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R E S E A R C H A R T I C L E

Nephro-protective Activity of Methanol Extract of *"Cassia tora''* Seeds in Cisplatin Induced Nephrotoxicity in Mice

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A B S T R A C T

Kidneys have sensitive tasks, especially when they deal with unwanted substances, which have to be cleared from the system, principally toxins. Kidneys play an important role in the regulation of our endocrine and acid-base balance, erythropoiesis (creation of new red blood cells), blood pressure etc., a real multi-tasking entity inside our body. So it becomes problematic when kidney functions declines which may be induced by diseases which may not have direct relation to renal pathophysiology. Nephrotoxicity is a lethal effect of few substances, toxic chemicals and therapeutic medications on the kidney leading to renal injury. There are different forms of toxicity. Some medications predominantly needed renal excretion and the dose should be adjusted for the reduced renal function conditions (e.g. Heparin). The incidence of nephrotoxicity from amino glycosides has been increasing from 2 to 3% in 1969 to 20% over the past decade. Persons with renal failure are at increased risk for macro vascular and micro vascular disease. Currently available synthetic nephroprotective agents produce serious side effects. This leads to a demand for herbal products with nephroprotective activity and fewer side effects. Hence the effects of oral administration of methanol extract of Seeds of Cassia tora has been studied in cisplatin induced acute renal failure in swiss albino mice. The disease induced mice treated with methanol extract of seeds of Cassia tora at two doses 250 mg/kg and 500 mg/kg, extract high dose 500 mg/kg kept as test control without treatment of cisplatin. Test extracts exhibited a significant dose dependent nephroprotective activity compared to disease control. The results indicate that the methanol extract of Cassia tora is endowed with nephroprotective activity.

Keywords: *Cassia tora*, Cisplatin, Kidneys, Nephroprotective Activity.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Nature has always stands as a golden mark to demonstrate the outstanding phenomenon of symbiosis. Today a vast store of knowledge concerning therapeutic properties of different plants has accumulated. India has a rich flora that is widely distributed throughout the country [1]. Herbal medicines have been used for the treatment and cure of various diseases and physiological conditions in traditionally practiced methods such as Unani, Ayurveda, and Siddha [2]. From previous studies done on Cassia tora and due to the presence of effective phytochemical constituents, methanol extract of the plant seeds were selected for evaluating hypoglycemic activity. Various drugs available in the market for hypoglycemic activity and none of the drugs are not up to mark for showing its efficacy. From literature survey it was found that Cassia tora effective in treatment of anti-ulcer, anti-shigellosis, anti-genotoxic, anti-proliferative, anti-oxidant, anti-arthritic, wound healing activity etc [3-38]. The nephroprotective study period is 6 days. Animals used are male swiss albino mice.

2. Materials and Methods

Experimental Animals

Male albino mice of 20-22 grams weighed were used for present study. The animals were housed in polypropylene cage (6 animals per cage), the standard conditions were maintained (12 hours light and 12 hours dark cycle, 23 ± 5° C and 40-60% humidity). The standard mice diet, water was provided ad libitum. All the animals were collected from the central animal house SICRA Labs Pvt Ltd, IDA-Kukatpally, Hyderabad and all experiments were conducted according to the ethical norms approved by CPCSEA, Ethical Committee IAEC reg.no. 1821/PO/Re/S/15/ CPCSEA).

Experimental Procedure

Induction of Nephrotoxicity by Cisplatin: On 3rd day, cisplatin (15 mg/kg bw) was administered intraperitoneally.

Preparation of Test Drug: The test drugs were prepared by 2% tween 80. Test drugs were given by oral gavage i.e. per oral route at a dose of 0.4 ml/kg body weight. All drugs were prepared freshly before administration.

Experimental Procedure

Cisplatin induced Nephrotoxicity:

1. Control group:

Saline was given orally for six consecutive days and on the 3rd day a single intraperitoneal (i.p.) injection of saline was given;

2. Disease Control group: Saline was given orally for six consecutive days and on the 3rd day also a single i.p. injection of cisplatin (15 mg/kg bw) was given;

3. Test group 1:

Cassia tora seeds methanol extract (250 mg/kg/day bw) was given orally once daily for six consecutive days and on the 3rd day a single i.p. injection of cisplatin was given.

4. Test group 2:

Cassia tora seeds methanol extract (500 mg/kg/day bw) was given orally once daily for six consecutive days and on the 3rd day a single i.p. injection of cisplatin was given.

5.Test Control Group:

Cassia tora seeds methanol extract (500 mg/kg/day bw) was given orally once daily for six consecutive days. After completion of treatment period, blood was collected by retro-orbital sinus puncture. Serum was separated by centrifuging at 2500 rpm for 15 min and analyzed for various biochemical parameters.

Assessment of kidney function

Biochemical parameters i.e., Estimation of Blood urea nitrogen [40,41], Serum Creatinine [42], Total protein [43,44] were analyzed according to the reported methods. The kidneys were removed, weighed and morphological changes were observed. A 10% of kidney homogenate was used for antioxidant studies such as, superoxide dismutase (SOD), GSH, MDA, Catalase, Nitric oxide. The biochemical parameters were estimated as per the standard procedure prescribed by the manufacturer's instruction manual provided in the standard kit using Semi Auto analyzer.

Statistical Analysis

The obtained results were expressed as Mean ± SEM. Comparison between control and treatment groups were performed by one way analysis of variance (ANOVA) followed by Dunnets test. The statistical significance criterion was $p< 0.05$ (95% level). $P<0.05$ is considered as significant39.

3. Results and Disussion

In Cisplatin treated group of animals weight of kidneys were appreciably increased as compared to normal animals and test control animals (group1st and 5th) and treating with methanol extract (group 4th) showed significant decrease ($p<0.01$) in kidney weight.

In Cisplatin treated group (2nd) animals, the concentration of Blood urea nitrogen, Creatinine, Total protein were appreciably increased than normal animals and test control animals (group1st and 5th) which indicates severe nephrotoxicity. Treating (group 3rd and 4th) with methanol extract of Cassia tora seeds showed significant decrease ($p<0.001$) in concentration of Blood urea nitrogen, Creatinine, Total protein compared to Cisplatin treated groups (2nd).

Appreciable reduction in activity of SOD and Reduced glutathione, Catalase in cisplatin treated animals (2nd) as compared to normal animals and test control animals (group1st and 5th). Treating group 3, 4 with methanol extract of Cassia tora seeds significantly prevented decrease in the level of SOD and reduced glutathione, Catalase activity as compared to cisplatin treated rats (2nd).

Nevertheless considerable increase in activity of lipid peroxidase and Nitric oxide in cisplatin treated animals (2nd) was reported. Treating (group 3, 4) with methanol extract of Cassia tora seeds significantly prevented increase in the level of lipid peroxidase and Nitric oxide. Thus strongly inhibit lipid peroxidation in isolated tissue via its antioxidant activity.

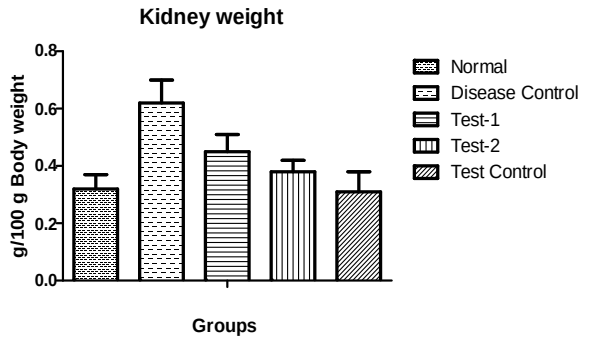

Fig 1: Effect of the Methanol Extract of Seeds of *Cassia tora* on Wet Kidney Weight

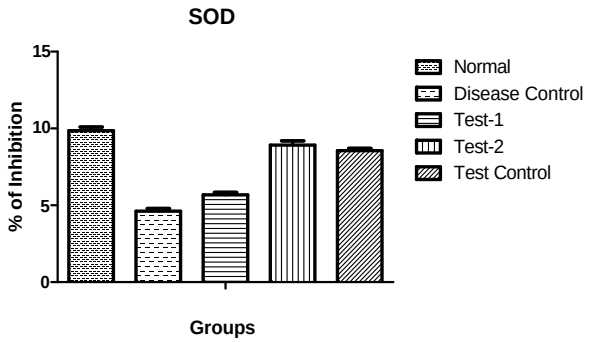

Fig 5: Effect of the Methanol Extract of Seeds of *Cassia tora* on Superoxide dismutase

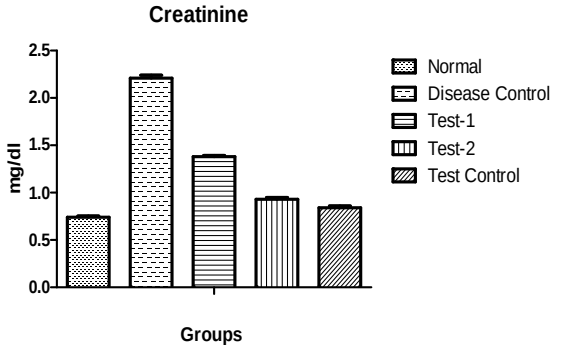

Fig 2: Effect of the Methanol Extract of Seeds of *Cassia tora* on Creatinine

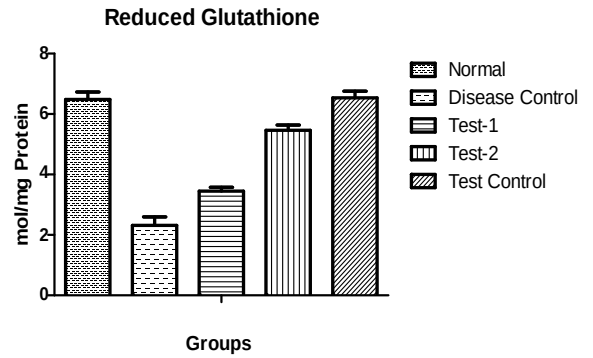

Fig 6: Effect of the Methanol Extract of Seeds of *Cassia tora* on reduced glutathione

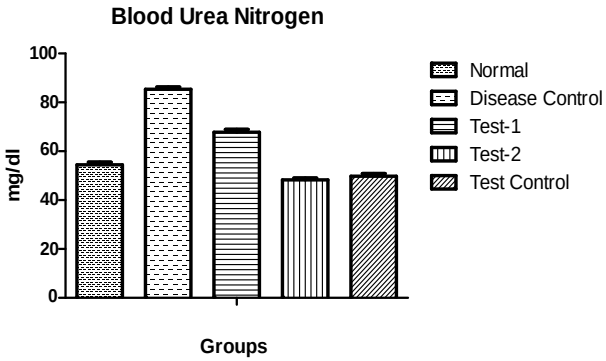

Fig 3: Effect of the Methanol Extract of Seeds of *Cassia tora* on Blood Urea Nitrogen

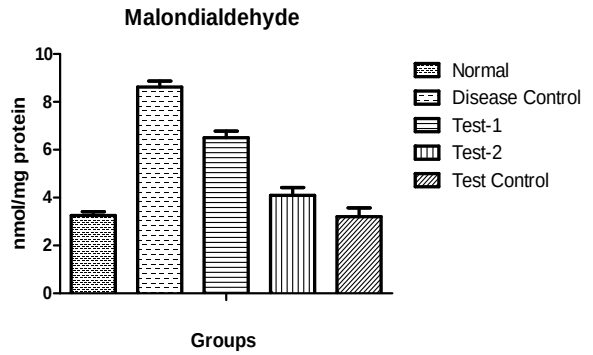

Fig 7: Effect of the Methanol Extract of Seeds of *Cassia tora* on Lipid Peroxidation

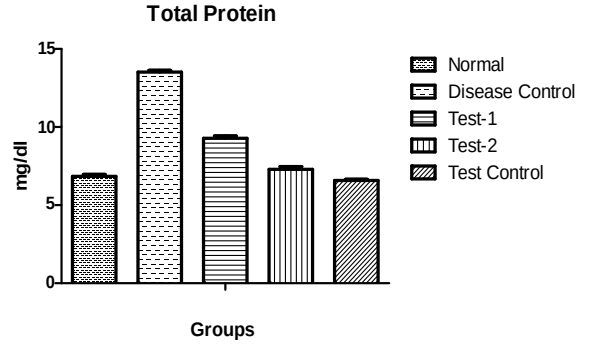

Fig 4: Effect of the Methanol Extract of Seeds of *Cassia tora* on Total Protein

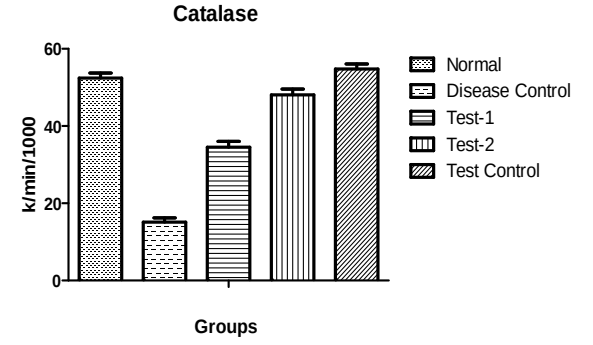

Fig 8: Effect of the Methanol Extract of Seeds of *Cassia tora* on Catalase

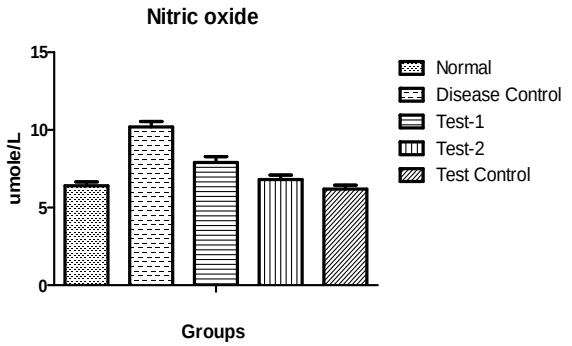

Fig 9: Effect of the Methanol Extract of Seeds of *Cassia tora* on Nitric Oxide

Discussion

Cisplatin is a platinum anticancer drug, has been widely prescribed in treatment regimen of malignant tumors. But the main dose-limiting factor of cisplatin is nephrotoxicity. The underlying mechanisms involved in nephrotoxicity are oxidative stress, inflammation and renal cell apoptosis [50]. Previous phytochemical screening studies of methanol extract of the seeds of Cassia tora revealed the presence of Anthraquinone glycosides, flavonoids, alkaloids, tannins. Anthraquinone glycosides and Flavonoids have been reported to show their antioxidant activity by different mechanisms by attenuating or quenching or scavenging free radicals or by blocking or inhibiting enzymatic systems which are responsible for free radical generation [55-57]. Cisplatin nephrotoxicity is occurs by consequences of the transport of cisplatin into renal epithelial cells and damaging mitochondrial and DNA there by activating the pathways of multiple cell death and survival resulting in triggering a robust inflammatory response [51]. In renal diseases, the serum urea accumulates because the rate of serum urea production exceeds the rate of clearance. Elevation of urea and creatinine levels in serum was taken as the index of nephrotoxicity [53]. Creatinine derives from endogenous sources by tissue creatinine breakdown. Thus serum urea concentration is often considered a more reliable renal function prediction than serum creatinine [54].

Previous conducted mechanistic studies about cisplatin-induced nephropathy showed variously implicated key upstream events. Research findings demonstrated that elevated oxidative stress was one of the basic and primary features, which results in lipid peroxidation, increase in nitric oxide levels and GSH, SOD, Catalase depletion. Cisplatin nephrotoxicity often associated with lipid per oxidation results in increase in levels of MDA ultimately leads to increase in kidney weight. In the present study Cisplatin induced nephrotoxicity was established single administration of 12 mg/k p.o. cisplatin on 3rd day. This toxicity established by marked elevation in the circulating levels of blood urea nitrogen, serum creatinine, total protein in the disease Control(group 2) mice when compared to untreated(group 1) and Test Control (group 5).

However these changes were attributed by pre-treatment with single daily graded doses of methanol seed extract of Cassia tora for 6 days. Administration of plant extract orally significantly decreased the blood urea nitrogen and creatinine and total protein in treatment groups compare to toxicant group. Apart from the direct nephrotoxic effect of cisplatin in group 2, the acute elevation in the measured biochemical parameters could also be attributed to increased catabolic state of the rats due to the prolong anorexia associated with cisplatin nephrotoxicity. Treatment of cisplatin-treated mice disturbed renal oxidant status indicated by elevation in lipid peroxidation and decrease in SOD, GSH, Catalase levels treatment with Cassia tora seeds extract here alleviated the disturbed renal status could partially attributed to the protective action of Cassia tora seeds extract at an early stage of cisplatin-induced nephrotoxicity and protected against increase in wet kidney weight compared to cisplatin treated group.Thus findings suggest that the potential use of methanol extract of Cassia tora seeds may be therapeutically useful as a nephron protective agent. Therefore further studies to explain their mechanisms of action should be conducted to aid the discovery of new therapeutic agents for the treatment of renal diseases.

Table 1: Effect of the Methanol Extract of Seeds of *Cassia tora* on Wet Kidney Weight

Group	Group	Drug	Kidney Weight
1	Normal	Saline	0.32±0.05
2	Disease Control (Cisplatin)	12 mg/kg	0.62±0.08
3	Test-1 (Cisplatin and Extract)	12 mg/kg +250mg/kg	0.45±0.06
4	Test-2 (Cisplatin and Extract)	12 mg/kg +500mg/kg	0.38±0.04*
5	Test Control (Extract)	500mg/kg	0.31±0.07**

Table 2: Effect of the Methanol Extract of Seeds of *Cassia tora* on Creatinine

Group	Group	Drug Treatment	Creatinine
1	Normal	Saline	0.74± 0.014
2	Disease Control (Cisplatin)	12 mg/kg	2.21±0.03
3	Test-1 (Cisplatin and Extract)	12 mg/kg +250mg/kg	1.38±0.012***
4	Test-2 (Cisplatin and Extract)	12 mg/kg +500mg/kg	0.93±0.019***
5	Test Control (Extract)	500mg/kg	0.84± 0.02***

Table 3: Effect of the Methanol Extract of Seeds of *Cassia tora* on Blood Urea Nitrogen

Group	Group	Drug Treatment	Blood Urea Nitrogen
1	Normal	Saline	54.48± 1.06
2	Disease Control (Cisplatin)	12 mg/kg	85.35±.90
3	Test-1 (Cisplatin and Extract)	12 mg/kg +250mg/kg	67.76±1.2***
4	Test-2 (Cisplatin and Extract)	12 mg/kg +500mg/kg	48.26±0.75***
5	Test Control (Extract)	500mg/kg	49.79± 1.10***

Table 4: Effect of the Methanol Extract of Seeds of *Cassia tora* on Total Protien

Group	Group	Drug Treatment	Total protein
1	Normal	Saline	6.84±0.13
2	Disease Control (Cisplatin)	12 mg/kg	13.52±0.11
3	Test-1 (Cisplatin and Extract)	12 mg/kg +250mg/kg	9.28±0.15***
4	Test-2 (Cisplatin and Extract)	12 mg/kg +500mg/kg	7.29±0.18***
5	Test Control (Extract)	500mg/kg	6.58±0.07***

Table 5: Effect of the Methanol Extract of Seeds of Cassia tora on Superoxide Dismutase

Group	Group	Drug Treatment	SOD
1	Normal	Saline	9.85±0.24
2	Disease Control (Cisplatin)	12 mg/kg	4.62±0.18
3	Test-1 (Cisplatin and Extract)	12 mg/kg +250mg/kg	5.68±0.17**
4	Test-2 (Cisplatin and Extract)	12 mg/kg +500mg/kg	8.92±0.28***
5	Test Control Extract	500mg/kg	8.56±0.15***

Table 6: Effect of the Methanol Extract of Seeds of *Cassia tora* on Reduced Glutathione

Group	Group	Drug Treatment	GSH
1	Normal	Saline	6.48±0.25
2	Disease Control(Cisplatin)	12 mg/kg	2.32±0.28
3	Test-1 (Cisplatin and Extract)	12 mg/kg +250mg/kg	3.45±0.13**
4	Test-2 (Cisplatin and Extract)	12 mg/kg +500mg/kg	5.46±0.18***
5	Test Control (Extract)	500mg/kg	6.54±0.22***

Table 7: Effect of the Methanol Extract of Seeds of *Cassia tora* on Lipid per oxidation

Group	Group	Drug	MDA
1	Normal	Saline	3.25±0.16
2	Disease Control (Cisplatin)	12 mg/kg	8.62±0.25***
3	Test-1 (Cisplatin and Extract)	12 mg/kg +250mg/kg	6.5±0.28***
4	Test-2 (Cisplatin and Extract)	12 mg/kg +500mg/kg	4.1±0.32***
5	Test Control (Extract)	500mg/kg	3.20±0.37***

Table 8: Effect of the Methanol Extract of Seeds of *Cassia tora* on Catalase

Group	Group	Drug	Catalase
1	Normal	Saline	52.4±1.32
2	Disease Control (Cisplatin)	12 mg/kg	15.1±1.1
3	Test-1 (Cisplatin and Extract)	12 mg/kg +250mg/kg	34.5±1.54***
4	Test-2 (Cisplatin and Extract)	12 mg/kg +500mg/kg	48.1±1.5***
5	Test Control (Extract)	500mg/kg	54.8±1.3**

Table 9: Effect of the Methanol Extract of Seeds of *Cassia tora* on Nitric oxide

Group	Group	Drug	Nitric oxide
1	Normal	Saline	6.4±0.26
2	Disease Control (Cisplatin)	12 mg/kg	10.2±0.34
3	Test-1 (Cisplatin and Extract)	12 mg/kg +250mg/kg	7.9±0.38
4	Test-2 (Cisplatin and Extract)	12 mg/kg +500mg/kg	6.8±0.29
5	Test Control (Extract)	500mg/kg	6.2±0.24

4. Conclusion

The present study was conducted to evaluate the Nephro-protective Activity of 90% Methanolic aqueous Extract of seeds of *Cassia tora* using Cisplatin induced Nephrotoxicity. The effect of nephro-protective activity of 90% Methanolic aqueous Extract of seeds of Cassia tora seems to be effective and significant at a dose of 500 mg/kg b.w p.o. against Cisplatin induced Nephrotoxicity by attenuating disturbed biochemical and antioxidant parameters. The presence of Anthraquinone glycosides and flavanoids which have anti-oxidant property could be responsible for nephro-protective activity, and is more likely to be involved in the reaction with free radicals and thereby showing the nephro-protective activity.

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