting from the body's inability to produce or properly use insulin\(^1\). Diabetes mellitus occurs in several forms, approximately 10% of diabetes patients have type 1 diabetes mellitus, an autoimmune disease that destroys insulin-producing beta cells in the pancreas leading to decrease in the concentration of insulin in the body and the remainder have type 2 (Non insulin dependent diabetes mellitus). Type 2 diabetes mellitus is a metabolic disorder characterized by a progressive decline in insulin action (insulin resistance, followed by the inability of pancreatic \(\beta\) cells to compensate for insulin resistance)\(^2\). The \(\beta\) cells normally compensate for insulin resistance by secreting greater amount of insulin in order to maintain glucose homeostasis. In non insulin dependent diabetes mellitus this \(\beta\) cell function becomes impaired due to insulin resistance leading to deterioration in glucose homeostasis and subsequent development of impaired glucose tolerance\(^3\). Diabetes mellitus is recognized as a major risk factor for cardiovascular diseases (CVD) such as atherosclerosis, heart attack, stroke, etc. About 75% of deaths among men with diabetes and 57% among women with diabetes are attributable to CVD\(^4\).

Insulin and oral hypoglycaemic agents are the most widely used drugs for lowering blood sugar in diabetes but these drugs also have various side effects such as hypoglycaemia, weight gain (sulfonylurea), lactic acidosis (biguinides) and all of these drugs can cause liver and renal damage. Before the development of modern pharmaceutical treatments, doctors were completely dependent on the use of medicinal herbs for prevention and treatment of disease\(^5\). Research has accumulated in support of...
the evidence of the lipid lowering properties of some antidiabetic medicinal plants such as *Syzygium cumini* (Linn.) Skeels, *Tinospora cordifolia* (Willd.) Miers ex Hook.f. & Thoms., *Ocimum sanctum* Linn., etc. Ethnobotanical information also indicates that more than 800 plants are used as traditional remedies for the treatment of diabetes throughout the world\(^7,8\). There is still an unmet need for scientific proof of the antidiabetic activity of medicinal plants and phytopharmaceuticals with fewer side effects.

*F. arnottiana* Miq. is a glabrous tree or shrub belonging to family Moraceae. It is commonly known as *Paras Pipal*. It is distributed throughout India, mostly in rocky hills at 1,350m elevations\(^9\). The leaves of the plant are used for controlling fertility. Bark of the plant is used as astringent, aphrodisiac, demulcent, depurative and emollient. It is also useful in inflammation, diarrhoea, diabetes, burning sensation, leprosy, scabies, wounds and skin diseases\(^11\). The fruits of the plant contain \(\beta\)-sitosterol, gluanol acetate, glucose, friedelin\(^12\). Therefore, the present study was conducted to evaluate the sugar lowering potential of bark extract of this plant on streptozotocin induced NIDDM rats.

**Materials and Methods**

**Bark and chemicals**

*F. arnottiana* bark was collected from the forest of Dehra Dun in the month of April. The plant was identified and authenticated and deposited in the department. Streptozotocin was purchased from Calbiochem, Germany. Standard antidiabetic drug glibenclamide was obtained from Ranbaxy Research Laboratories, Gurgaon, India. Analytical grade chemicals including various organic solvents (petroleum ether, chloroform, acetone and methanol) from E. Merck India Ltd and Ranbaxy Laboratories India were used for the extraction and phytochemical study of the constituents.

**Preparation of different plant extracts**

Bark was shade dried at room temperature, ground into fine powder and then extracted (amount 450g) with solvents of increasing polarity such as petroleum ether, chloroform, acetone and methanol for 24h with each solvent by hot extraction using Soxhlet apparatus at a temperature of 60ºC. The extracts were concentrated under reduced pressure using a rotary evaporator to constant weight and collected and preserved in desiccator for further studies.

**Phytochemical study**

A portion of residue from each extract was subjected to phytochemical analysis in order to see the presence of sterols, alkaloids, carbohydrates, tannins, phenols, etc. in the bark extracts\(^13,14\).

**Determination of blood sugar level in diabetic rats**

**Animals**

Wistar albino rats of either sex were randomly bred in the Institutional animal house. The animals were housed in standard polypropylene cages and maintained under controlled room temperature (22° ± 2°C) and humidity (55±5%) with 12:12 h light and dark cycle. All the animals were provided with commercially available rat normal pellet diet and water *ad libitum*. The guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) of the Govt. of India were followed and prior permission and clearance were obtained from the institutional animal ethics committee for conducting the animal experiments.

**Acute toxicity studies**: Acute toxicity studies were carried out on Swiss albino mice\(^15\). Active acetone extract at doses of 100, 300, 500, 1000 and 3000 mg/kg was administered to five groups of mice, each group containing 6 animals. After administration of extracts the animals were observed for the first 3h for any toxic symptoms followed by observation at regular intervals for 24 h up to 7 days. At the end of study the animals were also observed for general organ toxicity, morphological behaviour and mortality.

**Induction of diabetes**

The method of Portha *et al* was followed for the induction of diabetes. Diabetes mellitus was induced in five day - old neonates (50 animals) by intraperitonial injection of streptozotocin (90 mg/kg in 0.1M citrate buffer \(pH 4.5\))\(^16,17\). The control group received equivalent amount of citrate buffer. The animals were allowed to live with their respective mothers and weaned from breast feeding at 4 weeks of age. Eight weeks after injection of streptozotocin, the rats were checked for fasting blood sugar (FBS) level by glucose oxidase-peroxidase method. Animals showing FBS more than 150 mg/dl were considered as diabetic (38 animals) and included for the study.

**Treatment protocol**

The diabetic animals were divided into six groups,
each containing six animals, and one group of normal non diabetic animals. All the extracts of *F. arnottiana* bark was given at a dose of 100 mg/kg, orally for a period of 21 days as a suspension in Tween 80 to different groups of diabetic animals.

Gr I : Normal animals received Tween 80 in a dose of 1% suspension in distilled water.
Gr II : Diabetic animals received Tween 80 in a dose of 1% suspension in distilled water.
Gr III : Diabetic animals received standard antidiabetic drug glibenclamide (5mg/kg, p.o.)
Gr IV : Diabetic animals received Petroleum ether extract (100mg/kg, p.o.)
Gr V : Diabetic animals received chloroform extract (100mg/kg, p.o.)
Gr VI : Diabetic animals received acetone extract (100mg/kg, p.o)
Gr VII : Diabetic animals received methanol extract (100mg/kg, p.o.)

At the end of the experimental period the animals were fasted overnight for 8h and blood was taken from the retro orbital plexus under mild ether anesthesia, serum was separated out and blood sugar level was evaluated by the method of glucose oxidase-peroxides method using span diagnostic kits.

**Antihyperglycaemic assay: Oral glucose tolerance test:** The six groups of diabetic animals and one group of normal animals were fasted overnight. Hyperglycaemia was induced by oral administration of 75% glucose solution.

The standard oral glucose tolerance test was performed on all animals before and after giving the treatment.

**Statistical analysis**

The results were expressed as Mean ± SEM. The unpaired t-test was used for analyzing the data between two groups. Statistical analysis of data was initially performed by using analysis of variance (ANOVA) when the overall ANOVA was significant, unpaired t-test was applied to study the difference among the groups.

**Results and Discussion**

**Phytochemical study**

After phytochemical investigation it was found that petroleum ether extract of the bark showed the presence of sterols. Chloroform extract showed the presence of carbohydrates and alkaloids. Acetone and methanol extracts showed the presence of phenols, alkaloids and tannins.

**Acute toxicity studies**

Acute toxicity studies revealed that *F. arnottiana* bark extracts were not showing any toxic symptoms when administered orally to mice. The lethal dose (LD<sub>50</sub> value) was 3g/kg body weight.

**Effect on fasting blood sugar and post prandial blood sugar level of diabetic rats**

The effect of different extracts on serum glucose level in the diabetic rats shown in Table 1 revealed that all the extracts caused reduction in blood glucose level but maximum reduction was found

<table>
<thead>
<tr>
<th>Groups</th>
<th>Blood sugar (mg/dl) before treatment</th>
<th>Blood sugar (mg/dl) after treatment</th>
<th>% reduction in blood sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (diabetic rats)</td>
<td>253 ± 1.3</td>
<td>235 ± 0.8</td>
<td>-</td>
</tr>
<tr>
<td>Normal (TWEEN 80, 1 ml/kg, p.o.)</td>
<td>90 ± 0.8</td>
<td>96 ± 1.1</td>
<td>-</td>
</tr>
<tr>
<td>Diabetic + Standard drug (5 mg/kg, p.o.)</td>
<td>250± 1.1</td>
<td>90 ± 1.3***</td>
<td>67</td>
</tr>
<tr>
<td>Diabetic + Pt. ether (100 mg/kg, p.o.)</td>
<td>254± 1.2</td>
<td>143 ± 0.9 *</td>
<td>43</td>
</tr>
<tr>
<td>Diabetic + Chloroform (100 mg/kg, p.o.)</td>
<td>260± 1.5</td>
<td>137 ± 1.2 *</td>
<td>45</td>
</tr>
<tr>
<td>Diabetic + Acetone (100 mg/kg, p.o.)</td>
<td>240 ± 4.5</td>
<td>116 ± 1.35 **</td>
<td>51</td>
</tr>
<tr>
<td>Diabetic + Methanol (100 mg/kg, p.o.)</td>
<td>257 ± 2.4</td>
<td>132 ± 0.06*</td>
<td>48</td>
</tr>
</tbody>
</table>

Results are expressed as Mean ± SEM. Results of the test and standard groups are compared with the control group.

*P<0.05, **P<0.01, ***P<0.001
Preliminary phytochemical screening revealed the presence of phenolic compounds and saponins in the bark extract. The active ingredient in the extract that reduces the blood sugar is not known at present. Estimation of insulin level and insulin receptor may give more insight into the mechanism of its antidiabetic action. There is ongoing research to isolate and characterize the bioactive compound(s) responsible for the antidiabetic activity of *F. arnottiana*.

**Acknowledgements**

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**References**


5. Jenson T, Stender and Deckert T, Abnormalities in plasma concentration of lipoprotein and fibrogen in type 1 (insulin

<table>
<thead>
<tr>
<th>Groups</th>
<th>Glucose tolerance test (before treatment)</th>
<th>Glucose tolerance test (after treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1h</td>
<td>2h</td>
</tr>
<tr>
<td></td>
<td>1h</td>
<td>2h</td>
</tr>
<tr>
<td>Normal (Tween 80, 1ml/kg, p.o.)</td>
<td>120± 0.5</td>
<td>80± 0.7</td>
</tr>
<tr>
<td>Control (diabetic animals)</td>
<td>320± 1.2</td>
<td>223± 1.1</td>
</tr>
<tr>
<td>Standard (5mg/kg, p.o.)</td>
<td>310± 0.8</td>
<td>185± 1.5</td>
</tr>
<tr>
<td>Pt. ether (100 mg/kg, p.o.)</td>
<td>316± 0.12</td>
<td>212± 0.9</td>
</tr>
<tr>
<td>Chloroform (100 mg/kg, p.o.)</td>
<td>280± 0.4</td>
<td>209± 0.8</td>
</tr>
<tr>
<td>Acetone (100 mg/kg, p.o.)</td>
<td>305± 0.6</td>
<td>195± 1.6</td>
</tr>
<tr>
<td>Methanol (100 mg/kg, p.o.)</td>
<td>309± 0.5</td>
<td>209± 0.9</td>
</tr>
</tbody>
</table>

Results are expressed as Mean ± SEM. Results of the test and standard groups are compared with the control group.

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

Acetone extract showed 51% reduction (*P<0.01) as compared to glibenclamide which showed 67% reduction in fasting blood sugar. Table 2 summarizes the effect of the bark extracts on post prandial sugar level. There is no significant decrease in the glucose level in animals without treatment. *F. arnottiana* and glibenclamide treatment caused significant decrease in blood sugar level after 2 hours.

Administration of streptozotocin caused rapid destruction of pancreatic β cells in rats, which led to impaired glucose-stimulated insulin release and insulin resistance, both of which are marked feature of type II diabetes. The hypoglycaemic effect of plant extracts is generally dependent upon the degree of pancreatic β cell destruction and useful in moderate streptozotocin induced diabetes. The lesser the degree of pancreatic β cells destruction, the more useful the herb is in treating diabetes in animals.

**Conclusion**

Among all the extracts tested, acetone extract caused significant reduction in the serum blood glucose level as compared to glibenclamide. Acetone extract caused 51% reduction in FBS level in diabetic animals whereas glibenclamide caused 67% reduction in sugar level. Acetone extract also caused a significant (*P<0.01) decrease in post-prandial blood sugar level in diabetic animals. Preliminary phytochemical screening revealed the presence of phenolic compounds and saponins in the bark extract. The active ingredient in the extract that reduces the blood sugar is not known at present. Estimation of insulin level and insulin receptor may give more insight into the mechanism of its antidiabetic action. There is ongoing research to isolate and characterize the bioactive compound(s) responsible for the antidiabetic activity of *F. arnottiana*.
dependent diabetic patients with increased urinary albumin excretion, *Diabetology*, 1998, 31, 142-146.


