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Original Research Article

Evaluation of Nephroprotective Activity of Ethyl Acetate Fraction from Alcoholic Extract of Cichorium Intybus Root in Albino Rats

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Conflict of interest: Nil

Abstract

Gentamicin is an aminoglycoside antibiotic used to treat a variety of bacterial infections, but have adverse effects on the kidneys. When administered, it is excreted in the urine, which means that kidney cells are almost constantly exposed to it. Prolonged use or high doses of gentamicin can lead to progressive kidney failure. Variety of herbal plants can be used for the prevention and treatment of kidney damage. Therefore, the nephroprotective activity of alcoholic extract of Cichorium intybus (200 and 400 mg/kg) was evaluated on gentamicin (80 mg/kg) induced nephrotoxicity in albino rats. The study period was from 0- 10 days and blood samples were collected at 10th day. Serum urea and creatinine are the reliable markers to access the renal function. The results were analysed by ANOVA. The gentamicin caused a significant ($p \leq 0.01$) increase in levels of serum urea, creatinine and blood urea nitrogen. Statistically significant decrease in levels of serum urea, creatinine and blood urea nitrogen was observed in the Chicorium intybus extract treated group as compared to gentamicin treated. Results revealed significantly improved renal cortical histopathology and kidney weight. The findings suggested that ethyl acetate fraction of alcoholic extract of Cichorium intybus root have marked nephroprotective activity in dose dependent manner.

Keywords: Cichorium intybus, root, nephroprotective activity, nephrotoxicity, gentamicin, ethyl acetate fraction.

Introduction

Kidney is the principal excretory organ of the body and helps in preserving the balance of electrolytes and water. Certain medications undergo substantial metabolism in the kidney. Along each excretion pathway, potentially hazardous compounds are exposed to the tubules and the surrounding interstitium. In the further regions of the tubules, drugs have the ability to precipitate, crystallise, or form casts, which can lead to tubular obstruction. Each and every component that passes through the glomerulus enters the proximal tubule. [1] A variety of drugs, including NSAIDS, antibiotics, and chemotherapeutic agents, can damage the kidneys and lead to the development of nephritic syndrome, chronic interstitial nephritis, and sudden renal failure. Free radicals are highly reactive molecules containing one or more unpaired electrons in their outermost shell and the only way of neutralizing them and their harmful effects is through anti-oxidants which help in the breakdown of chemical reactions that cause transfer of electrons from healthy cells into free radicals. [2] One might consider aminoglycosides to be the accepted benchmark for this form of damage. [3] Nephrotoxicity affects ten to twenty-five percent of patients on aminoglycoside treatment. Because of its clinical efficacy, low rates of drug resistance, and affordable cost, gentamicin remains the primary choice for treating many serious infections. The nephrotoxicity and ototoxicity of aminoglycosides are their main adverse effects. [4] Numerous plants like Aerva javanica, [5] Cassia auriculata [6],

Hygrophila spinose [7], Ocimum sanctum [8], Bauhinia variegata[9]. Possess nephroprotective qualities due to the presence of diverse phytoconstituents. These include essential oils, alkaloids, flavonoids, and terpenoids, which produce antioxidant properties. [10] Exogenous antioxidants are necessary to reduce the elevated amount of oxidative stress that causes a number of diseases. Investigations on plant-based antioxidant sources has been done because of the vital role that antioxidants play. [11] Cichorium intybus, commonly referred to as chicory (Kasni), is a woody perennial plant native to Northern Asia, the Mediterranean region, and Europe that grows vertically. It is one of the herbal plants which has a wide range of pharmacological actions including antimicrobial activity [12], anthelminthic [13], antimalarial [14], hepatoprotectives [15], Antidiabetic [16], gastroprotective [17] Anti-inflammatory [18], analgesic [19] antioxidant [20], Antiallergic [21] and anticancer [22]

However, there is limited literature regarding use of C. intybus for nephroprotective effects. Because of its remarkable preclinical therapeutic potential, the current study evaluated the nephroprotective activity of Cichorium intybus root against Gentamicin-induced nephrotoxicity in rats, paying particular attention to biochemical aspects. It has been observed that the alcoholic extract of Indian Cichorium species exhibit potent antioxidant properties due to presence of phytoconstituents like flavonoids, polyphenols, glycosides etc.23 there are limited studies on nephroprotective effect of Cichorium intybus roots. Therefore, the present study was designed to explore the nephroprotective activity of ethyl acetate fraction from alcoholic extract of Cichorium intybus roots (Family-Asteraceae) on albino rats.

Material and Methods

Plant Material: The dry extract of Cichorium intybus roots were purchased from the BIOZEMIA TECHNOLOGIES, (251-B, Waqf Nagar, Dadabari, Kota -324009, Kota, Rajasthan) in the month of September 2023.

Preparation of Extract

The dried extract of Cichorium intybus root was acquired from legitimate source Annexure-1. A solution of sodium bicarbonate was combined with 750 g of dry extract for inactivation then macerated with alcohol for 24 hrs at room temperature. 780 ml of solution was obtained after filtration. Using a rotatory evaporator, 300 ml of concentrated extract was obtained. As solvents Petroleum ether, chloroform, and ethyl acetate were used in sequential order of polarity as solvents for fractionation. Rotatory evaporator was used for concentrating the petroleum ether, chloroform and ethyl acetate fraction. The ethyl acetate fraction of Cichorium intybus root yielded high in flavonoids. The final extract was obtained in a semi-solid state with a percentage yield of 1.6%.[24]

Preliminary phytochemical test for flavonoids

Test for flavonoids – Alkaline Reagent Test: Test drug solution + NaOH, intense yellow color is formed which turns to colorless on addition of few drops of dil. Acid.

Preparation of dose- 200 mg of ethyl acetate fraction of Cichorium intybus root extract was mixed with a pinch of Carboxy Methyl Cellulose diluted in 10 ml of distilled water. Preparation of dose for both the groups for one day was to be 1000mg/50ml.

Ethical approval-The study was evaluated and approved by the Institutional Animal Ethical Committee (IAEC) SGTU/IAEC/2023/08.

Experimental Animals -Twenty four male albino rats weighing between 150-250 gm were brought from CCSEA approved animal facility. The entire animal experimentation was carried out in accordance with recent CCSEA guidelines. Standard food pellets (ad libitum) and RO water were provided.

Study Duration – The study has been conducted for the period of two weeks after IAEC Approval (SGTU/IAEC/2023/08).

Study Design. Twenty-four male albino rats were randomized into four groups. Picric acid was used for labeling of rats. The body weight of each rat was taken on day 1. The control group Group I was given normal saline. Group II received Gentamicin (80 mg/kg) intraperitoneally from day 1 to day 9. Group III (pretreatment group) one-hour pretreatment with ethyl acetate fraction of Chicorium intybus (EAFCI) 200 mg/kg orally was given followed by gentamicin (80 mg/kg) IP. Group IV received one-hour pretreatment with EAFCI 400mg/kg orally followed by gentamicin (80mg/kg) IP.

Serum-specific renal function parameters were observed at the end of the study using whole blood samples obtained from heart punctures under ketamine anaesthesia (serum urea, creatinine, BUN and serum electrolyte) on the 10th day. The kidneys were excised after euthanisation.

Table 1: Groups and Treatment schedule

Groups	Description of study groups	Dosage (mg/kg)	No. of animals	Route of administration
Group I	Control – Normal Saline	10 ml/kg	6	Orally
Group II	Gentamicin	80 mg/kg	6	IP
Group III	EAFCI	Pretreatment with EAECI 200mg/kg + Gentamicin (80 mg/kg)	6	Orally + IP
Group IV	EAFCI	Pretreatment with EAECI 400 mg/kg + Gentamicin (80 mg/kg)	6	Orally + IP

Statistical analysis: All the categorical and measurement data was recorded in MS excel and analyzed by using SPSS Software version 29 IBM CORP. All Continuous data was measured in mean and standard deviation. Graphical representation was also be done in MS office 2010. ANOVA (Analysis of variance) test was applied for all continuous data. Post hoc analysis (Bonferroni test) will be done for pairwise comparison between the groups. P-value is set to be as 0.05 level of significance.

Results: In this present study, fig. 1 revealed the comparison of serum urea, serum creatinine, blood urea nitrogen, potassium, sodium and ESR with respect to control, Gentamicin, EAFCI 200mg and EAFCI 400mg groups.

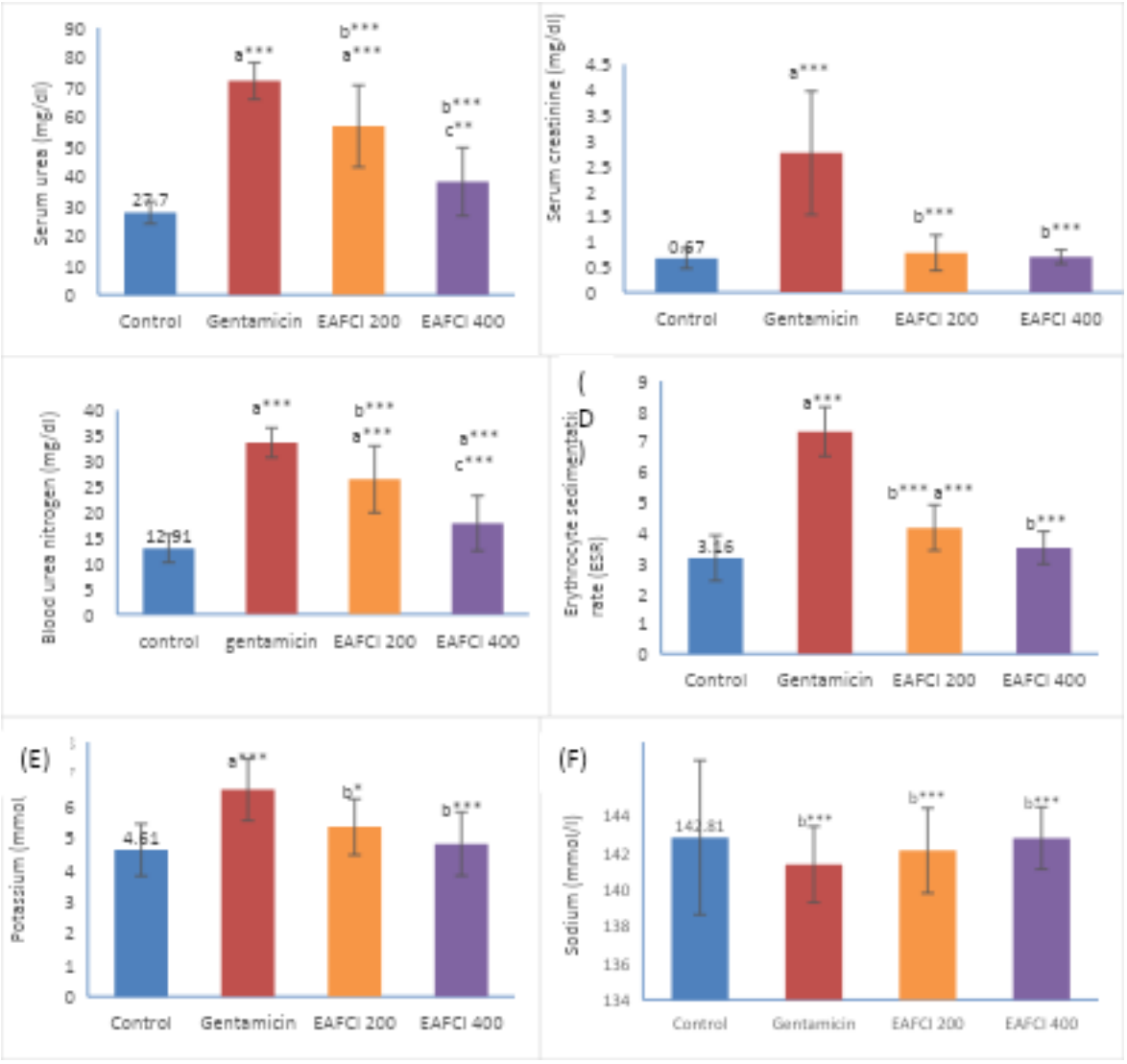

Figure 1: Effect of administration of Ethyl acetate fraction of Chicorium intybus (EAFCI) 200 mg/kg and EAFCI 400 mg/kg on serum urea (A), creatinine (B), blood urea nitrogen (C) erythrocyte sedimentation rate (D), potassium (E) and sodium (F) in GM – administered rats. The data are presented as mean ± SD, (n=6). a as compared to control, b as compared to gentamicin, c as compared to EAFCI 200 mg/kg. p value : <0.05–>0.01*, ≤0.01–>0.001 , ≤0.001–>0.0001*****

Histopathological Examination: The kidneys of all animals in the experiment were prepared for histopathological evaluation. The tissues were fixed in 10% neutral buffered formalin, embedded in paraffin wax, cut into 3-4 µm thin sections, stained using haematoxylin and eosin stain.

The microsections were examined under both low power (10 X magnification) and high power (40 X magnification) and representative photos were taken using camera.

The control group showed normal tubular and glomerular architecture. Rats treated with gentamicin, displayed a number of structural changes. Nearly all tubules showed haematuria; renal tubules showed vacuolation and severe necrosis; and more than half of the proximal convoluted tubule epithelial cells exhibited desquamation, proteinaceous cast. There was also a significant infiltration of inflammatory cells. However, it was discovered that pre-treatment with an EAFCI extract at 200 and 400 mg/kg may prevent the damages that has been caused by Gentamicin. Results from EAFCI 400 mg/kg were better to those from EAFCI 200 mg/kg. EAFCI 200 mg/kg demonstrated mild inflammatory cell infiltration, haematuria in some tubules, and desquamation, while only inflammatory cell infiltration was seen in EAFCI 400 mg/kg.

Figure 2: Photomicrographs of kidneys (under 10X AND 40X magnifications respectively; (H & E).

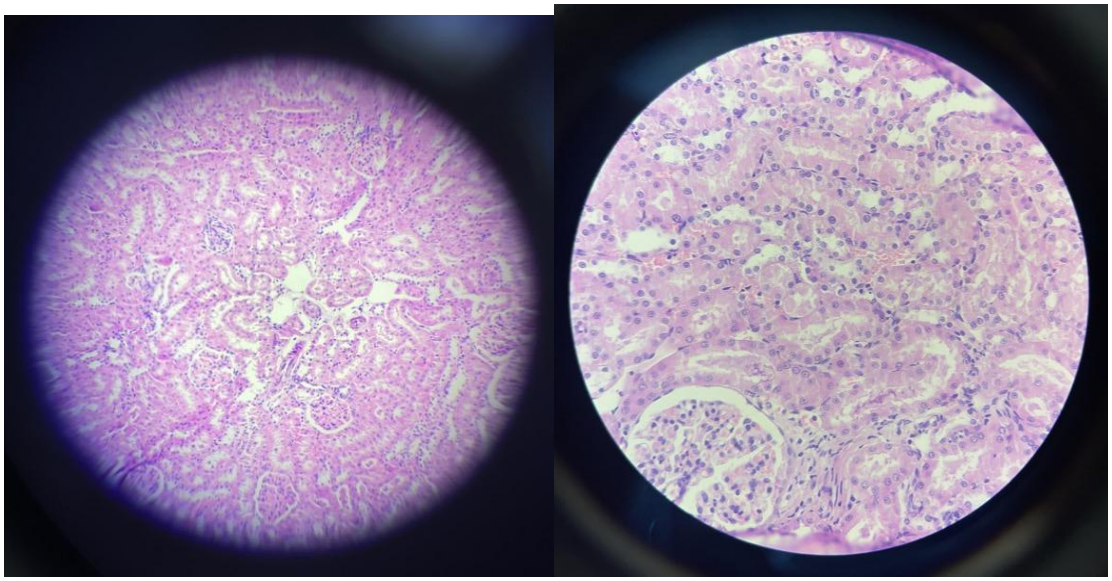

Figure 2: A. (10X magnification) B. (40X magnification) Control group showing normal glomeruli and normal tubules.

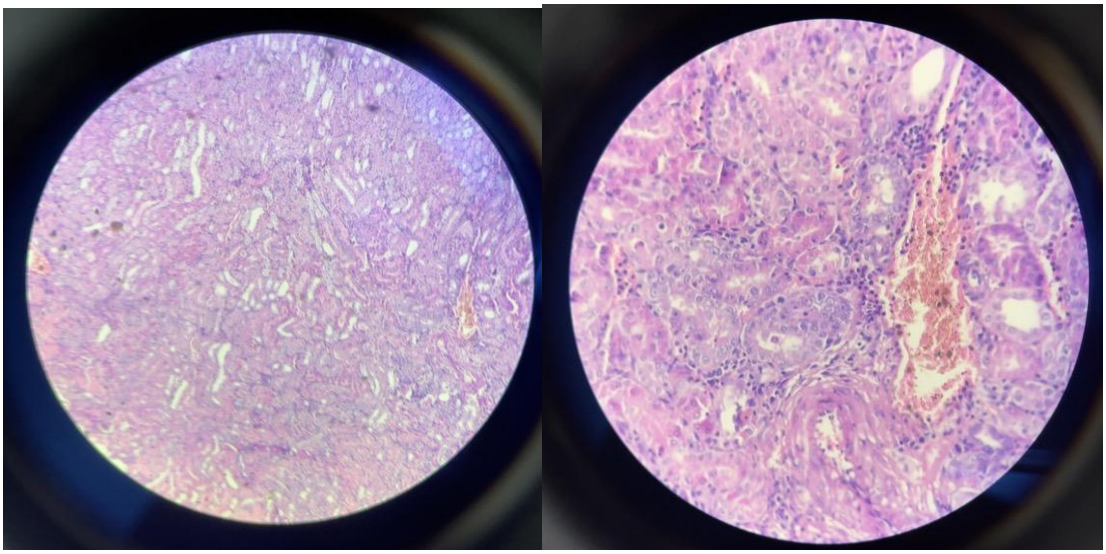

Figure 2: C. (10X magnification) D. (40X magnification) Gentamicin (80mg/kg) group showing nearly all tubules having haematuria; renal tubules has vacuolation and severe necrosis; and more than half of the

proximal convoluted tubule epithelial cells exhibited desquamation, significant infiltration of inflammatory cells.

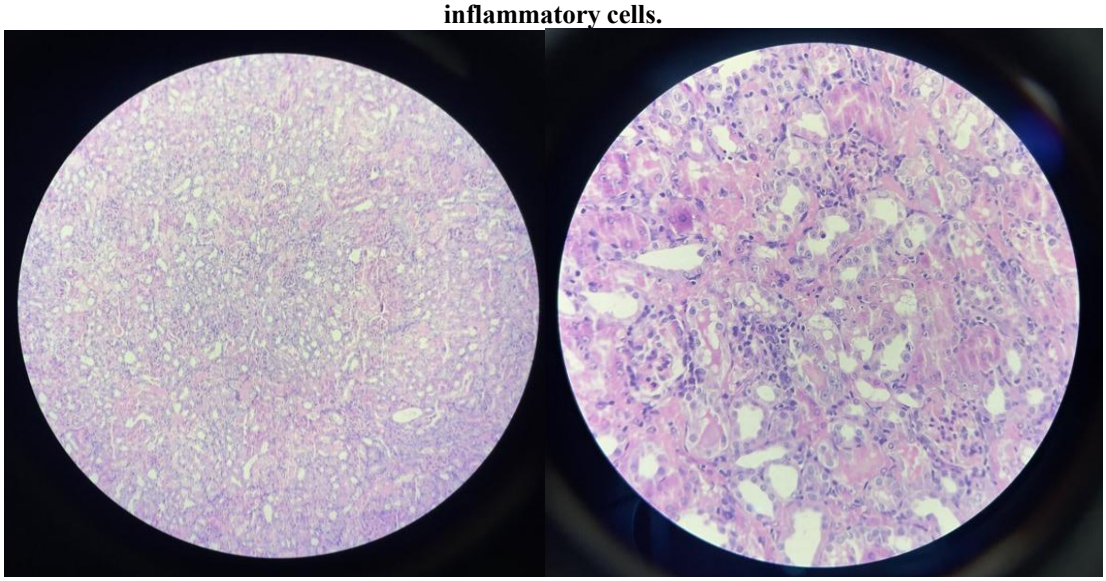

Figure 2: E. (10X magnification) F. (40X magnification) Pretreatment group with EAFCI 200 mg/kg + Gentamicin (80 mg/kg) showing mild inflammatory cell infiltration, haematuria in some tubules, and desquamation.

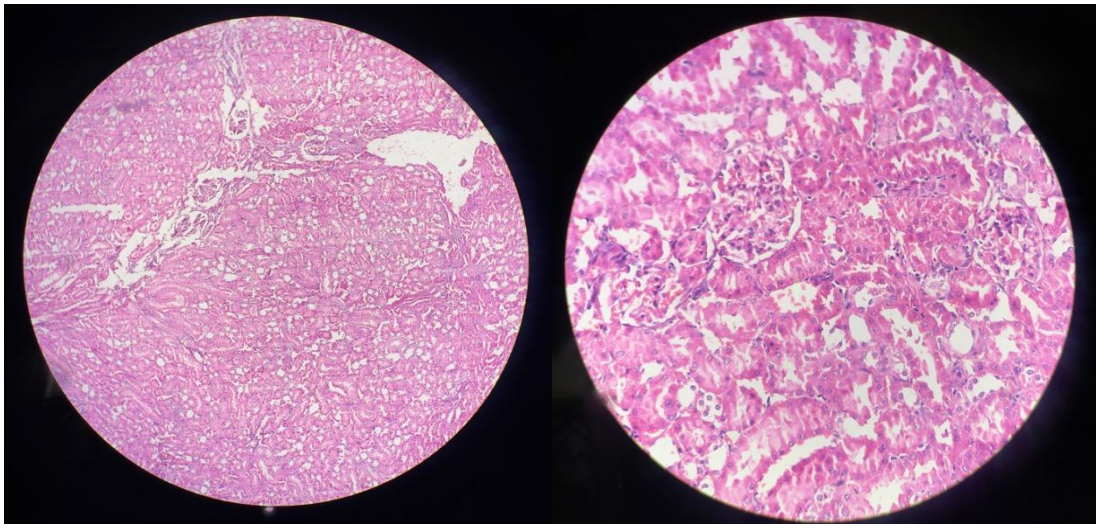

Figure 2: G. (10X magnification) H. (40X magnification) Pretreatment group with EAFCI 400 mg/kg + Gentamicin (80 mg/kg) showing only inflammatory cell infiltration.

Discussion

Gentamicin has been reported by several researchers to be effective in examining the nephroprotective properties of natural plants. [25] It is commonly used to cause nephrotoxicity in animal models for research purposes. The primary mechanism of GM-induced toxicity is thought to be the generation of ROS, which causes severe necrosis from lipid peroxidation and denaturation of proteins. Numerous investigations documented the GM-induced renal toxicity, which was characterised by elevated apoptosis and may have contributed to the tubular necrosis caused by GM accumulation. [26]

The main causes of acute renal failure brought on by various antibiotics and anticancer drugs include intratubular obstruction and/or direct damage to tubule epithelial cells. Aminoglycosides frequently induce renal damage. Aminoglycosides typically cause acute renal failure after 7 to 10 days of exposure because they accumulate in the proximal tubule cells. Patients who are elderly, have a history of chronic renal failure, or are exposed to other nephrotoxic treatments concurrently are at higher risk of developing renal failure when using most nephrotoxic medications. The incidence of nephrotoxic acute renal failure can be decreased by adjusting the dosage of likely nephrotoxins based on body size and weight. Reducing the amount or frequency of these medicines in individuals who already have renal impairment is one strategy to accomplish this. Various studies have suggested that the antioxidant properties of plants have nephroprotective effects on renal damage generated

by gentamicin. Plants are a good source of antioxidants. [27] The presence of terpenoids, glycosides, saponins, flavonoids, phenols, steroids, and ascorbic acid was confirmed through phytochemical examination of R. damascena and C. intybus. Because of their potential as antioxidants, flavonoids and phenols are thought to offer nephroprotection. [28]

Serum urea and creatinine levels that are elevated can serve as reliable markers of renal damage. According to earlier research by Nitha and Janardhanan (2008), GM elevated serum levels of urea and creatinine, which resulted in nephrotoxicity, accumulation of gentamicin, which is actively carried into the proximal tubules leading to proximal tubular damage, modifies the renal circulation, and lowers GFR, is the cause of the elevated levels of serum creatinine and urea. [29] Our research is in accordance with the findings of Tanweer Khaliq's work, which used an intraperitoneal dose of gentamicin (80 mg/kg) to induce nephrotoxicity in albino rabbit to found elevated levels of biochemical markers.

The present investigation aligns with Tanweer Khaliq's study, which examined the nephroprotective potential of Cichorium Intybus root against Gentamicin-induced nephrotoxicity. The researcher employed Cichorium Intybus root extract administered via gavage tube at doses of 250 and 500 mg/kg. The nephroprotection resulting from Cichorium intybus root has alleged antioxidant qualities was also demonstrated by their research. [30].

The erythrocyte sedimentation rate was found to be in the normal range in control group. The Serum potassium, sodium, blood urea nitrogen and serum creatinine levels, which are the biochemical markers for kidney damage were found to be normal in this group. The BUN levels were observed to be in the normal range which depicts the normal functioning of the kidney. The histopathologic examination of the kidney showed normal glomerulus and tubular structure. Comparing these rats to control rats, there was a significant increase in serum potassium. The ESR of these rats increased significantly as well as compared to the control group. Serum creatinine, serum urea and BUN are biochemical markers used to assess renal function.

As compared to the control group, serum urea has been increased significantly in rats treated with gentamicin, serum creatinine increased significantly and BUN have raised significantly. Renal function deficiency has been suggested by this biochemical evidence. Histopathological findings was also in favour with the biochemical parameters. Histopathological findings which showed presence of haematuria in almost all tubules, desquamation, more than half of the PCT dilatation, necrosis and inflammatory cell infiltrate shows the established kidney injury. Since these are waste products that are eliminated from the blood in urine, a rise in blood urea and serum creatinine levels is thought to be an indirect indicator of renal dysfunction. As a result, there is a delay between the onset of renal impairment and the elevation of these parameters. [31]

Histopathological analysis of kidneys revealed alterations that could indicate serious renal injury. When combined, these findings suggest that at 9-day, 80 mg/kg gentamicin treatment can cause considerable nephrotoxicity. Rats given Gentamicin 40 mg/kg intraperitoneally for six days also showed signs of proximal tubular necrosis, according to research by B.H. Ali et al. It was also proven that this dosage of gentamicin was nephrotoxic. [32]

Nonetheless, patients with aberrant renal function are more likely to experience prolonged periods of increased blood levels and have lower clearance of Gentamicin. AKI is also significantly predicted by impaired baseline renal function, as demonstrated by our findings and those of other investigations. [33]

It is established that low renal function reduces electrolyte excretion. Comparing the rats to the gentamicin group, there was a considerable decrease in serum potassium in the pre-treatment group. Erythrocyte sedimentation rate significantly lowered as well. Serum creatinine, blood urea and BUN levels which are biochemical markers used to assess renal function has also been significantly decreased as compared to the gentamicin group.

In the present study, ethyl acetate fraction of ethanolic extract of Cichorium intybus roots of 400 mg/kg resulted in much lower levels of serum urea and creatinine compared to the group that has received gentamicin, and noticed better results than EAFCI 200 mg/kg. The protective effect was confirmed by proximal tubular histopathological analysis, which yielded positive findings. Histopathological findings showed better architecture of kidneys in this group.

Our research has claimed that EAFCI 400 mg/kg showed better results than 200 mg/kg which has also been evidenced by the biochemical and histopathological examination.

No other investigation was conducted on the ethyl acetate fraction of ethanolic extract of Cichorium intybus root. The Evaluation of Nephroprotective Activity of Ethyl acetate Fraction from alcoholic extract of Cichorium intybus roots (Family-Asteraceae) on albino rats was demonstrated by the current study. To fully understand why the ethanolic extract of Cichorium intybus root responds more strongly to lowering elevated kidney indicators, more research is required. To observe the effect,

different administration via various methods and at increasing dosages can be further explored.

Conclusion

The present study explored ethyl acetate fraction from alcoholic extract of Chicorium intybus roots has potential nephroprotective activity against gentamicin induced nephrotoxicity. Due to presence of flavonoids in this fraction, it is having antioxidant and free radicals scavenging property. The biochemical and histopathological findings of EAFCI 400 mg/kg have shown better nephroprotective activity as compared to EAFCI 200 mg/kg against gentamicin induced nephrotoxicity. However, further studies should be designed to explore the molecular mechanisms associated with nephroprotective activity along with dose modifications.

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