Effect of ethanol extract of *Graptophyllum pictum (L.)* Griff. on cisplatin induced nephrotoxicity in rats

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S u m m a r y

The purpose of the present study is to investigate whether the alcoholic extract of *Graptophyllum pictum* (L.) Griff. could decrease the intensity of nephrotoxicity in albino rats. Cisplatin at a single dose of 12 mg/kg body weight was administered intraperitonially to albino male Wistar rats. Nephrotoxicity was assessed by determining the serum creatinine and urea levels as well as renal antioxidant status in rats after cisplatin administration. Ethanolic extract of *G. pictum* at 150 and 300 mg/kg body weight was administered orally after cisplatin injection for 15 days. The extracts could significantly reduce the elevated serum creatinine and urea levels. Renal antioxidant defence systems, such as superoxide dismutase, catalase, glutathione peroxidase activities and reduced glutathione level, depleted by cisplatin therapy were restored to normal by treatment with the extract. Cisplatin induced lipid peroxidation was also found markedly reduced by treatment with the extract. This result indicated that ethanolic extract of *G. pictum* rendered significant preventive effect against cisplatin induced nephrotoxicity.

Key words: *antioxidant, Acanthaceae, free radical oxidative stress, cisplatin-induced renal damage, nephrotoxicity, Graptophyllum pictum*

INTRODUCTION

Graptophyllum pictum Linn (*Acanthaceae*) commonly called caricature plant or Joseph's coat has not been documented earlier as a therapeutic agent. Therefore, no literature on its use is available. It was mainly used as an ornamental plant to adorn the home gardens in Nigeria. Elsewhere it was reportedly used in folk medicine as poultice on cuts, wounds and all kinds of swellings and for the treatment of ulcer, abscess, hemorrhoids etc. [1-2]. Some pharmacological studies on this plant crude extract were reported for anti-inflammatory [3], oxytocic and anti-implantation activity [4]. The present study on probable nephroprotective action was done based on the local use of the plant for this purpose. This plant is used in several households in and around Udupi for some kidney and urinary problems, where the fresh leaves of the plant are crushed and mixed with milk and given to the patient early in the morning into empty stomach. Ayurvedic physician in Sagar near Shimoga uses this plant successfully. By keeping its use in the treatment of renal impairments, the present study investigates the scientific basis for the use of the plant in the management of nephrotoxicity using the cisplatin model.

Chemotherapy and radiotherapy are the most common methods of cancer treatment. Cisplatin (Cis-diamino dichloro platinum II) is currently one of the most important chemotherapeutic drugs used in treatment of a wide range of solid tumors - head, neck, ovarian and lung cancers. However, the clinical usefulness of this drug is limited due to the induction of nephrotoxicity, a side effect that may be produced in various animal models. Cisplatin gets accumulated in the tubular epithelial cells of proximal kidney tubule, causing nephrotoxicity characterized by morphological destruction of intracellular organelles, cellular necrosis, loss of microvilli, alterations in the number and size of the lysosomes and mitochondrial vacuolization, followed by functional alterations including inhibition of protein synthesis, GSH depletion, lipid peroxidation and mitochondrial damage. Several distinct mechanisms have been proposed for cisplatin cytotoxicity in renal tubule cells, including direct DNA damage [5], activation of caspase [6], mitochondrial dysfunction [7], formation of reactive oxygen species [8], effects on the endoplasmic reticulum [9] and activation of TNF-α mediated apoptotic pathways. It has also been reported that cisplatin-induced nephrotoxicity is closely associated with an increase in lipid peroxidation in the kidney. In addition, cisplatin has been found to lower the activities of antioxidant enzymes and to induce depletion of GSH.

A large number of studies have reported the beneficial effects of a variety of antioxidants in cisplatin-induced nephrotoxicity [10]. Agents such as SOD, dimethyl thiourea and GSH have been shown to reduce the degree of renal failure and tubular cell damage when administered simultaneously with cisplatin in rat [11]. Much attention has been given to the possible role of dietary antioxidants in protecting the kidney against cisplatin-induced nephrotoxicity. There is a large number of evidence on the chemoprotecting activities of vitamin C, E, curcumin, selenium, bixin and other dietary components that scavenge free radicals induced by exposure to cisplatin.

MATERIALS AND METHODS

Plant material

Plants were collected from Udupi district, Karnataka, India, in the months of August-September, 2004. The botanical identity of the plant material was confirmed by Dr. Gopalkrishna Bhat, Professor of Botany, Poorna Prajna College, Udupi, Karnataka, India. A voucher herbarium specimen PP 910 has been deposited in the Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal, India. The plants were shade dried and powdered.

Animals

Healthy adult male albino rats (100–200 g) of *Wistar* strain aged 60–90 days were used for the study and obtained from Central Animal House, M.A.H.E, Manipal. The rats were housed in polypropylene cages and maintained under standard conditions (12/12 h light/dark cycle; 25±3°C; 35–60% humidity). The animals had free access to standard lab chow (Hindustan Lever Ltd. Mumbai, India) and tap water. The study was conducted after obtaining clearance from Institutional Animal Ethical Committee (IAEC/KMC/07/2007–2008).

Preparation of ethanol extract

The shade dried powdered plant was exhaustively extracted with 95% ethanol, using Soxhlet apparatus. Then total ethanol extract was concentrated *in vacuo* to a syrupy consistency. The extract (GPE) was stored at 15-20°C in sealed desiccators.

Experimental design

Animals were divided into five groups each of six rats. Group I: Normal control rats administered gum acacia daily for 15 days. Group II: normal rats were treated with ethanol extract of *G. pictum* 300 mg/kg for 15 days. Group III: Rats were treated with a single i.p. dose of cisplatin 12 mg/kg was kept as nephrotoxic control. On 6th and 15th day blood was withdrawn and checked for nephrotoxicity. Group IV & Group V: Rats were treated with a single i.p. dose of cisplatin 12 mg/kg on first day followed by *G. pictum* ethanol extract 150 mg/kg and 300 mg/kg from 6th day to 15th day for 10 days.

At the end of the experimental period the rats were anaesthetized and sacrificed by cervical dislocation. Blood samples were collected by heart puncture for measuring serum urea and serum creatinine levels. The kidneys were excised, rinsed in ice cold saline and then homogenized with Tris-Hydrochloric buffer (pH 7.4). The tissue homogenates were used for the estimation of various antioxidant properties.

Determination of lipid peroxidation

The extent of lipid peroxidation was assessed by measuring the amount of thiobarbituric acid-reactive substances (TBARS). Briefly, 500 mg of tissue was gently minced in 4.5 ml of 0.25 M sucrose. The minced tissues were gently homogenized and then centrifuged at 2000 rpm for 30 min, and 0.1 ml of the supernatant was treated with a buffer containing 0.75 ml of thiobarbituric acid (0.8%, w/v), 0.75 ml of 20% acetic acid (pH = 3.5) and 0.1 ml of sodium dodecylsulfate (8.1%, w/v). The volume of this solution was made up to 2 ml with distilled water and the mixture was heated in a boiling water bath for 60 min. The absorbance was then measured at 532 nm [12].

GSH determination

Reduced glutathione was determined using the glutathione reductase 5, 5´-dithiobis-2-nitrobenzoic acid (DTNB) recycling procedure. Briefly, 100 mg of tissues was homogenized in a buffer containing EDTA (0.2 M) to obtain 4% (w/v) whole homogenate. Then, 1.5 ml of the suspension was taken and mixed with a buffer containing 2.5 ml distilled water and 0.5 ml of 50% TCA. Then the mixture was centrifuged at 3000 rpm for 15 min, and 1 ml of the supernatant was mixed with 1 ml of Triss buffer (0.4 M, pH = 8.9) and 0.1 ml of DTNB (0.01 M). The absorbance was measured after 5 min at 412 nm [13].

Superoxide dismutase (SOD) determination

This activity was assayed by its ability to inhibit reactions dependent on the generation of $0_{2\cdot}$ by a xanthine-xanthine oxidase system. The reactions used were the conversion of Nitro-Blue Tetrazolium into formazan, which was assayed spectrophotometrically at 560 nm [14].

Catalase (CAT) determination

Catalase activity was determined from the rate of decomposition of H_2O_2, monitored by decrease of absorbance 240 nm following the addition of tissue homogenate [15].

Tissue glutathione peroxidase (GPx) determination

Glutathione peroxidase is the general name of an enzyme family with peroxidase activity, whose main role is to protect the organs from oxidative damage. The biochemical function of GPx is to reduce lipid hydro peroxides to their corresponding alcohols and to reduce free H_2O_2 to H_2O. GPx remaining is measured using DTNB, which gives a yellow colored complex [16].

Histopathological studies

Two animals from each group were sacrificed on the day of blood withdrawal and kidneys were isolated. The kidney sections were stained with hematoxyline and eosin and then observed under light microscope.

Statistical analysis

Results are given as mean ±SEM. Data were analyzed using one-way ANOVA followed by post hoc Sheffe's test using SPSS computer software version 7.5. The statistical significance of difference was taken as $p<0.05$.

RESULTS

Effect of *G. pictum* on kidney MDA level

Table 1 shows the concentration of TBARS in the normal cisplatin-induced nephrotoxic rats. Cisplatin caused an elevation of TBARS level which decreased upon administration of GPE.

Table 1.

Protective effect of *G. pictum* extract against cisplatin-induced GSH depletion and MDA in kidney of rats

group	treatment (mg/kg)	GSH (μg/mg protein)	MDA (ng/mg protein)
normal	–	15.8±0.94	0.43±0.23
normal + GPE	300	16.2±1.5	0.52±0.09
cisplatin	12	6.8±0.49[a]	1.02±0.04[a]
cisplatin + GPE	150	12.3±0.39[b]	0.62±0.05[b]
cisplatin + GPE	300	14.8±0.92[b]	0.48±0.26[b]

All data are presented as mean ±SEM, n=6, [a]p<0.001 significantly different with respect to normal group. [b]p<0.001 significantly different when compared with cisplatin group.

Effect of *G. pictum* on GSH level

Cisplatin treated rats showed decreased concentration of GSH in the kidney. This was reverted back to normal level after treatment with GPE (tab. 1).

Effect of *G. pictum* on serum creatinine and serum urea level

Serum creatinine and urea level were significantly elevated in the cisplatin treated animals compared to the control group. The increase of serum creatinine and urea levels was reverted back to normal after the treatment with GPE (tab. 2).

Table 2.

Effect of *G. pictum* on serum creatinine and serum urea level

group	treatment (mg/kg)	urea (mg/dl)	creatinine (mg/dl)
normal	–	36.06±3.53	0.32±0.016
normal + GPE	300	35.09±1.65	0.53±0.049
cisplatin	12	32.8±32.8	4.90±0.68
cisplatin + GPE	150	58.31±6.48[b]	1.13±0.057[b]
cisplatin + GPE	300	39.44±1.92[b]	0.52±0.03[b]

All data are presented as mean ±SEM, n=6, [ap]p<0.001 significantly different with respect to normal group. [b]p<0.001 significantly different when compared with cisplatin group.

Effect of *G. pictum* on CAT, GPx and SOD levels

Cisplatin treatment lowered the CAT and also showed decrease in concentration in the nephrotoxic group which was increased upon administration of GPE (fig. 1). Similar results were observed in GPx and SOD activity values are shown in figures 2 and 3.

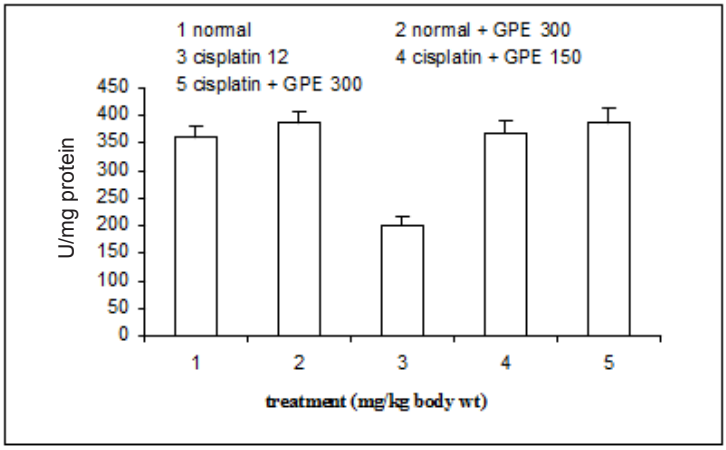

Figure 1. Effect of GPE at 150 and 300 mg/kg on CAT level in kidney of cisplatin induced nephrotoxic rats *in vivo*

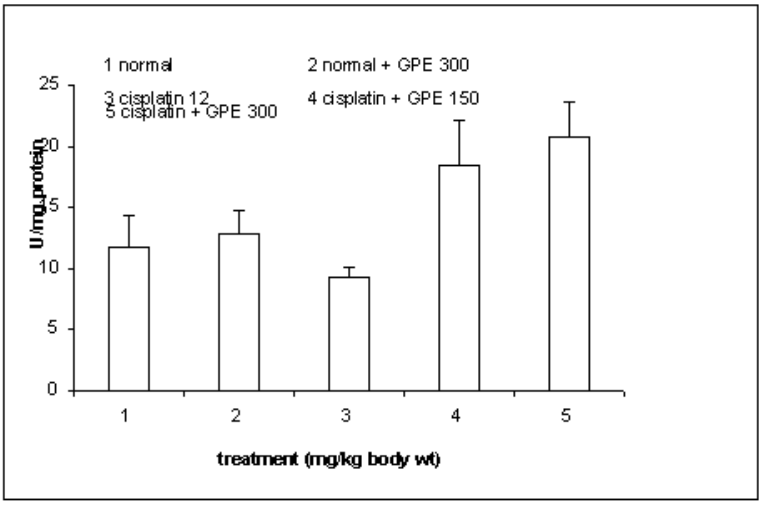

Figure 2. Effect of GPE at 150 and 300 mg/kg on GPx level in kidney of cisplatin induced nephrotoxic rats *in vivo*

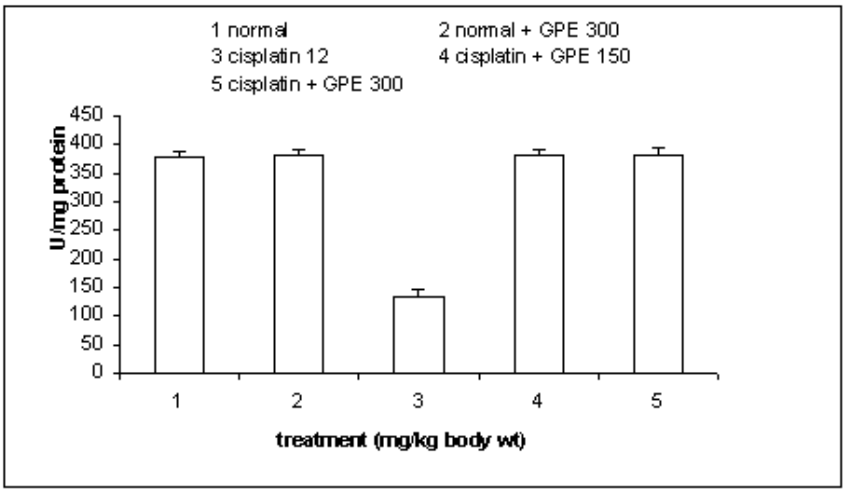

Figure 3. Effect of GPE at 150 and 300 mg/kg on SOD level in kidney of cisplatin induced nephrotoxic rats *in vivo*

Effect of *G. pictum* on histopathological features of cisplatin-induced renal damage

The presence of peritubular and glomerular congestion, tubular casts, epithelial degeneration, interstitial edema, blood vessel congestion and infiltration by inflammatory cells, which are features of acute tubular necrosis, were observed in the histopathological sections of rats treated with cisplatin. The extract reversed the acute tubular necrosis and other features of damage (tab. 3, fig. 4a, b, c, d and e).

Table 3.

Effect of *G. pictum* on histopathological features of renal damage induced by cisplatin (12 mg/kg)

effect	control	cisplatin 6th day	cisplatin 16th day	cisplatin + GPE 150 mg/kg	cisplatin + GPE 300 mg/kg
glomerular congestion	–	+++	+++	–	+
tubular casts	–	+++	+++	+	+
peritubular congestion	–	+++	+++	–	–
epithelial desquamation	–	+++	+++	+	–
blood vessel congestion	–	+++	+++	–	–
interstitial edema	–	+++	+++	+	–
inflammatory cells	–	+++	+++	+	+

(–) normal; (+) mild effect; (+++) severe effect

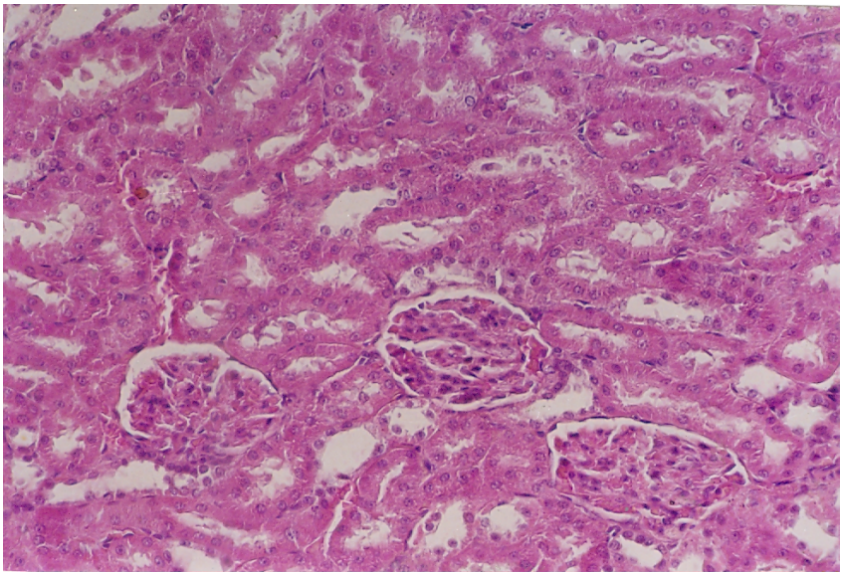

Figure 4.
a) Photomicrograph of normal kidney showing normal glomeruli and tubules

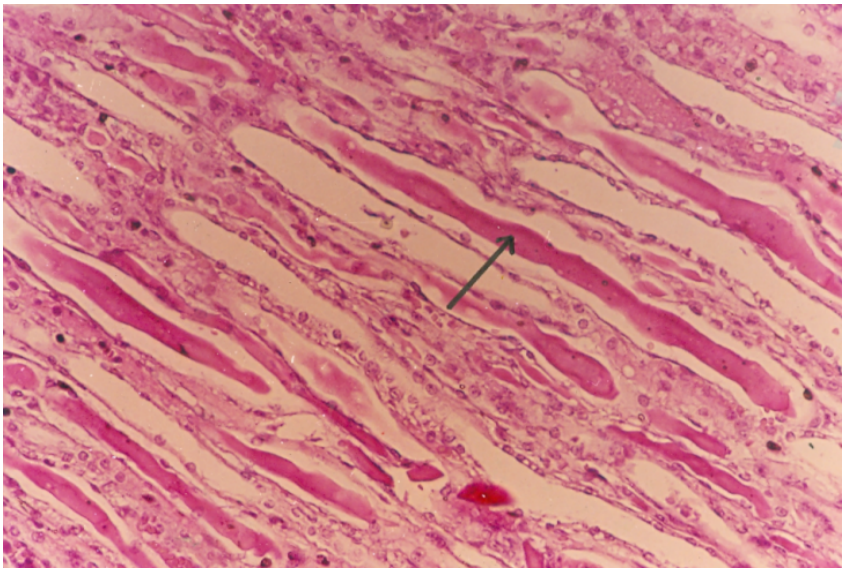

Figure 4.
b) Photomicrograph of kidney treated with cisplatin showing tubular casts on 6th day

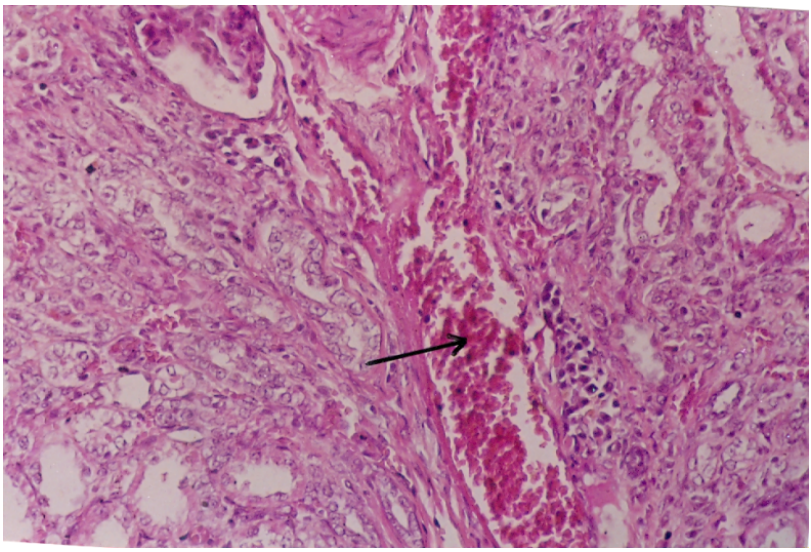

Figure 4.
c) Photomicrograph of kidney treated with cisplatin on 16th day showing tubular casts, glomerular congestion, epithelial desquamation and blood vessel congestion

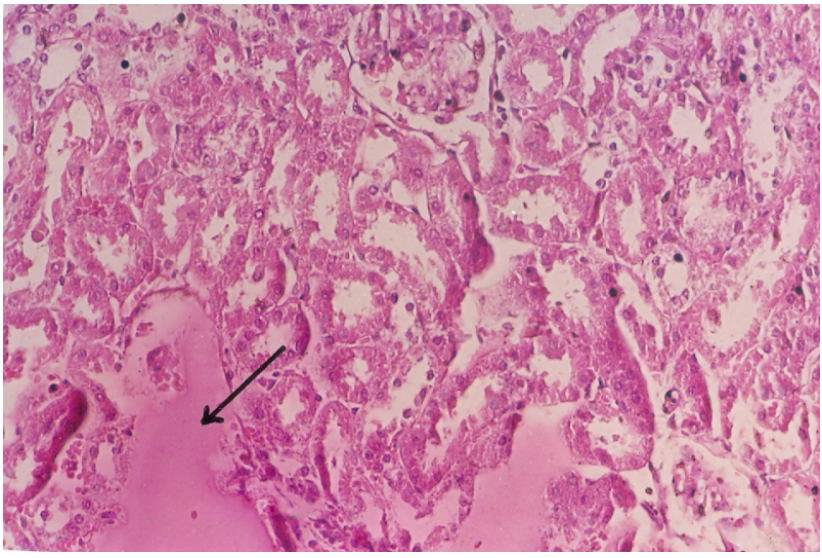

Figure 4.
d) Photomicrograph of kidney following ethanol extract of *G. pictum* 300 mg in cisplatin treated group showing normal glomeruli, no tubular casts, or epithelial desquamation, only peritubular oedema

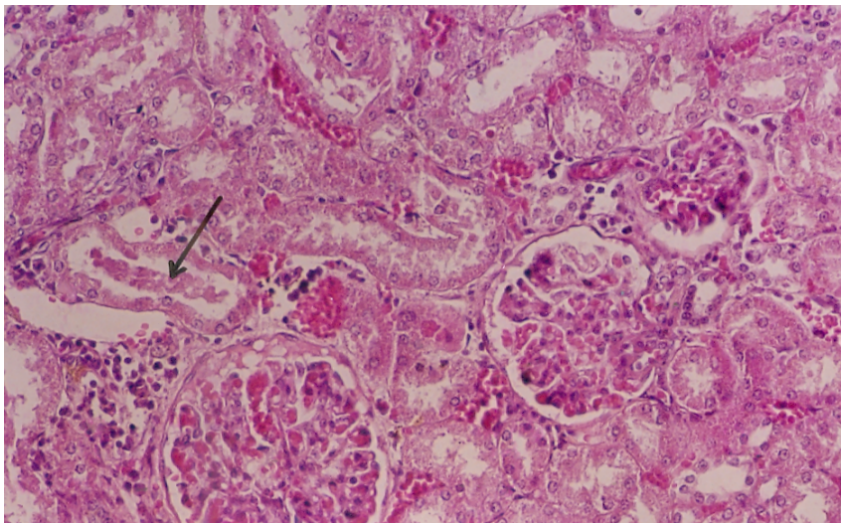

Figure 4.
e) Photomicrograph of kidney following ethanol extract of *G. pictum* 150 mg in cisplatin treated group showing no glomerular congestion, no tubular casts, only peritubular congestion

DISCUSSION

Extensive use of cisplatin for the management of oncological therapy is usually accompanied by long term non-hematological toxicity such as nephrotoxicity [17]. Several lines of evidence reported so far states that reactive oxygen species play a deleterious role in causing nephrotoxicity [18]. It has been recognized that the nephrotoxic effect of cisplatin has been witnessed by the spectrum of cytotoxic injury ranging from mild sublethal changes to a catastrophic necrotic death which leads to inflammatory response [19].

Histological changes of rat kidney after cisplatin treatment revealed acute tubular necrosis which confirms irreversible kidney injury. Cisplatin intoxication also showed a severe atrophy of glomerulus which was apparent due to the reduction in its size. Marked dilation of proximal convoluted tubules with slogging of almost entire epithelium due to desquamation of tubular epithelium was evident. Cellular debris in the tubular lumen and increased tissue in the interstium is also an indication of cisplatin-induced renal necrosis.

ROS such as hydrogen peroxide, the superoxide anion, and hydroxyl radicals are generated under normal cellular conditions and are immediately detoxified by endogenous antioxidants, like GSH, catalase and superoxide dismutase, but excessive ROS accumulation by cisplatin causes an antioxidant status imbalance and leads to lipid peroxidation and GSH depletion [20]. The basic effect of cisplatin-induced toxicity on the

cellular membrane is believed to be peroxidation of membrane lipids. The depletion of glutathione at early intervals in treated animals may be due to its utilization in large amounts to combat the acute cisplatin-induced free radical damage, as glutathione is a major nonenzymatic antioxidant. The measurement of lipid peroxidation as thiobarbituric acid reacting substances (TBARS) is a convenient method of monitoring the oxidative damage in tissues. Reactive oxygen species cause peroxidation of membrane lipids with devastating effect on functional states. The preservation of cellular membrane integrity depends on protection or repair mechanisms capable of neutralizing oxidative reactions. Our data show that cisplatin-induced malondialdehyde (MDA) production was significantly decreased by the p.o. administration of GPE *in vivo* and it also attenuated cisplatin-induced GSH depletion in mice. It has been suggested that cisplatin is able to generate ROS and that it inhibits the activities of antioxidant enzymes in renal tissues. In the present study the reduced activities of GPx, SOD and catalase in kidneys of mice treated with cisplatin were restored by administration of GPE to a considerable extent indicating the ability of GPE to eliminate oxidative stress.

Cisplatin has been thought to bind to the renal base transport system. Cisplatin induces hypomagnesemia through its renal toxicity possibly by a direct injury to mechanisms of magnesium reabsorption in the ascending limb of the loop of Henle as well as the distal tubule. The primary symptoms of cisplatin nephrotoxicity are inhibition of protein synthesis and intracellular GSH and protein-SH depletion, resulting in lipid peroxidation and mitochondrial damage. The peroxidation of membrane lipids may account for its nephrotoxicity [21]. Available evidence suggests that cisplatin exerts its nephrotoxic effects by generating of free radicals [22-23]. GSH and protein-SH form the major cellular anti-oxidant defence systems, which control lipid peroxidation. From these pathomechanisms of cisplatin nephrotoxicity, it is clear that the nephrotoxicity of cisplatin involves reactive radicals. Thus, the reasonable cellular-protective agents against cisplatin toxicity may have at least some antioxidant properties to prevent GSH depletion and/or scavenge the intracellular reactive oxygen species.

Present observations support the hypothesis that the mechanism of nephrotoxicity is related to the depletion of the antioxidant defence system. Cisplatin treatment has been shown to induce loss of copper and zinc in kidneys. The decrease in SOD activity in renal tissues following cisplatin administration might be due to the loss of copper and zinc [24]. The activity of Catalase and GPx is also found to decrease after cisplatin administration resulting in the decreased ability of the kidney to scavenge toxic hydrogen peroxide and lipid peroxides.

Numerous studies have shown that cisplatin induces renal damage by free radical generation. Hence, antioxidants and free radical scavengers of natural and synthetic origin might provide nephroprotection in cisplatin-induced renal injury [25]. The experimental results reveal that the ethanol extracts of *G. pictum* could help prevent nephrotoxicity manifested consequently to cisplatin chemotherapy. The effect is mainly due to the capacity of the extract to restore renal antioxidant defence system.

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WPŁYW WYCIĄGU ALKOHOLOWEGO Z *GRAPTOPHYLLUM PICTUM* (L.) NA DZIAŁANIE CISPLATYNY WYWOŁUJĄCEJ NEFROTOKSYCZNOŚĆ U SZCZURÓW

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S t r e s z c z e n i e

Celem niniejszej pracy było zbadanie właściwości wyciągu alkoholowego z *Graptophyllum pictum* (L.) zmniejszającej nefrotoksyczność indukowaną cisplatyną u szczurów. Cisplatynę podawano szczurom dootrzewnowo w pojedynczej dawce w ilości 12 mg/kg masy ciała. Nefrotoksyczność oceniono na podstawie określenia stężenia kreatyniny w surowicy, poziomu mocznika, a także aktywności przeciwutleniającej nerek u szczurów. Wyciąg alkoholowy z *G. pictum* podawano dożołądkowo w dawkach od 150 do 300 mg/kg masy ciała przez 15 dni po uprzednim podaniu cisplatyny. Wykazano, że podawanie ekstrakty mogą istotnie obniżyć stężenie mocznika i kreatyniny podwyższone przez cisplatynę. Ponadto podawanie cisplatyny wywołało zaburzenia w działaniu dysmutazy ponadtlenkowej, kata-

lazy, peroksydazy glutationowej, powodując zaburzenia mechanizmów obronnych nerek oraz obniżenie poziomu glutationu, natomiast ich prawidłowe funkcjonowanie zostało przywrócone po podaniu ekstraktu. Badanie również wykazało, że wzrost poziomu peroksydacji tłuszczów wywołany za pomocą cisplatyny zostaje znacznie zmniejszony w wyniku podawania ekstraktu. Przedstawione wyniki badań wskazują na prewencyjne działanie wyciągu alkoholowego otrzymanego z *G. pictum* przeciwko nefrotoksyczności indukowanej cisplatyną.

Słowa kluczowe: *przeciwutleniacze, Acanthaceae, wolne rodniki, stres oksydacyjny, cisplatyna wywołująca zaburzenia pracy nerek, nefrotoksyczność, Graptophyllum pictum*

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