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Research Article

PROTECTIVE ROLE OF *TINOSPORA CORDIFOLIA* AGAINST CISPLATIN- INDUCED NEPHROTOXICITY

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ABSTRACT

The importance of *Tinospora cordifolia* stem extract was investigated for its possible curative effect in male wistar rats against the cisplatin induced nephrotoxicity. Oral administration of plant extract cured the cisplatin induced kidney damage. There was an increase in serum creatinine, blood urea nitrogen and alkaline phosphatase in rats treated with Cisplatin (5mg/kg body weight, i.p). Administration of Cisplatin followed by alcoholic extract of *Tinospora cordifolia* (500mg/kg body weight, p.o) decreased the increased levels of serum creatinine, blood urea nitrogen and alkaline phosphatase in rats. These biochemical observations were supplemented by histopathological examination of kidney section. Results of this study revealed that the alcoholic stem extract of *Tinospora cordifolia* has curative action against Cisplatin induced nephrotoxicity.

Keywords: Nephrotoxicity, Cisplatin, Tinospora cordifolia.

INTRODUCTION

Tinospora cordifolia Willd (Guduchi) belonging to the family Menispermaceae is a well known Ayurvedic drug. It is categorized as " Rasayana" in traditional Indian System of Medicine "Ayurveda" and is used as general tonic because of its anti-inflammatory, anti-arthritic, anti-allergic, anti-malarial and immunomodulatory properties[1].

The chemical constituents reported from this shrub belong to different classes such as alkaloids, diterpenoids, lactones, glycosides, steroids, sesquiterpenoids, phenolics, aliphatic compounds and polysaccharides[2]. Phenols and alkaloids of this plant have been reported as antioxidants[3]. Extracts of different parts of Guduchi are well researched for immunomodulatory and adaptogenic activities.

Various other pharmacological actions and medicinal uses of Guduchi have also been reported. Chemopreventive activities of *Tinospora cordifolia* including antineoplastic[4], hepatoprotective[5], neuroprotective[6], protection against radiation[7] and lead damage[8] have been reported. These activities are attributed to its immunomodulatory and antioxidant property.

Cisplatin is an antineoplastic agent with remarkable curative effect against cancer, but there are many side effects, nephrotoxicity being the most serious one, which has influenced its clinical use. Cisplatin induced nephrotoxicity is closely related with oxidative stress and generation of free radicals[9]. Several antioxidants such as melatonin[10], lycopene[11] and narigenin[12] have been tested to protect against Cisplatin induced nephrotoxicity. Inhibition of free radicals, free radical scavenging and antioxidant activity of active constituents of *Tinospora cordifolia* are documented[13,14]. Hence it could be a potential candidate to counteract the cisplatin induced nephrotoxicity.

In the present study activity of alcoholic extract of *Tinospora cordifolia* against Cisplatin induced nephrotoxicity in rats was investigated.

MATERIALS AND METHODS

Plant material

The stem of *Tinospora cordifolia* was collected from Indus herbs, Bangalore and it was authenticated from NADRI (National Ayurveda Dietetics Research Institute) Bangalore bearing the authentication number RRCBI/MCW/03.

Preparation of crude extract of *Tinospora cordifolia*

The powdered material was extracted by soxhlation for 16hrs using alcohol as solvent. The extract was then concentrated using rotatory evaporator. The dried extract was used for the study.

The suspension of extract was made in 1% Tragacanth solution.

Maintenance of animals

In-house laboratory bred 6 week old male wistar rats were selected for the study. Animals were maintained under controlled temperature at 20±2^{0}c and relative humidity of 50-60% with an alternating 12hr light/ dark cycle. Food and water provided ad libitum. The research work was approved by Institutional Ethical Committee (Ref -NoAACP/M-109).

Experimental protocol

Rats were divided into 4 groups of 6 each.

Group 1: Served as Control, which received 1% suspension of tragacanth.

Group 2: Served as Drug control, which received alcoholic extract of *Tinospora cordifolia* in 1% tragacanth for 7 consecutive days (500/kg b.w, p.o).

Group 3: Served as Challenge, which received Cisplatin (5mg/kg b.w, i.p) on day one.

Group 4: Served as Treatment group, which received Cisplatin (5mg/kg b.w,i.p) single dose on the day one followed by *Tinospora cordifolia* extract single dose on the 8th day for seven consecutive days.

Biochemical assay

Serum creatinine was assayed according to Jaffe's kinetic method[15], Blood urea nitrogen was assayed according to Berthelot end point assay[16] and Alkaline phosphatase according to pNPP- AMP

(IFCC), kinetic assay[17] using Autospan kits.

Histopathological analysis

Rats were euthanized under light anaesthesia with ether and the kidneys were dissected out. Kidneys were perfused with buffered saline to remove blood and then the left kidney was fixed in 10% neutralized buffered formalin for histopathology studies. Histopathological studies were done at Deepak Diagnostics, Bangalore.

Statistical analysis

The results were expressed as mean± SEM and analyzed with one way analysis of variance between the two groups and followed by Tukey's Multiple comparison test. Probability values $p \leq 0.05$ were considered significant.

RESULTS AND DISCUSSIONS

Tinospora cordifolia has been reported as radioprotective, antitumour and antioxydent agent It has also been credited with beneficial properties to reduce the damage due to oxidative stress and radiation. Therefore in the present study we investigated the possible beneficial effect induced by cisplatin which is one of the widely used chemotherapeutic agent for treatment of several human malegnencies.

Control animals treated with vehicle and *Tinospora cordifolia* (500mg/kg) did not show any significant change in serum creatinine (0.375±0,0088mg/dl) and BUN (17.0266±0.3377mg/dl) levels. Cisplatin (5mg/kg) treatment caused a significant increase in serum creatinine to 1.233±0.0557mg/dl ($p<0.001$) after 7 days compared to control group. The results are shown in Table no. 1. These results are in accordance with previous studies[18].

Cisplatin – induced elevation in serum creatinine, BUN and ALP indicates renal tissue damage. *Tinospora cordifolia* treatment (500mg/kg) group showed a significant decrease ($p<0.05$) in serum creatinine to 1.1356±0.0801mg/dl, BUN ($p<0.001$) to 40.84±3.708mg/dl and ALP ($p<0.001$) to 179.59±2.211mg/dl ($p<0.001$) compared to cisplatin treated groups. The restoration of the levels of BUN & ALP by *Tinospora cordifolia* indicates its curative action.

Histopathological examinations indicated that there were no abnormalities in *Tinospora cordifolia* (500mg/kg) treated rats compared to control (vehicle treated) as shown in Photos 1, 2. There was no glomerular congestion with no evidence of edema, hemorrhage, inflammation or tubular necrosis. The histopathology of kidneys of challenge group indicated that the cisplatin treatment caused severe tubular necrosis. The stoma was edematous with separation of tubules. The tissue was densely infiltrated by chronic inflammatory cells composed of small lymphocytes. Many of the glomeruli showed diffused eosinophilic sclerosis. Tubular atrophy and tubular dialation were also present confirming the nephrotoxic effect of cisplatin at the dose used (Photo 3). *Tinospora cordifolia* treatment in group treated with Cisplatin showed mild renal tissue damage. The stroma showed mild degree of oedema, No evidence of congestion, haemorrhage, glomerular atrophy but tubular atrophy was present. These results indicated curative effect of *Tinospora cordifolia* against cisplatin- induced nephrotoxicity.

Inhibition of the generation of free radicals and free radical scavenging activity is important in the protection against cisplatin-induced nephrotoxicity[14]. Since *Tinospora cordifolia* is well established for its rejuvinative and antioxidant property[3] it is possible that the mechanism of nephrocurative action observed in the present study may be attributed to its antioxidant activity due to the presence of phenolic and flavanoidal compounds.

Table 1: Effect of treatments on Serum Creatinine, Blood urea nitrogen & Alkaline phosphatase

Sl No.	Groups	Serum Creatinine (mg/dl)	Blood urea nitrogen (mg/dl)	Alkaline phosphatase
1.	Control (vehicle, 0.5ml)	0.425±0.0291	17.636±0.5078	150.5066±0.6352
2.	*Tinospora cordifolia* (500mg/kg, p.o)	0.375±0.0088$^{\#}$	17.0266±0.3377$^{\#}$	147.8933±0.2182$^{\#}$
3	Cisplatin (5mg/kg, i.p)	1.233±0.0557$^{\#\#\#}$	136.3016±4.784$^{\#\#\#}$	343.17±1.501$^{\#\#\#}$
4	Treatment Cisplatin (5mg/kg, i.p) + *Tinospora cordifolia* (500mg/kg, p.o)	1.1356±0.0801*	40.84±3.708***	179.59±2.211$^{***,\#}$

Values are expressed as Mean±SEM

Statistical analysis:

One way ANOVA followed by Tukey's Multiple Comparison Test; #($p<0.05$) vs control group; ***($p<0.001$) vs challenge group

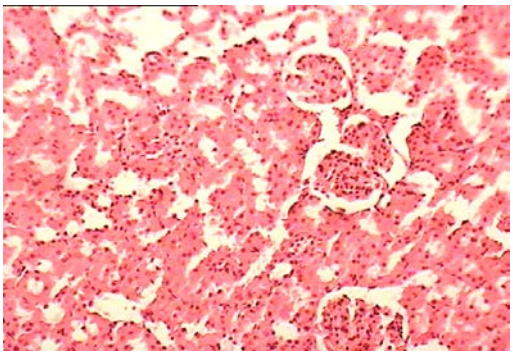

Photo. 1: Histopathology of Control treated rats

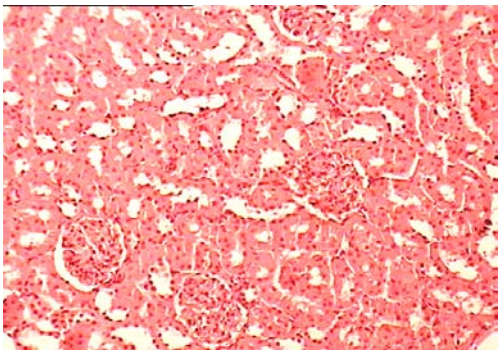

Photo. 2: Histopathology of Drug control treated rats

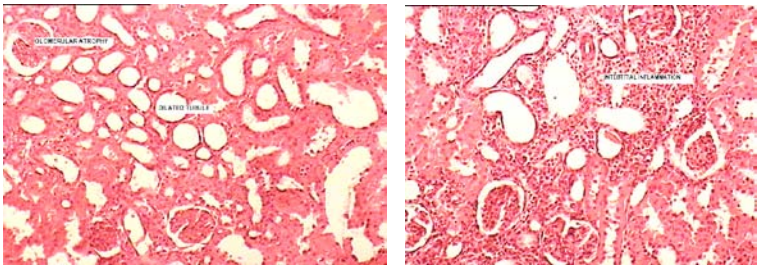

Photo. 3: Histopathology of Challenge treated rats

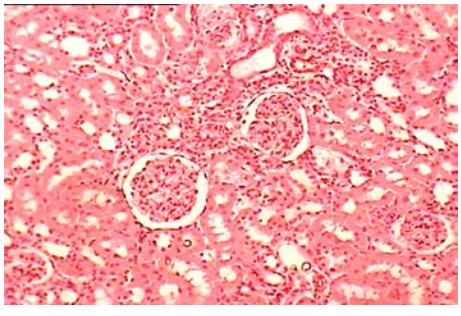

Photo. 4: Histopathology of Treatment rats

CONCLUSION

Alcoholic extract of *Tinospora cordifolia* can be used in combination with Cisplatin for treatment against various malignancies with beneficial effect against nephrotoxicity.

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