Phyto Chemical Screening and Evaluation of Nephroprotective Activity of Ethanolic Extract of Leaves of Sebastiana Chamaelea in Chemically Induced Nepro Toxic Rats

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Abstract

The plant contains alkaloids, Glycosides, Flavonoids, Tanins Proteins, Amino Acids. The renal antioxidant status, such as SOD, CAT, GPx activities, and reduced GSH concentration are significantly decreased in the cisplatin treated group of animals compared to the control group. The declined antioxidant status partially explains the mechanism of nephrotoxicity induced by cisplatin. The histopathological evaluation of the kidney preparations in treatment group also revealed a decreased cisplatin-induced tubular necrosis. Cisplatin-induced renal damage is associated with increased renal vascular resistance and histopathological damage to proximal tubular cells. On the other hand, an increase in GSH levels in the renal tissue indicates that pretreatment with EESC was due to oxidative stress. The effects of EESC on cellular GSH may be due to antioxidant effects. The treatment with EESC prevented the lipid peroxidation by enhancing the renal CAT, SOD and GPx activities. it was shown that cisplatin treatment induced renal damage and pretreatment with ethanolic extract of *Sebastiana chamaelea* (EESC) provided protective effect against this cisplatin-induced nephrotoxicity. However, before concluding a potential usefulness of ethanolic extract of *Sebastiana chamaelea* (EESC) as adjunct to the cisplatin therapy, further clinical investigation is needed.

Key words: Phyto Chemical Screening, Nephroprotective Activity, Ethanolic Extract, Leaves, Sebastiana Chamaelea

INTRODUCTION

The kidneys play an important role in human physiology, maintaining fluid homeostasis, regulating blood pressure, erythrocyte production and bone density, regulating hormonal balance, and filtering and removing nitrogenous and other waste products [1,2]. Chronic kidney disease (CKD) is characterized by a progressive loss of functions while acute kidney injury (AKI) is an abrupt reduction in kidney function. Both CKD and AKI have increased worldwide and are considered one of the leading public health problems [2,3]. A projection of health concerns by 2040 ranked CKD as the fifth leading cause of death worldwide [3]. In addition, kidney diseases have been recognized as risk factors for severe forms of COVID-19 [4]. The increase of their prevalence is associated with the increase of diabetes Mellitus (DM) and hypertension as the main reported causes of kidney dysfunctions, although various factors can trigger this physiopathology. Factors are classified, based on the pathway they led to kidney damage, as pre-renal, intrinsic, and post-renal factors.

According to clinical criteria, pre-renal diseases are related to a decrease in renal perfusion or alteration in the systemic circulation, which will first compromise the glomerular filtration rate (GFR) and secondly lead to more severe alterations in the kidney structure. These dysfunctions are reflected in clinical analyses by changes in biomarker levels; for example, an increase in serum creatinine; and fluctuations in urine flow [5,6]. Several diseases have been identified as pre-renal factors such as bleeding, trauma, shock, hypertension, cirrhosis, diabetes, systemic infections, hypotension, autoimmune diseases, rhabdomyolysis, disorders of the gut microbiota, liver damage, and intravascular volume depletion [7]. The factors that directly cause kidney damage are intrinsic, whether heavy metals, trauma, Wegener's granulomatosis, proteinuria, congenital abnormalities, drug toxicity, renal atheroembolic disease, arthralgias, lupus erythematosus, or kidney cancer. Histologically, the main diagnoses are ischemic acute tubular necrosis, nephrotoxic acute tubular necrosis, and glomerulonephritis [8]. Any other health disorders which can indirectly induce kidney failures that occur after the physiological action of the kidney are post-renal diseases. Among these post-renal factors, mainly related to urinary flow disorders, are the ureter and urethra obstruction due to blood clots, lithiasis, or tumor growth, which can lead to increased pressure inside tubules, and as a consequence, the GFR is compromised, and a urinary tract infection (UTI) [9] is caused.

Kidney diseases can be addressed at several levels according to the physiological pathway of the original cause. Each pre-renal and post-renal disease currently has pharmacological treatments; however, most of the drugs used cause adverse effects and sometimes lead to intrinsic kidney damage. Among them are non-steroidal anti-inflammatory drugs (NSAID), proton pump inhibitors, antibiotics, and chemotherapy [10,11,12,13]. Nephrotoxicity of drugs administrated as treatments for pre-renal and post-renal diseases, as well as for other diseases, is now considered as a risk factor of acute and chronic kidney conditions. To avoid the adverse effects caused by medication, different alternatives have been sought to treat these pathologies.

Plants have been traditionally used as treatments for various diseases, among them several pathologies identified as pre-, intra-, and post-renal factors. The medicinal characteristics of plants have been attributed to their secondary metabolites, which can protect against pathogens or have important physiological benefits to prevent some diseases [14,15]. Plants provide a wide range of bioactive compounds which act as antioxidants, anti-inflammatory, diuretic, anticancer, and antimicrobial [16,17,18]. Further, nephroprotective agents from plants mitigate processes such as interstitial nephritis, altered intraglomerular hemodynamics, tubular necrosis, or glomerulonephritis [19]. Previous works have already reviewed the usages of plants and phytochemicals as nephroprotective agents providing an important understanding of how extracts or single compounds interfere with molecular pathways to mitigate kidney diseases [2,20]. However, they usually focused on intrinsic damage such as nephrotoxicity, omitting the pre-renal and post-renal factors, and to our knowledge, no classification of nephroprotective plants according to pre-, intra-, and post-renal diseases have been reported.

The present study was undertaken to find out the effect of the potential nephroprotective effect of *Sebastiana chamaelea* and their effects on cisplatin induced nephrotoxicity in wistar rats. Plants have played a weighty role in maintaining human health and improving the quality of human life for thousands of years and have several precious components of medicines, seasonings, beverages, cosmetics and dyes. Herbal medicines are based on the premise that plants contain natural substances that can promote health and alleviate illness. In recent times, focus on plant research has increased all over the world and large evidence has collected to show immense potential of medicinal plants used in various traditional systems. Today we are witnessing a great deal of public interest in the use of herbal remedies. Many western drugs had their origin in plant extract. There are many herbs, which are preponderantly used to treat cardiovascular problems, liver disorders, central nervous system, digestive and metabolic disorders. Given their potential to generate significant therapeutic effect, they can be useful as drug or supplement in the treatment, management of many diseases. Herbal drug or medicinal plants, their extracts and isolated compounds have demonstrated spectrum of biological activities. Such have been used and continued to be used as medicine in folk–fore or food supplement for various disorders. The present investigation was undertaken to study the effect of *Sebastiana chamaelea* on changes in kidney parameters such as Blood urea nitrogen, serum creatinine, urea and anti- oxidant enzymes in cisplatin-induced nephrotoxicity in rats. The effects produced by this plant extract on different parameters were compared with silymarin.

METHODS:

Whole plant of *Sebastiana chamaelea* were collected from Chittoor district forest,shed dried for a week in a shadow and blended to coarse powder.

About 500gm of dried fine powder of *Sebastiana chamaelea* were soaked in the extractor and macerated for 30 hrs with petroleum ether. There it is reflexed successfully with chloroform, after that it is extracted with alcohol and water by continuous hot percolation method using soxhlet apparatus for 40 hrs separately. Ethanolic extracted was filtered and concentrated in vacuum using rotary flask evaporator under reduced pressure. After concentration ethanolic extract of *Sebastiana chamaelea* given brownish residue stored in air tight container were subjected to qualitative test for identification of various plant constituents.

Table. No 1: QUALITATIVE CHEMICAL ANALYSIS OF ETHANOLIC EXTRACT OF *Sebastiana chamaelea* .

SI.NO	Test for plant constituents	*Boerhaavia diffusa Linn.*
1	***Test for alkaloids***	
	a. Mayer's Test	+
	b. Dragendorff's Test	+
	c. Wagner's Test	+
	d. Hager's Test	+
2	***Test for Glycosides***	
	a. Legal's Test	+
	b. Baljet's Test	+
	c. Borntrager's Test	+
	d. Keller-Killani's Test	+
3	***Test for Flavanoids***	
	a. Ferric chloride Test	+
	b. Shinoda's Test	+
	c. Fluorescence Test	+
	d. Reaction with alkali and acid	+
4	***Test for Tannins and Phenolic Compounds***	
	a. 5% Ferric chloride solution test	+
	b. Reaction with lead acetate	+
	c. Gelatin test	_
6	***Test for Proteins and amino acids***	
	a. Ninhydrin Test	+
	b. Biuret Test	+
	c. Millon's test or Cole's Mercuric Nitrate test	+
	d. Xanthoprotein test	+
7	**Test for Carbohydrates**	
	a. Molisch's test	-
	b. Fehling’s test	-
	c. Benedict's test	-

EXPERIMENTAL MODELS

For the study of Nephroprotective and antioxidant activity an animal model was added that would satisfy the following conditions.

- ❖ The animal should develop nephrotoxicity rapidly and reproducibly.
- ❖ Pathological changes in the site of induction should result from kidney damage.
- ❖ The symptoms should be ameliorated or prevented by a drug treatment effective in human beings.
- ❖ The drug tested should be administered orally.
- ❖ Drug dosage approximate the optimum therapeutic range for human, scaled the test animal weight.

LABORATORY ANIMAL MODELS

Induction of nephro toxicity and free radicals in animal model:

The *invivo* mechanisms of cisplatin nephrotoxicity are complex and involve oxidative stress, inflammation and apoptosis. Apoptotic markers include proteins from both pro- apoptotic and anti-apoptotic elements. Bak is a pro-apoptotic member of the Bcl-2 family of apoptotic proteins. The Bcl-2 related proteins interact with one another through the formation of homo and heterodimers.

The susceptibility of cells to apoptotic stimuli is thought to be controlled by the relative ratios of the different Bcl-2 family proteins. This protein localizes to mitochondria and functions to induce apoptosis. It interacts with and accelerates the opening of the mitochondrial voltage- dependent anion channel, which leads to a loss in membrane potential and the release of cytochrome c.

MATERIALS AND METHODS:

Animal

In-house laboratory bred 6 week old 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 animal Ethical Committee.

Experimental protocol

Rats were divided into 5 groups of 6 each.

Group 1: Served as Normal Control, which received 10ml/kg of normal saline.
Group 2: Served as Toxic control, which received Cisplatin (7.5mg/kg b.w, i.p) on day one.
Group 3: Served as positive control which received Cisplatin (5mg/kg b.w, i.p) on day one followed by silymarin (50mg/kg b.w, orally) for 10 days.
Group 4: Served as Treatment group, which received Cisplatin (5mg/kg b.w,i.p) single dose onthe day one followed by at a dose of 200mg/kg orally for 10 days.
Group 5: Served as Treatment group, which received Cisplatin (5mg/kg b.w,i.p) single dose on the day one followed by EESC at a dose of 400mg/kg orally for 10 days.

BIOCHEMICAL ASSAY

On day 11 cisplatin injection was administered to all groups except normal control. After 72 hrs of cisplatin injection animals were sacrificed using ether anesthesia; blood samples were collected by retro orbital puncture for measuring BUN,Scr,Alp and urea. Kidneys were quickly removed and washed with ice –cold normal saline and homogenates (10%w/v) were prepared in PBS.A part of the homogenate was used for the estimation of glutathione (GSH) and lipid per oxidation. The remaining homogenate was centrifuged at 5000 rpm for 10 min at 4^{0}C; after removal of the cell debris, the supernatant was used for the assay of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX).

Serum creatinine was assayed according to Jaffe's kinetic method, Blood urea nitrogen and urea was assayed according to Berthelot end point assay and Alkaline phosphatase according to pNPP- AMP (IFCC), kinetic assay using Autospan kits.

The GSH level was measured colorimetrically using 5, 5'- Dithio.bis (2 - nitrobenzoic acid) (DTNB) as the substrate. The concentrations of malondialdehyde (MDA) as indices of lipidperoxidation were assessed. The SOD activity was determined by the Nitro blue tetrazolium (NBT) reduction method. The GPx activity was determined by the method. The CAT activity was determined from the rate of decomposition of H_2 O_2, method.

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 Apollo diagnostics, Madurai.

Statistical analysis:
The results were expressed as Mean± S.E.M and analyzed with one way analysis of variance between the two groups and followed by newmann keuls multiple range tests. Probability values p≤ 0.05 were considered significant.

Table No. 2: Effects of ethanolic extract of *Sebastiana chamaelea* on renal malondialdehyde, glutathione,catalase, and superoxide dismutase, glutathione peroxidase (gp_x) activities in treated rats.

Group No.	TREATMENT DOSE (mg/Kg)	MDAu/ mg Protein	GSH u/mg Protein	CAT u/mg protein	SODu/mg Protein	GPX u/mg Protein
I	Normal control 10ml/kg normal saline	2.11±0.18	15.15±0.40	55.30±1.40	15.30±0.40	23.20±0.90
II	Toxic control 7.5mg/kg Cisplatin induced	4.90±0.42^{*a}	4.40±0.20^{*a}	10.45±0.35^{*a}	6.15±0.16^{*a}	10.10±0.32^{*a}
III	Positive control 50mg/kg Silymarin	2.85±0.24^{*b}	13.40±0.36^{*b}	40.90±0.75^{*b}	13.05±0.32^{*b}	20.15±0.56^{*b}
IV	Treatment control EESC 200 mg/kg	3.65±0.32^{*b}	10.52±0.26^{*b}	29.45±0.45^{*b}	10.90±0.25^{*b}	16.40±0.62^{*b}
V	Treatment control EESC 400mg/kg	3.05±0.26^{*b}	11.25±0.30^{*b}	34.50±0.68^{*b}	12.60±0.28^{*b}	18.25±0.68^{*b}

- Values are expressed as Mean ± SEM.
- Values are found out by using one way ANOVA followed by Newmann kevl's multiple range tests.
- *a – values are significantly different from Normal control at P< 0.01.
- *b – values are significantly different from Toxic control (G2) at p< 0.01.

Table. No 3: Effect of EESC on serum creatinine, blood urea nitrogen &alkalinephosphatase

Group. No.	TREATMENT DOSE (mg/Kg)	Serum creatinine	Blood urea nitrogen mg/dl	Alkaline phosphate mg/dl	Urea mg/dl
I	Normal control 10ml/kg normal saline	0.05±0.02	18.55±0.58	155.60±0.75	17.2±0.40
II	Toxic control 7.5mg/kg Cisplatin induced	1.310±0.05*a	104.30±5.55*a	345.20±1.58*a	78.6±1.65*a
III	Positive control 50mg/kg Silymarin	0.796±0.03*b	38.75±1.28*b	186.75±0.90*b	24.5±0.48*b
IV	Treatment control EESC 200 mg/kg	0.870±0.04*b	56.10±2.05*b	248.60±1.05*b	46.4±0.56*b
V	Treatment control EESC 400mg/kg	0.805±0.03*b	44.25±1.60*b	210.45±0.96*b	38.2±0.50*b

- Values are expressed as Mean ± SEM.
- Values are found out by using one way ANOVA followed by Newmannkeul's multiple rangetests.
- *a – values are significantly different from Normal control at P< 0.01.
- *b – values are significantly different from Toxic control (G2) at p< 0.01.

RESULTS AND DISCUSSION

In acute oral toxicity study the extract was found to be safe up to a dose of 2000 mg/kg. In the present studies, the cisplatin treated animals showed a significant increase in blood urea, blood urea nitrogen and serum creatinine. As shown in serum creatinine, Blood urea nitrogen (BUN), and blood urea levels were significantly higher after 72 h respectively, after administration of single dose of cisplatin when compared to the control group. The pre-treatment with Ethanolic extract of *Sebastiana chamaelea* (EESC) p.o. significantly ($P < 0.01$) lowered the elevated serum urea creatinine, and Blood urea nitrogen (BUN). When compared to the cisplatin group. The pre-treatment with silymarin showed a marked decrease in concentrations of blood urea, serum creatinine, Blood urea nitrogen and alkaline phosphatase.

Effects of EESC on renal oxidant/antioxidant status:

In cisplatin treated group the activities of antioxidant enzymes like SOD, CAT and GPx and levels of GSH were found to be significantly decreased with marked increase in MDA as compared with control ($P < 0.01$). The pre-treatment of EESC and silymarin was found to significantly elevate the decreased activities of SOD, CAT and GPx ($P < 0.01$). The activities of renal SOD, CAT and GPx in the cisplatin treated, cisplatin plus EESC and cisplatin plus silymarin administered groups were given in [Table no:3]. Administration of EESC and silymarin also inhibited the cisplatin-induced elevation in the MDA. The decrease in the GSH levels in renal tissues induced by cisplatin was prevented by the administration of EESC and silymarin ($P < 0.01$)

Effects of EESC on kidney histology:

Treatment with cisplatin caused a marked necrosis in proximal tubules and degeneration of the tubular epithelial cells [Figure.No:23] The pre-treatment with EESC and silymarin decreased the cisplatin induced tubular necrosis when compared with cisplatin treated group.

Discussion:

The impairment of kidney function by cisplatin is recognized as the main side effect and he most important dose limiting factor associated with its clinical use. Several investigators reported that the alterations induced by cisplatin in the kidney functions were characterized by signs of injury, such as increase of products of lipid peroxidation (LPO) and changes in GSH levels in kidney tissue, creatinine and urea levels in plasma.

The renal antioxidant status, such as SOD, CAT, GPx activities, and reduced GSH concentration are significantly decreased in the cisplatin treated group of animals compared to the control group. The declined antioxidant status partially explains the mechanism of nephrotoxicity induced by cisplatin. The renal accumulation of platinum and covalent binding of renal protein may also play a role in the nephrotoxicity. In the present study, increased serum creatinine and urea were observed in cisplatin treated rats may be due to reduction in glomerular filtration rate. The impairment in kidney function was accompanied by an increase in MDA concentrations in kidney tissue. The above findings were well-correlated with the renal histological results. These observations indicated that cisplatin induced nephrotoxicity and the results are in accordance with previous findings. The pre-treatment of EESC provides a significant protection against cisplatin-induced nephrotoxicity with lowering the level of plasma creatinine and blood urea in cisplatin treated animals.

Decreased concentration of GSH increases the sensitivity of organs to oxidative and chemical injury. The role of GSH, non-protein thiols in the cells, in the formation of conjugates with electrophilic drug metabolites, most often formed by cytochrome P-450- linked monooxygenase, is well-established.Studies with a number of models show thatthe metabolism of xenobiotics often produced GSH depletion. Reduced renal GSH can markedly increase the toxicity of cisplatin. The depletion of GSH also seems to be a prime factor that permits lipid peroxidation in the cisplatin-treated group. Moreover, the protection of GSH is also by forming the substrate for the GPx activity that can react directly with various aldehydes produced from the peroxidation of membrane lipids. The enhanced GPx activity could partially explain the protection of bio membranes from oxidative attack.

Decreased SOD activity could cause the initiation and propagation of lipid peroxidation in the cisplatin treated group. This may be either due to loss of copper and zinc, essential for the activity of enzyme or due to ROS induced inactivation of enzyme proteins. The decrease in activities of CAT and GPx could enhance the lipid peroxidation. Thus, the levels of MDA, as a result of lipid peroxidation, were increased in the cisplatin- treated animals. Although, the exact mechanism of cisplatin-induced nephrotoxicity is not well-understood, several investigators have shown that cisplatin nephrotoxicity isassociated with LPO in renal tissue. LPO is ascribed to a free radical-mediated chain reaction that damages cell membranes, and inhibition of this process by EESC is mainly attributed to the ability of scavenger free radicals.[135] In the present investigation, pre- treatment with EESC inhibited the increase in LPO induced by cisplatin in renal tissue, indicating antioxidant activity of EESC.

The histopathological evaluation of the kidney preparations in treatment group also revealed a decreased cisplatin-induced tubular necrosis. Cisplatin-induced renal damage is associated with increased renal vascular resistance and histopathological damage to proximal tubular cells. On the other hand, an increase in GSH levels in the renal tissue indicates that pretreatment with EESC was due to oxidative stress. The effects of EESC on cellular GSH may be due to antioxidant effects. The treatment with EESC prevented the lipid peroxidation by enhancing the renal CAT, SOD and GPx activities.

CONCLUSION

In conclusion, it was shown that cisplatin treatment induced renal damage and pretreatment with ethanolic extract of *Sebastiana chamaelea* (EESC) provided protective effect against this cisplatin-induced nephrotoxicity. However, before concluding a potential usefulness of ethanolic extract of *Sebastiana chamaelea* (EESC) as adjunct to the cisplatintherapy, further clinical investigation is needed.

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