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EVALUATION OF NEPHROPROTECTIVE ACTIVITY OF *COCOS NUCIFERA* L. SPROUT AGAINST DRUG INDUCED NEPHROTOXICITY IN EXPERIMENTAL ANIMALS.

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ABSTRACT

This experimental animal study evaluates the protective effects of *Cocos nucifera* L. sprout on cisplatin -induced nephrotoxic rats over 14 days. Wistar rats were randomly divided into six groups (n=6). Group I rats received 0.5 % CMC, while Group II rats were treated daily 0.5 % CMC (p.o.) with cisplatin 5 mg/kg (i.p) on 11th day.

Group III were administered daily oral doses of 5 mg/kg cystone (p.o.) with cisplatin 5 mg/kg (i.p) on 11th day. Groups IV, V, and VI were administered daily oral doses of 100 mg/kg, 150 mg/kg, and 200 mg/kg HAECN, respectively, with cisplatin administered on the 11th day. On the 15th day, blood samples were collected for serum creatinine, BUN, protein, sodium & potassium analysis. The kidneys were harvested for histopathological examination. Results indicated that group I (0.5% CMC-treated rats) showed a normal gain in body weight compared to the DC group. In group II, there were significant increases in serum creatinine and BUN, sodium, along with decreases in body weight, protein & potassium levels as well as acute tubular nephritis. These effects were significantly reversed in cystone- and HAECN-treated rats in a dose-dependent manner, suggesting that HAECN has nephroprotective effects due to its antioxidant properties.

Key words - Cisplatin, nephroprotective activity, *Cocos nucifera* L. sprout, nephrotoxicity, rats, renal function parameters.

INTRODUCTION

Among critically ill hospitalized patients, acute renal failure (ARF) is common, and its fatality rates have remained high and essentially stable over the past few decades. According to reports, the number of ARF cases is rising, and over 50% of dialysis patients die. The necessity for effective preventive measures is highlighted by the fact that although new drugs and therapies have been developed due to breakthroughs in understanding of ARF, the improvement in mortality rates has been minimal. There have been attempts to create medications using conventional and natural materials to treat ARF, which is frequently accompanied by acute tubular necrosis. However, a number of medications, such as chemotherapeutic medicines, aminoglycosides, and non-steroidal anti-inflammatory drugs, can cause nephrotoxicity, which can result in ARF and other renal problems. [1-5]

Cisplatin, a widely used anticancer drug, is known for its effectiveness against tumors but also for its significant nephrotoxic side effects. [6] Several mechanisms are involved in the nephrotoxicity caused by this drug, with the most important being the production of reactive oxygen species (ROS) and subsequent tissue oxidative damage. Reactive oxygen species, especially hydroxyl radicals, lead to lipid peroxidation, cell membrane degradation, protein and nucleic acid oxidation, and tissue damage. These effects result in a reduction in glomerular filtration, leading to acute nephrotoxicity. [7-9]

The nephrotoxicity of cisplatin necessitates dose reductions and hospitalization for some patients. [10, 11] Despite hydration therapies, about one-third of patients receiving Cisplatin suffer irreversible kidney damage. [12, 13] Thus, there is a growing global interest in finding ways to reduce cisplatin-induced nephrotoxicity in nephrotoxic patients. Herbal medicines have a long history and form the basis of many modern drugs, often derived from plants. Their effectiveness is frequently attributed to antioxidants, which help in preventing and treating various diseases and mitigating medication side effects. [14, 15]

Cystone is a well-known herbal medicine used for kidney stones and urinary tract infections, containing nine plant extracts. It has shown anti-carcinogenic effects in mice and protective effects against Cisplatin-induced nephrotoxicity by inhibiting lipid peroxidation. Despite numerous studies, many of which are animal-based, the results on Cystone's efficacy in preventing cisplatin toxic effects are controversial. [16, 17]

Cocos nucifera L. sprouts are a valuable phytomedicine derived from the basal portion of the coconut embryo, known as the haustorium. This edible sprout, formed during germination, is rich in proteins, carbohydrates, fibers, vitamins, and enzymes. These nutrients contribute to reducing the harm that isoproterenol causes to the heart, boost metabolic processes, and facilitate digestion. [18] They also help prevent colon cancer, reduce high blood pressure, treat anemia, relieve diarrhea, constipation, and constipation, and lower cholesterol. Their omega-3 fatty acids reduce LDL cholesterol, which lowers the risk of heart attack and stroke, and they block the hormone that causes appetite, ghrelin. Their potassium content also aids in regulating blood pressure. [19] In addition to boosting circulation and oxygenation, minimizing the risk of heart attacks, cardiac arrest, and strokes, and dilating blood vessels, coconut sprouts contain anti-diabetic qualities. Coconut sprouts are also rich in antioxidants (vitamins) and phytoconstituents, which have strong antibacterial, anti-inflammatory, and antioxidant effects. [20]

There remains a lack of comprehensive knowledge on the causes and pathogenesis of drug-induced nephrotoxicity, complicating the development of effective interventions. Therefore, further research is crucial to better understand and manage this disorder, aiming to prevent severe clinical outcomes. The present study aimed to investigate the nephroprotective activity of *Cocos nucifera* L. sprout against cisplatin-induced nephrotoxicity in experimental animals.

MATERIALS AND METHODS

MATERIALS:

Experimental animals:

Wistar Albino Rats (200-250 grams) of either sex, obtained from the Crystal Biological solutions, Handewadi, Pune were used for the study. The experimental design & research plan along with animal handling and disposal procedure were approved from Institutional Animal Ethical Committee of Rajgad Dnyanpeeth's College of Pharmacy, Bhor. IAEC approval number: RDCOP/Pcol-07/IAEC/2023-24/07**.** Animals were kept in polycarbonate cages that were covered by raw dust that was changed every three days under standard laboratory conditions (27 ± 2 °C) and relative humidity of 45-55 % under 12h light: 12h dark cycle. The rats were given free access to water and standard diet pellets *ad libitum*.

Drugs and chemicals

Cisplatin was purchased from Poona Hospital Medical Store, Pune, India. Cystone tablet (A polyherbal formulation) was procured from Himalaya Drug Company, Bengaluru, India. Ethanol & Carboxy methyl cellulose were obtained from research lab. All other chemicals, solvents and reagents used during the experiments were of analytical grade.

Apparatus and Instruments

Apparatus such as a Hot air oven (BTI29) for solvent evaporation, oral gavage feeding for dose administration, a syringe for blood collection, electronic balance (Shimadzu: Ay120) were used.

METHODS:

Collection & Authentication of plant material

Germinated coconut *(Cocos nucifera)* was procured from local market of Hadapsar (Bhaji mandai), Pune, India. Authentication of *Cocos nucifera* L. sprout was done at Baburaoji Gholap College, Arts, Science & Commerce, Sangvi, Pune-411027 by Dr. R. B. Bhagat, Assistant Professor, Dept.of Botany (Authentication number Bot/BGC-29/AUTH/2023-24).

Preparation of HAECN

Solvent extraction of the cotyledons was performed by cold percolation method, using the solvents ethanol & water (1:1). Extraction by cold percolation was carried out by the addition of 100 ml of solvent to 10 g of the sliced cotyledon. The extracts were maintained at 30 ± 2°C in a temperature-controlled shaker for 48 h and then filtered. The extracts thus obtained cold percolation were concentrated to obtain the crude. The crude was diluted with hydroalcoholic solvents for further analysis. [21]

Phytochemical Analysis of HAECN [22, 23]

Phytochemical screening of HAECN was carried out by the well-established standard methods (Raaman, 2006.) HAECN was evaluated for the presence of phytochemical constituents such as alkaloids, glycosides, flavonoids, steroids, carbohydrates, saponins, tannins, terpenoids, proteins, coumarins, etc. The chemicals/ reagents used for phytochemical identification were of A R grade.

Acute toxicity study

Acute oral toxicity study for *Cocos nucifera* L.sprout was carried out according to OECD guidelines 425.

In vivo model

Duration of study: 15 days
Inducer: Cisplatin
Standard: Cystone tablet [25]

Experimental design

A total of 36 Wistar Albino rats with an average body weight of 200-250 g of either sex have taken for study. Grouped them into six sets, with each set containing six animals. Group I kept as normal control, Groups II was kept as disease control & group III was kept as positive control given by standard cystone 5mg/kg b.w., p.o route for 14 days. Groups IV, V and VI were considered as test groups were induced with nephrotoxicity by administrating cisplatin 5 mg/kg b.w. I.p. route on 11th day [26] and treatment with HAECN for 14 days in cisplatin induced rats.

Table 1: Treatment schedule for effect of HAECN in cisplatin induced nephrotoxicity in rats. [24]

Sr. No	Group	Duration in days & Drug treatment	Dose
I	NC	14 days: Vehicle- 0.5 % CMC	0.5 % CMC -1 ml/kg (p.o)
II	DC	14 days: 0.5 % CMC administered & on 11th day : Cisplatin administered.	0.5 % CMC-1 ml/kg (p.o) & Cisplatin- 5mg/kg,(i.p)
III	STD	14 days: Cystone administered. on 11th day: Cisplatin administered.	Cystone- 5 mg/kg (p.o) & Cisplatin- 5mg/kg, (i.p)
IV	T1CN	14 days: HAECN was administered & on 11th day: Cisplatin administered	HAECN -100 mg/kg (p.o) & Cisplatin- 5mg/kg,(i.p)
V	T2CN	14 days: HAECN was administered & on 11th day : Cisplatin administered	HAECN -150 mg/kg (p.o) & Cisplatin- 5mg/kg,(i.p)
VI	T3CN	14 days: HAECN was administered & on 11th day: Cisplatin administered.	HAECN -200 mg/kg (p.o) & Cisplatin- 5mg/kg,(i.p)

Evaluation parameters

Body weight evaluated on 1st, 7th, 15th day of study.

Biochemical parameters like blood urea nitrogen level, serum creatinine, serum total protein, serum sodium & serum potassium as well as histopathological study of kidney were evaluated on 15th day of study. Results of histopathological evaluation were obtained in the form of nephroprotective pathological grade.

Table 2: Pathological grade

Sr. No.	Pathological grade	Description
1	0	No abnormality detected
2	+	Damage/active changes up to less than 25%
3	++	Damage/active changes up to less than 50%
4	+++	Damage/active changes up to less than 75%
5	++++	Damage/active changes up to more than 75%

Statistical analysis

Results were expressed as mean $\pm$ SEM. Statistical analysis was carried out by one-way ANOVA test followed by **"Dunnett's multiple comparison test."** $p<0.05$ was considered.

RESULTS

Physical properties of HAECN

- **Appearance**: Slightly turbid, semisolid, light to dark brown colour
- **Solubility**: Soluble in water and alcohol.
- **pH**: 4.5

- **Organoleptic Properties**: Characteristic coconut aroma and taste.
- **% Yield**: 4.6 % w/w

Phytochemical Analysis of HAECN

The result of phytochemical screening of hydroalcoholic extract of *Cocos nucifera* L. sprout showed the presence of flavonoids, alkaloids, terpenoids, saponins, proteins, carbohydrates, tannin & glycosides. (Table 3).

Table 3: Phytochemical analysis of HAECN

Sr. No.	Phytochemical Tests	Results
1	Flavonoids: Shinoda Test	+
2	Alkaloids: Mayer's Test	+
3	Steroids: Salkowski Test	-
4	Coumarin test	-
5	Terpenoids: Salkowski Test	+
6	Saponins: Foam Test	+
7	Proteins: Biuret Test	+
8	Carbohydrates: Molisch's Test	+
9	Glycosides: Legal's Test	+
10	Tannin: Lead acetate	+

"+" stands for the presence of phytochemicals and "–" stands for the absence of phytochemicals.

***In-vivo* nephroprotective activity**

Acute oral toxicity

The *Cocos nucifera* L. Sprout AOT has already been completed. Dosage maximum tolerated: 2000 mg/kg. [27]

Effect of HAECN in cisplatin induced nephrotoxicity in rats

This study used a nephrotoxicity model generated by cisplatin. On the eleventh day, nephrotoxicity was induced in all experimental groups except group I using cisplatin (5 mg/kg) administered intraperitoneally.

Group I received 0.5 percent CMC as a vehicle. Group III, which served as the synthetic standard group, received a dose of cystone (5 mg/kg, p.o.). In a model induced by cisplatin, the remaining IV, V, and VI groups were administered HAECN at doses of 100 mg/kg, 150 mg/kg, and 200 mg/kg, respectively, for a period of 14 days.

On the first, seventh, and fifteenth day, the body weight of every animal in each group was recorded. The application of HAECN in cisplatin-induced nephrotoxicity in rats' model revealed that, in comparison to the normal control group, the administration of cisplatin (5 mg/kg. i.p.) resulted in a decrease in body weight on days 7 and 15, as well as in serum protein & potassium level and increases in serum creatinine, BUN & sodium level on day 15. In comparison to the disease control group, treatment with cystone (5 mg/kg p.o.) resulted in a significant ($P<0.0001$) decrease in serum creatinine, BUN level & sodium level respectively

as well as significant (P<0.0001) increase in body weight, serum protein & serum potassium level respectively.

When compared to the disease control group, treatment with HAECN (100 mg/kg, 150 mg/kg, 200 mg/kg, p.o.) resulted in a little change in body weight on day 7 and a considerable (P<0.0001) rise in body weight on day 15.

In comparison to the disease control group, treatment with HAECN (200 mg/kg, p.o.) demonstrated significant (P<0.0001, P<0.0001, P<0.001) decreases in serum creatinine, serum BUN & serum sodium level respectively. Additionally, treatment demonstrated significant (P<0.001) increases in serum protein & serum potassium level respectively.

When compared to the disease control group on day 15, treatment with HAECN (150 mg/kg, p.o.) demonstrated a significant (P<0.001) decrease in serum creatinine, BUN & sodium level respectively, as well as a significant (P<0.001, P<0.01) increase in serum protein & potassium level respectively.

When compared to the disease control group on day 15, treatment with HAECN (100 mg/kg, p.o.) demonstrated a significant (P<0.001, P<0.01, P<0.05) decrease in serum creatinine, serum BUN & sodium level respectively, as well as a significant (P<0.01, P<0.05) increase in serum protein & potassium level respectively. (Table no.4 & 5)

Kidney histopathology from groups I demonstrates no abnormal alterations. Mild (+2) to moderate (+3) pathogenic alterations are seen in Groups II. Group IV has moderate (+2) pathological changes while Group III, V and VI exhibits negligible pathogenic alterations (+1).

Table 4: Effect of HAECN on body weight in cisplatin induced nephrotoxicity in rat

Group	Treatment	Body weight (gm) (Mean + SEM)		
		Day 1	Day 7	Day 15
I	NC	236.41+1.63	244.43+3.31	241.77+2.14
II	DC	237.82+2.65	217.89+2.26###	205.24+2.71####
III	STD	240.04+ 1.99	225.27+3.12ns	2.91+1.36****
IV	T1CN	241.33+2.93	228.56+3.42ns	222.93+2.56****
V	T2CN	240.31+1.68	229.36+3.29ns	229.05+1.42****
VI	T3CN	242.05+2.15	227.32+3.17ns	30.42+1.16****

Table 5: Effect of HAECN on serum creatinine, BUN & protein on cisplatin induced nephrotoxicity in rats

Group	Treatment	Creatinine (mg./dl)	BUN (mg/dl)	Protein (gm/dl)
I	NC	0.49 ± 0.01	14.45 ± 0.39	7.16 ± 0.16
II	DC	1.90 ± 0.20$^{####}$	24.71 ± 1.26$^{####}$	5.26 ± 0.20$^{####}$
III	STD	0.70 ± 0.04****	16.45 ± 0.36****	6.64 ± 0.21****
IV	T1CN	1.17 ± 0.14***	20.98 ± 0.71**	6.28 ± 0.18**
V	T2CN	1.15 ± 0.08***	20.17 ± 0.33***	6.38 ± 0.16***
VI	T3CN	1.07 ± 0.10****	19.44 ± 0.68****	6.40 ± 0.14***

Table No. 6: Effect of HAECN on serum sodium & potassium on cisplatin induced nephrotoxicity in rats

Group	Treatment	sodium (mmol/L)	potassium (mmol/L)

I	NC	142.03 ± 3.26	4.91 ± 0.16
II	DC	170.92 ± 2.14####	3.19 ± 0.08####
III	STD	144.65 ± 4.71****	4.38 ± 0.10****
IV	T1CN	157.37 ± 3.66*	3.86 ± 0.21*
V	T2CN	151.81 ± 2.09***	4.00 ± 0.16**
VI	T3CN	149.88 ± 2.35***	4.13 ± 0.14***

All results in Table 4, 5, 6 are expressed as mean ± S.E.M, (n = 6) #### p< 0.0001 compared to Normal control; * p<0.05, ** p<0.01, *** p<0.001 & **** p<0.0001 compared to DC. NC: Normal control; DC: Disease control; STD: Standard Cystone (0.5 mg/kg, p.o.); T1CN: Hydroalcoholic extract of *Cocos nucifera* L. sprout (100 mg/kg, p.o.); T2CN: Hydroalcoholic extract of *Cocos nucifera* L. sprout (150 mg/kg., p.o.); T3CN: Hydroalcoholic extract of *Cocos nucifera* L. sprout (200 mg/kg, p.o.).

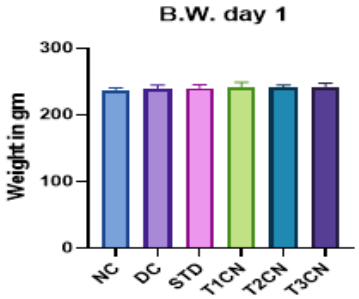


Figure 1 : Effect of HAECN on B.W. in cisplatin induced nephrotoxicity in rats on day 1

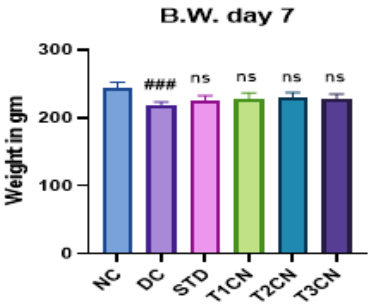


Figure 2 : Effect of HAECN on B.W. in cisplatin induced nephrotoxicity in rats on day 7

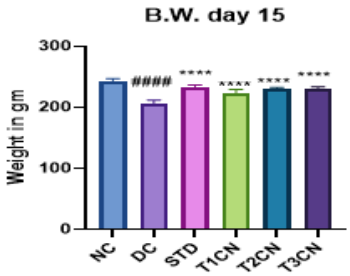


Figure 3 : Effect of HAECN on B.W. in cisplatin induced nephrotoxicity in rats on day 15

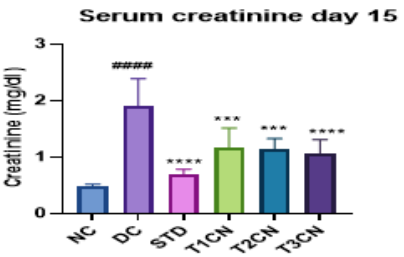


Figure 4 : Effect of HAECN on serum creatinine in cisplatin induced nephrotoxicity in rats on day 15

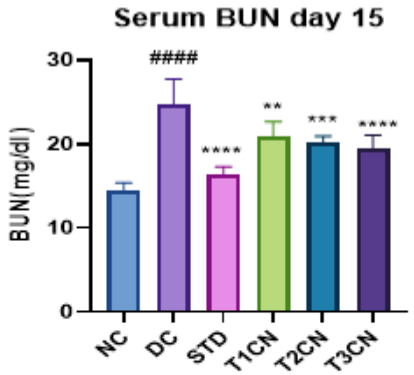


Figure 5 : Effect of HAECN on serum BUN in cisplatin induced nephrotoxicity in rats on day 15

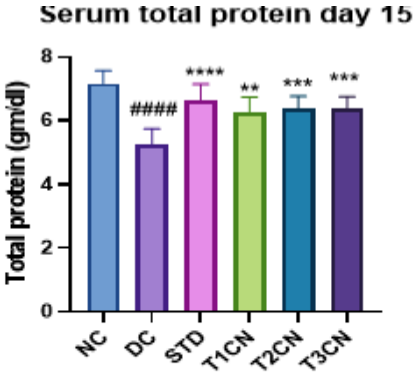


Figure 6 : Effect of HAECN on serum total protein in cisplatin induced nephrotoxicity in rats on day 15

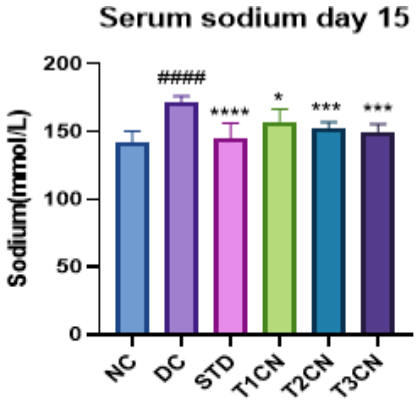


Figure 7 : Effect of HAECN on serum sodium in cisplatin induced nephrotoxicity in rats on day 15

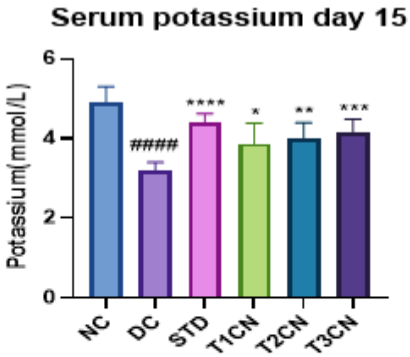
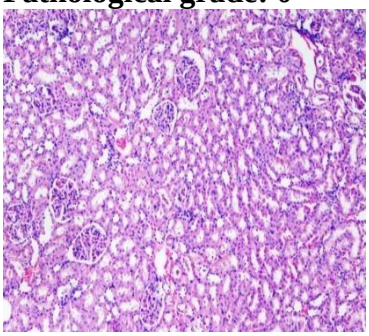


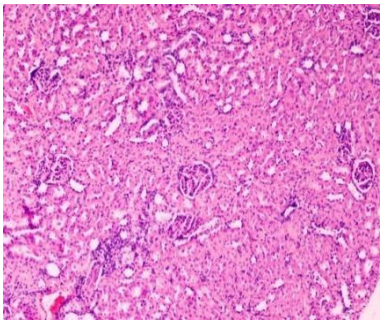
Figure 8 : Effect of HAECN on serum potassium in cisplatin induced nephrotoxicity in rats on day 15

Effect of HAECN on histopathology of kidney in cisplatin induced nephrotoxicity in rats

Group I: Normal Control
Pathological grade: 0

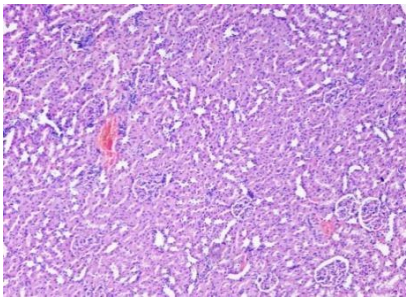


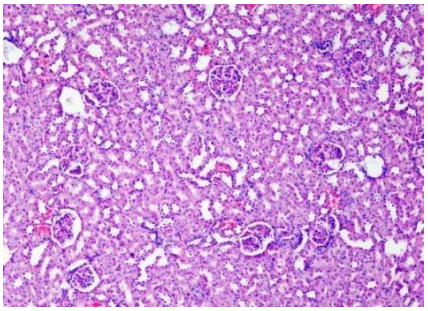
Group II: Disease Control
Pathological grade: ++ to +++



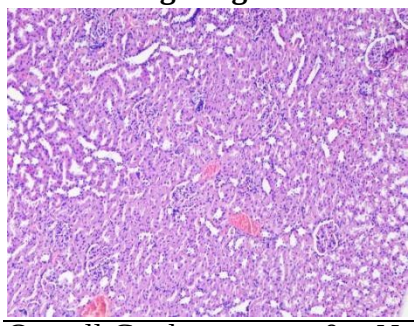
Group III: Standard
Pathological grade: +

Group IV: T1 (100mg/kg)
Pathological grades: (++)

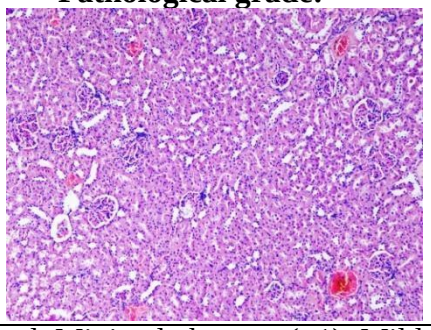




Group V: T2 (150mg/kg)
Pathological grade: +



Group VI: T3 (200mg/kg)
Pathological grade: +



Overall Grade score as- 0 = No Abnormality Detected, Minimal changes (+1), Mild changes (+2), Moderate changes (+3), Severe changes (+4).

Discussion:

Cisplatin is known as an inducer of acute renal failure, among the primary modes of action of cisplatin are chromosomal damage, lipid peroxidation, induction of cell death, and activation of internal and external apoptotic pathways. This medication has a unique effect on kidney tubule toxicity, especially in the proximal tubule. [28] The present study showed that cisplatin-induced groups elevate the serum creatinine, blood urea nitrogen, sodium level & decrease body weight, serum protein & potassium level compared to the normal control group ($p < 0.05$). These indicate the rat induce toxicity and high-level kidney dysfunction.

The nephrotoxicity caused by cisplatin is attributed to multiple mechanisms, the most significant of which are tissue oxidative damage and the generation of active oxygen species. Reduced glomerular filtration and acute nephrotoxicity are the results of lipid peroxidation, cell membrane disintegration, protein and nucleic acid oxidation, and tissue deterioration caused by active oxygen species, particularly radical hydroxyl. [29]

In this study, the elevation of serum creatinine, BUN & sodium level was induced by cisplatin and decreased by HAECN. This effect may be associated with antioxidant activity and phytochemical of *Cocos nucifera* L. sprout. The decrease in serum creatinine, BUN & sodium level and increase in body weight, serum protein & potassium in the 100, 150 and 200 mg/kg HAECN induced groups compared to cisplatin ($p < 0.05$) indicates the protective effect of HAECN. This may be due to the bioactive secondary metabolite such as flavonoid, terpenoids, and vitamins present in the HAECN.

It has been determined that the high nutrient value of coconut sprouts includes proteins, carbohydrates, low calories, a higher content of fibers, vitamins, and enzymes that support the body's metabolic processes and chemical reactions that aid in digestion and reduce the damage that isoproterenol causes to the heart. [18] In addition, they lower cholesterol, treat anemia, alleviate constipation, diarrhea, and high blood pressure. They also aid in the prevention of colon cancer. It is also discovered that the coconut sprout inhibits the hunger hormone ghrelin. The omega-3 fatty acids in the sprouts are thought to reduce the incidence of heart attacks and strokes by lowering LDL (low-density lipoprotein) cholesterol levels.

Additionally, the potassium in the sprouts lowers blood pressure. [19] In addition to all of these benefits, coconut sprouts have anti-diabetic qualities and improve circulation and oxygenation, lower the risk of heart attacks, cardiac arrest, and strokes, and dilate blood vessels. Additionally high in phytoconstituents and antioxidants (vitamin C&E, flavonoids such as quercetin) with potent antibacterial, anti-inflammatory, and antioxidant properties. [20] Based on the aforementioned research, group VI (200 mg/kg) exhibits the highest level of therapeutic benefit compared to groups IV (100 mg/kg) and V (150 mg/kg). At 200 mg/kg, *Cocos nucifera* L. sprout significantly protects the kidneys of rats and reduces nephrotoxic effects. Herbal remedies are long-lasting and well-known for their safety. HAECN's phytochemical composition, rich in antioxidants like vitamin C and E, flavonoids like quercetin, and phenolic compounds, can be responsible for its protective properties. These substances are well-known for their ability to counteract oxidative stress, bringing blood levels of creatinine, BUN, total protein, sodium, and potassium back to normal.

Considering the results obtained in the present investigation, it can be concluded that the hydroalcoholic extract of *Cocos nucifera* L. sprout possesses significant nephroprotective activity.

Conclusion:

Coconut sprout extract (HAECN) demonstrates significant nephroprotective effects against cisplatin induced nephrotoxicity in experimental models. The protective properties are attributed to the antioxidant compounds present in the sprout, such as vitamins C and E, flavonoids, and phenolic compounds. These substances help counteract oxidative stress, normalize blood levels of creatinine, BUN, total protein, sodium, and potassium. The hydroalcoholic extract of Cocos nucifera L. sprout possesses notable nephroprotective activity, suggesting its potential as a safe and effective herbal remedy for protecting kidney function against drug-induced damage.

Further research, including exact molecular mechanism responsible for its nephroprotective effect, LC-MS/MS spectrum analysis, & clinical trials are necessary for further characterization & confirm these benefits in humans.

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