Effect of *Ficus benghalensis* L. Latex Extract (FBLE) on Cisplatin Induced Hypotension and Renal Impairment in Wistar Rats

Yogesh Chand Yadav

Department of Pharmacology, Pharmacy College Saifai, Uttar Pradesh University of Medical Sciences, UP, India

**Abstract**

**Background and objective:** *Ficus benghalensis* is a remarkable tree from India that sends down its branches and great number of shoots, which take root and become new trunks [1]. Its chemical constituent’s flavonoids leucoanthocyanidin, leucoanthocyanin, friedelin, β sitosterol, quercetin-3-glactoside and rutin. Earlier, glucoside, 20-tetra-triaconthene-2-one, 6-heptatriacontene-10-one, pentatriacontan-5-one, beta sitosterol-alpha-D-glucose, and meso-inositol have been isolated from the bark of the *F. benghalensis* and it latex contains Caoythoue (2.4%), Resin, Albumin, Cerin, sugar, and Malic acid [2] and used for treatment of for diarrhea, dysentery, and piles [4]. The extract of *F. benghalensis* was reported to inhibit insulinase activity from the liver and kidney and it was also found to inhibit the lipid peroxidation. *F. benghalensis* was traditionally used for the treatment of mehavkar or urinary disorders [5] but no scientific studies have been undertaken to verify these claims. Thus, the purpose of current study was to investigate whether oral administration of *F. benghalensis* latex extract has possible protective effect against cisplatin induced hypotension and renal impairment in wistar rats. The total Phenolic and Flavonoid content of latex extract has excellent nephroprotective and normalized blood pressure.

**Keywords:** *Ficus benghalensis*; latex; Cisplatin; Hypotension; Renal impairment

**Introduction**

*Ficus benghalensis* is a remarkable tree from India that sends down its branches and great number of shoots, which take root and become new trunks [1]. Its chemical constituent’s flavonoids leucoanthocyanidin, leucoanthocyanin, friedelin, β sitosterol, quercetin-3-glactoside and rutin. Earlier, glucoside, 20-tetra-triaconthene-2-one, 6-heptatriacontene-10-one, pentatriacontan-5-one, beta sitosterol-alpha-D-glucose, and meso-inositol have been isolated from the bark of the *F. benghalensis* and it latex contains Caoythoue (2.4%), Resin, Albumin, Cerin, sugar, and Malic acid [2] and used for treatment of for diarrhea, dysentery, and piles [4]. The extract of *F. benghalensis* was reported to inhibit insulinase activity from the liver and kidney and it was also found to inhibit the lipid peroxidation. *F. benghalensis* was traditionally used for the treatment of mehavkar or urinary disorders [5] but no scientific studies have been undertaken to verify these claims. Thus, the purpose of current study was to investigate whether oral administration of *F. benghalensis* latex extract has possible protective effect against cisplatin induced hypotension and renal impairment in wistar rats. The total Phenolic and Flavonoid content of latex extract has excellent nephroprotective and normalized blood pressure.

**Materials and Methods**

**Phytochemical standardization**

Phytochemical identification and standardization of FBLE performed by TLC Method and HPTLC (CAMAG Switzerland, Linomet 5, and Scanner 3, Win Cat Software) Mobile phase: Butanol: Formic acid: Water (7.5 ml: 1.5 ml: 1.0 ml). HPTLC analysis performed by use of various standard amino acid markers like glutamine, glycine, cysteine, methionine, lysine, arginine etc., and extract in which one compound was identified on the extract track and their RF value 0.56 was similar to standard methionine marker. The methionine content of FBLE standardized that was found 0.842 ± 0.0364 % of standard methionine.

**Determination of total phenolic and flavonoid contents in FBLE**

The total Phenolic and Flavonoid content of latex extract determined by method [6,7] respectively.

**In vitro antioxidative activity**


**Animals**

Adult male Wistar rats (180-210 g) have an access to water and food ad libitum, and maintained under constant (25 ± 1°CAS), humidity (65 ± 10%) and a 12 h light/dark cycle. The experiment was carried out in accordance to the guidelines mentioned in the CPCSEA, and IAEC approved the experiment protocols (SVU/PH/IAEC/26.03.2010/02).

**Acute toxicity study**

Each group of Wistar rats fasted overnight prior to the experiment. Each group of rats fed FBLE dissolved in normal saline with increasing...
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dose like 5, 50, 100, 200, 400, 1000 2000 mg/kg body weight. The animals observed continuously for 2 h and then every 2 h up to 24 and 72 h for gross behavior changes. So LD₅₀ cut off of the extract was 2000 mg/kg body weight. FBLE dose regimen prepared like 1/10th and 1/5th of the respective LD₅₀ cut off values.

Cisplatin-induced renal injury

Five groups of rats (n=6) used, in which 1st group administered 5 ml/kg normal saline throughout the experiment for 16 days; 2nd control group received FBLE 400 mg/kg per day for 16 days; 3rd group (cisplatin treated) with single dose of cisplatin (5 mg/kg, i.p.) on 1st day and keep animals up to 6 days; 4th Group and 5th Group (Protective) FBLE (200 and 400 mg/kg, p.o.) for 1st to 10th day and single dose of cisplatin (5 mg/kg, i.p.) on 11th day and keep animals up to 16 days [11].

On the 6th day in cisplatin control and 16th day in control, protective were measured blood pressure by help of student physiograph (instruments & chemicals PVT. LTD, Ambala, India) after then blood withdrawn from retro-orbital sinus of rats for biochemical estimation for serum urea and creatinine levels using diagnostic kit from Span Diagnostic, “Kolkata on chemical analyzer (Microlab 3000) and also dissected out the kidneys for estimation of in vivo antioxidant enzymes and histopathological works [12].”

In vivo Antioxidant activity


Statistical analysis

Result were expressed as mean ± SEM, Statistical Analysis were performed with one way analysis of variance (ANOVA) followed by Dunnett’s test. P value less than <0.05 was considered significant.

Results

FBLE has revealed presence of glycoside, alkaloids, tannin (Phenolic compound), Flavonoids, and methionine amino acid (Figures 1 and 2). Total Phenolic and flavonoids content had obtained 2.76 ± 0.84 mg GAE/g and 1.84 ± 0.5 mg QE/g extract respectively.

In vitro antioxidant potential of FBLE was evaluated by scavenging effect of DPPH, ferric chloride, and phosphor-molybdenum. IC₅₀ values for DPPH, and phosphor-molybdenum were 28.63 ± 0.16 µg/ml, and 31.84 ± 0.12 µg/ml respectively (Figures 3 and 4).

Blood pressure of cisplatin-treated was decreased to 70 mmHg which is significantly increased 100 mmHg in protective groups.

The cisplatin-treated showed a significant increase urine volume, serum urea and creatinine levels, lipid peroxidation and decrease body wt. (Figure 2), GSH, SOD, CAT, Na⁺K⁺ ATPase, Ca⁺⁺ ATPase, Mg⁺⁺ATPase of kidney (Tables 1-3), on the 6th day as compared to the group I. They were significantly (p<0.01) recovered in protective regimen with treated dose at 200 and 400 mg/kg of FBLE.

Histopathological sections of the kidneys showed marked vasoconstriction, hyaline droplets, proinflammatory and tubular necrosis were observed cisplatin treated group III (Figure 5; Plates 1A-1C) in the protective regimen extract (200 and 400 mg/kg body wt., p.o.) reduced hyaline droplets, tubular dilation and recovery of tubular necrosis in which 400 mg/kg more effective reduction than 200 mg/kg (Figure 5; Plate 1D and 1E) respectively.

Discussion

In the present study, cisplatin-induced renal impairment was evidenced by an increase in serum urea and creatinine and acute tubular necrosis. These changes observed on 6th day after administration of a single dose 5 mg/kg cisplatin. FBLE normalized, raised serum urea, creatinine levels, lipid peroxidation and decreased blood pressure, GSH, SOD, CAT, Na⁺K⁺ ATPase, Ca⁺⁺ ATPase, Mg⁺⁺ ATPase of kidney. The histopathological report supported the biochemical findings.

Figure 1: HPTLC chromatogram (a) standard methionine RF= 0.57; (b) HPTLC chromatogram extract RF=0.56.

Table 1: Effects of methanol extract of Ficus benghalensis latex L. on the Urinary volume, Urea and Creatinine level in serum on 6th day after cisplatin administration.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Urine volume (ml/24 h)</th>
<th>Urea level in serum (mg/dl)</th>
<th>Creatinine level in blood serum (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.33 ± 0.33</td>
<td>24.16 ± 1.04</td>
<td>0.94 ± 0.05</td>
</tr>
<tr>
<td>Extract FBL</td>
<td>6.66 ± 0.66*</td>
<td>25.18 ± 1.85</td>
<td>0.96 ± 0.03*</td>
</tr>
<tr>
<td>Cisplatin treated</td>
<td>14.66 ± 0.88*</td>
<td>76.66 ± 2.24*</td>
<td>2.32 ± 0.10*</td>
</tr>
<tr>
<td>Protective (200 mg/kg)</td>
<td>8.66 ± 0.36*</td>
<td>50.66 ± 2.82*</td>
<td>1.53 ± 0.01*</td>
</tr>
<tr>
<td>Protective (400 mg/kg)</td>
<td>10.66 ± 0.42*</td>
<td>61.66 ± 1.09*</td>
<td>1.85 ± 0.08*</td>
</tr>
</tbody>
</table>

*: P<0.01 as compared to the control; **: P<0.01 as compared to the cisplatin treated group; *= P>0.05 as compared to cisplatin treated group.

Table 2: Effect of methanol extract of Ficus benghalensis latex L. on the lipid peroxidation and antioxidant enzymes of kidney on 6th day after cisplatin administration.

<table>
<thead>
<tr>
<th>Groups</th>
<th>µmol GSH/g</th>
<th>n Mole MDA/g</th>
<th>Ml Unit</th>
<th>Unit SOD/g</th>
<th>CAT (µ mole of H₂O₂/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>69.50 ± 1.54</td>
<td>14.00 ± 0.57</td>
<td>21.83 ± 0.94</td>
<td>323.33 ± 1.75</td>
<td></td>
</tr>
<tr>
<td>Extract FBL</td>
<td>68.34 ± 2.28*</td>
<td>14.98 ± 0.36*</td>
<td>20.43 ± 0.59*</td>
<td>319.53 ± 5.24*</td>
<td></td>
</tr>
<tr>
<td>Cisplatin treated</td>
<td>45.33 ± 1.66*</td>
<td>24.50 ± 0.61*</td>
<td>07.16 ± 0.60*</td>
<td>201.67 ± 3.33*</td>
<td></td>
</tr>
<tr>
<td>Protective (200 mg/kg)</td>
<td>58.66 ± 2.82*</td>
<td>15.00 ± 2.39*</td>
<td>15.83 ± 0.60*</td>
<td>285.83 ± 8.00*</td>
<td></td>
</tr>
<tr>
<td>Protective (400 mg/kg)</td>
<td>59.51 ± 2.44*</td>
<td>18.16 ± 0.74*</td>
<td>12.66 ± 0.66*</td>
<td>232.50 ± 4.42*</td>
<td></td>
</tr>
</tbody>
</table>

*: P<0.01 as compared to the control; **: P<0.01 as compared to the cisplatin treated group; *= P>0.05 as compared to cisplatin treated group.

Figure 2: Effect methanol Ficus benghalensis L. latex extract on average change body weight of various groups as compared to cisplatin treated group (3). Each group represents mean ± S.D. of six animals, **P<0.01, *P>0.05, **P>0.01, **P<0.01, **P>0.01 as compared to the cisplatin treated group.

Figure 3: % DPPH radical scavenging activity of FBLE.
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### Table 3: Effects of methanol extract of Ficus benghalensis L. latex on ATPase in kidney tissue of various groups on 6th day after cisplatin administration.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Na^+K^+ ATPase (mM of phosphate liberated/mg tissue)</th>
<th>Ca^{++} ATPase (mM of phosphate liberated/mg tissue)</th>
<th>Mg^{++} ATPase (mM of phosphate liberated/mg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>210.83 ± 2.64</td>
<td>102.83 ± 2.31</td>
<td>152.67 ± 0.88</td>
</tr>
<tr>
<td>Extract FBL</td>
<td>210.34 ± 2.37</td>
<td>101.51 ± 2.31</td>
<td>154.66 ± 1.66</td>
</tr>
<tr>
<td>Cisplatin treated</td>
<td>135.17 ± 2.51</td>
<td>64.33 ± 1.05</td>
<td>81.66 ± 1.05</td>
</tr>
<tr>
<td>Protective (200 mg/kg)</td>
<td>159.83 ± 2.08</td>
<td>71.53 ± 2.25</td>
<td>98.00 ± 2.19</td>
</tr>
<tr>
<td>Protective (400 mg/kg)</td>
<td>186.56 ± 2.46</td>
<td>98.28 ± 2.16</td>
<td>116.16 ± 2.56</td>
</tr>
</tbody>
</table>

*: P<0.01 as compared to the control; **: P<0.01 as compared to the cisplatin treated group;辅导: *P<0.05 as compared to cisplatin treated group.

Figure 4: % Phosphor-molybdenum radical scavenging activity of FBLE.

Figure 5: “Histopathology sections of kidney; Plate 1 (A) Vehicle-treated, Plate 1 (B) FBLE treated, Plate 1 (C) Cisplatin-treated rats (5 mg/kg, 6 days), Plate 1 (D) Protective (200 mg/kg), and Plate 1 (E) Protective (400 mg/kg).”
The FBLE treated dose 400 mg/kg body weight was observed more significant than 200 mg/kg body wt.

According to previous findings, it was conformed that the single dose of cisplatin (5 mg/kg, i.p.) causes a significantly increase in two serum markers of the kidney function, viz. serum urea and creatinine [20]. Present study was revealed that significantly decrease the level of urea and creatinine in blood serum after treatment with FBLE that was indicate FBLE has nephroprotective activity. A relationship between oxidative stress and nephrotoxicity had well demonstrated in many experimental models Evidence point. The regulation up to normal blood pressure could be protective effect of renal impairment and activation sympathetic nervous system.

In vitro studies of FBLE evaluated for its good antioxidant potential revealed DPPH, ferric chloride, phosphor-molybdenum of free radical scavenging effect with lower IC50 values. FBLE has been found to be a rich source of Caoytchoue (2.4%), Cerin, and Malic acid and present phytochemical data have been revealed tannin, Flavonoids, methionine. Yadav [21] also reported hepatoprotective effect of Ficus religiosa latex on cisplatin induced liver injury in Wistar rats. Deegan et al. [22], also reported that nephrotoxicity, cytotoxicity and renal handling of a cisplatin methionine complex in male wistar rats. The present phytochemical screening data has observed methionine which was antagonized cisplatin nephrotoxicity.

**Conclusion**

Finally, it is concluded that FBLE could be an ameliorated cisplatin hypotension and nephrotoxicity.

**Conflicts of Interest**

Author declares no conflicts of interest.

**Acknowledgement**

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**References**