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Original Article

Ethanolic Extract of aerial parts of *Achyranthes aspera* Attenuates Hepatotoxicity and Nephrotoxicity Induced by Cisplatin in Rat

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ABSTRACT

Background: The chemotherapeutic agents used to treat cancer are known to possess potent adverse effects like nephrotoxicity and hepatotoxicity among others. **Objectives:** The aim of this current study happened to be the isolation of phytoconstituent from *Achyranthes aspera* and assess the protective effect of the compound against cisplatin-induced hepato- and nephrotoxicity in rats. **Materials and Methods:** Toluene: Ethyl Acetate (9:1) was used as the solvent system to isolate the phenolic compound from ethanolic extract of the leaves and stem of *A. aspera*. The isolated compounds were studied using mass spectroscopy, 1H NMR, FT-IR and UV. The effect of the isolated phenolic was assessed by study of various factors like body weight, organ weight, serum biomarkers and histopathological studies. **Results:** The treatment of cisplatin led to a significant increase the weight of the organs, hepatic and kidney biomarkers in serum suggesting toxicity whereas the the isolated component reversed the elevated levels ($p<0.05$ compared to positive control). **Conclusion:** It could be concluded from the results that pretreatment with isolated component (coumarin) was able to attenuate the hepato-and nephron-toxicity induced by anticancer drug cisplatin.

Keywords: *Achyranthes aspera*, Cisplatin, Hepatotoxicity, Isolation, Nephrotoxicity.

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INTRODUCTION

Cancer is a diseased state in which a few body cells grow unchecked and may spread or metastasize to distant parts of the body. It remains the leading death reasons of mortality in persons with age 70 or less. It is expected that by the year 2040 around 13.6 million annual deaths would be due to cancer. The chemotherapeutic agents used to treat cancer are known to possess potent adverse effects. Nephrotoxicity is caused by methotrexate precipitating into the renal tubules.[1] Another possible adverse effect that might arise from greater dosages and intravenous administration is neurotoxicity.[2] Hepatotoxicity, a typical occurrence in people with renal impairment, is caused by the liver's suppression of DNA and RNA production.[3] Alkylating agents like cisplatin have been reported to cause myelosuppression, ototoxicity, neuropathy and nephrotoxicity.[4] Anthracyclines are known to produce cardiomyopathy and DNA damage-induced secondary leukemia.[5] Topoisomerase I Inhibitor carry the warning of diarrhea and myelosuppression.[6] The adverse reactions of vinca alkaloids comprise of leukopenia, thrombocytopenia and anemia while that of the taxanes include neutropenia and peripheral neuropathy. The newer anticancer molecules or the biologics are also associated with several toxicities including myelosuppression, peripheral neuropathy, hematological toxicities, diarrhea, cardiotoxicity, neutropenia, leukopenia and hepatotoxicity.[7] Nephrotoxicity and hepatotoxicity remain the most common adversities of cancer chemotherapy.

Cisplatin is one of the best and most innovative metal-based chemotherapy drugs available (Figure 1).

According to a report, worldwide sales of platinum-based anticancer medications total around $2 billion and cisplatin is used to treat about 50% of cancer patients.[8]

It provide treatment for variety of solid malignancies, including those of the testicles, ovaries, bladder, lung, cervix, head, neck and stomach, among others.[9-11] Basically, cisplatin attaches itself to either genomic DNA (gDNA) or mitochondrial DNA (mtDNA) to cause lesions in the DNA, prevent the production of mRNA, proteins and DNA, halt DNA replication and trigger a variety of transduction pathways that finally cause necrosis or apoptosis. The interaction of Cisplatin with DNA is instrumental in the anticancer effects of drug. Nonetheless, it is also responsible for

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most of the cytotoxic effects associated with Cisplatin. Treatment with cisplatin has been associated with a number of severe side effects, including as neurotoxicity, hepatotoxicity, nephrotoxicity and nausea.[12]

People utilised plants for medicinal purposes even before the ancient era. Among the ancient civilizations, India is well known for possessing an extensive array of medicinal plants. AYUSH colleges in India have standardized around 8,000 herbal remedies.

Achyranthes aspera (AA) belongs to the family Amaranthaceae, an important Indian medicinal plant distributed in the tropical and subtropical regions of India. Many sections of the plant have been found to contain secondary metabolites, such as proanthocyanidins, anthocyanidins, anthocyanins, carotenoids, coumarins, anthracenes, reducing sugars, fatty acids, glycoproteins, tannins, saponins, phenolic substances, phytosterol, cardiac glycosides, carbs and amino acids and anthraquinones.[13-17] Various scientific studies have explored the anti-microbial, anti-inflammatory, immuno-modulatory, antifertility, anti-hyperlipidemic, anti-diabetic, diuretic, antihypertensive, analgesic, antipyretic, anticancer, antidepressant and antispasmodic activities in various extracts or isolated components of the plant. Anticancer chemotherapy have been known to cause hepato and nephrotoxicities.[12] Despite the occurrence of flavones and phenolics in the plant in good amounts, the ability of plant in protecting anticancer drug induced toxicities. It was envisioned that isolate from extract of might be able to prevent anti-cancer drug induced toxicities and hence the present study evaluates the hepatoprotective and nephroprotective effect of isolate from ethanolic extract of AA against anticancer drug induced hepatotoxicity and nephrotoxicity in rat model.

Collection of plant

The leaves and stem of AA were collected as shown in Figure 1 from the local surrounding adjoining Geetanjali University, Udaipur, Rajasthan in the month of August and authenticated at Government College, Khimlasa, Sagar wide letter number 2023052.

Study of pharmacognostic features

The pharmacognostic features of the two plant material were studied by estimating its ash and extractive values as per reported procedures.[18-21]

Extraction of plant material

The powdered plant material prepared using the above procedure was used for extraction process. Briefly, 108 g of the powdered material was evenly packed in a thimble and placed in the Soxhlet device' extractor and defatted by extraction with petroleum ether for 8-10 hr. The defatted material was dried, weight and extracted with ethanol at 40-60°C as the solvent until a clear solution was visible in the siphon tube of the soxhlet apparatus. To minimise the volume, the extracts underwent vacuum evaporation concentration after being filtered to eliminate any remaining undissolved material. The leftover solvents were then evaporated over a water bath that was thermostatically heated after the concentrated extracts had been transferred to a 100 mL beaker. The dried extracts were stored in desiccators until used for further investigational procedures.[22,23]

Preliminary phytochemical testing

All the extracts were subjected to qualitative phytochemical testing procedures for determining if typical plant secondary metabolites are present or absent.[24]

Isolation of phytomolecule from AA

The active constituent from the ethanolic extract of AA was isolated using column chromatography after preliminary silica gel Thin Layer Chromatographic (TLC) analysis of the extract. The developed solvent system comprised of Toluene: Ethyl acetate: Acetic acid (4:1:0.2). Fractions of 20 mL were collected in Erlenmeyer flasks and the TLC of each flask content was performed. The fractions with similar TLC spots were pooled together and the solvent was removed by evaporation and the pure components can be further analyzed.[25] The characterization of the isolated product was performed by UV, NMR, FT-IR and Mass spectral studies.

Pharmacological Study

Animal

Male Wistar rats weighing around 200-250 g were used for the study after a week of acclimatization before the start of study. The CCSEA ethics committee gave its approval to the

Figure 1: *Achyranthes aspera* plant.

work and all experimental procedures were closely adhered to by IAEC regulations. Establishment Number: SKPCPER/IAEC/2022-01/02. The animal were maintained at 12 hour light and dark cycle in ventilated cages housing 4 animal per cage, with free access to food and water.

Acute toxicity evaluation

The Organisation for Economic Cooperation and Development's (OECD) standards 425 for evaluating substances for acute oral toxicity were followed in conducting the acute toxicity research.[25] Six male rats (n=6) received a dosage of an isolated product from AA (2000 mg/kg, p.o.) and were watched closely for 2 hr to assess behavioural, neurological and autonomic characteristics. They were also watched for any lethality or mortality over the next 24 and 72 hr.[26] One forth (200 mg/kg b.w.) of maximum tested dose was selected on the basis of our pilot study for further experiments. A higher dose (400 mg/kg bw) was also selected for the study.

Study Design

Animals are divided into 6 groups, each consisting 6 animals (Table 1).

Induction of hepato- and nephrotoxicity

Hepato- and nephrotoxicity in animal was induced by single dose intrapertioneal injection of Cisplatin at dose of 10 mg/kg on day 16 of the study for all the groups except group I. The total study duration was 21 days where in the day 1 begun with the treatment procedure as per the study design.

Assessment of protective effect

The animals were weighed and slaughtered at the conclusion of the experiment. Using 23 G1 syringes, trunk blood was drawn and placed in sterile falcon tubes. Serum was collected by centrifuging blood at 500×g for 15 min at 4°C. It was then stored at -80°C until biochemical analysis. The half of the organ was treated with liquid nitrogen and stored at -80°C for further biochemical analysis while the other portion was processed for histology.[27]

Estimation of serum markers of liver function and dyslipidemia

Serum analysis of various liver marker enzymes such as Alanine Aminotransferase (ALT/SGPT), Aspartate Aminotransferase (AST/SGOT), total bilirubin, conjugated bilirubin and unconjugated bilirubin were estimated by using standard diagnostic kits. The serum was also assessed for total protein, albumin content, globulin content, creatinine, sodium, potassium and Blood Urea Nitrogen (BUN) content using standard kit with the aid of biochemistry analyzer.

Histopathological Examination

The animal in each group were euthanized using cervical dislocation following ether anesthesia and the liver, heart, stomach and kidney (both) were isolated. The weight of each organ was recorded prior to processing for histopathological analysis. Hepatic and renal tissues were preserved in a fixative containing 100% alcohol (85 mL), glacial acetic acid (5 mL) and 40% formaldehyde (10 mL) for histological analysis. Tissue samples were dehydrated and then fixed in parafin to create blocks for microtomy. Using a microtome, tissues were sectioned into 4-5 µm sections, stained with Hemotoxilin-Eosin (HandE) and examined at 40X under a light microscope. Using the camera mounted to the microscope, pictures were taken at the same magnification and the histology parameters were examined.

RESULTS

The normal process was used to the dried plant parts in order to determine different physicochemical properties and 0.96±0.04 (%w/w) of foreign organic matter, 1.56±0.02 (%w/w) loss on drying and 0.69±0.11 (%w/w) swelling index was found. The ash (total, water soluble and acid insoluble) were found to be 6.34,

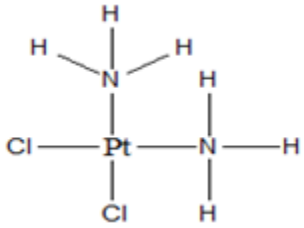

Figure 2: Chemical structure of cisplatin.

Table 1: Experimental design

Group	Type	Treatment	Dose
I	Negative control	Normal saline	10 mL/kg, i.p.
II	Positive control	Cisplatin	10 mg/kg, i.p.
III	Hepatoprotective standard	Silymarin+cisplatin	100 mg/kg, i.p+10 mg/kg, i.p.
IV	Nephroprotective standard	Cystone+cisplatin	5 mL/kg, i.p+10 mg/kg, i.p.
V	Test Group 1	Phytoextract+ Cisplatin	200 mg/kg, i.p+10 mg/kg, i.p.
VI	Test Group 2	Phytoextract+ Cisplatin	400 mg/kg, i.p+10 mg/kg, i.p.

5.21 and 1.87% respectively. The water and alcohol extractives were calculated to be 6.43 and 3.42% respectively.

Extraction and phytochemical screening

The petroleum ether extract was yellow in color and obtained in 0.390% yield whereas the ethanol extract was green and obtained in 2.674% yield. The significant yield of ethanolic extract suggests more of polar type phytoconstituents in the extract. The observations of phytochemical screening of AA extracts suggested the presence of alkaloids, terpenes, flavonoids, tannins, phenolics and glycoside in the ethanolic extract whereas only glycosides were found to be present in the petroleum ether extract of the plant.

TLC and isolation of phytoconstituent

The preliminary TLC of ethanol extract of AA extract was performed on different solvent systems. TLC performed in Toluene: Ethyl Acetate (9:1) with standard phenolic exhibited similar spots in AA extract. Hence Toluene: Ethyl Acetate (9:1) were used as the column chromatography mobile phase. By using the mobile phase in column chromatography, the active components were separated. of Toluene: Ethyl Acetate (9:1) to obtain fractions 01-02 (A), 03 (B), 04 (C), 05 (D), 06 (E), 07 (F), 08 (G), 09 (H) and 10 (I). The AA extract yielded 10 fractions with distinct colors The TLC comparison of the isolated products was also done for the confirmation of active constituents with standards (Figure 2). The Rf value of the standard phenolic was 0.29 and the same Rf value was obtained for fraction A. The other fractions either exhibited multiple Rf values or had Rf value different from the compound of interest.

Mass spectra of isolated fraction (Fraction A) of AA molecular ion [M^+] peaks at m/z 146.0478 corresponding to the molecular formula $C_9H_6O_2$ (Figure 3).

The compound isolated from the ethanolic extract was confirmed to be coumarin, based on the results of spectral study and TLC.

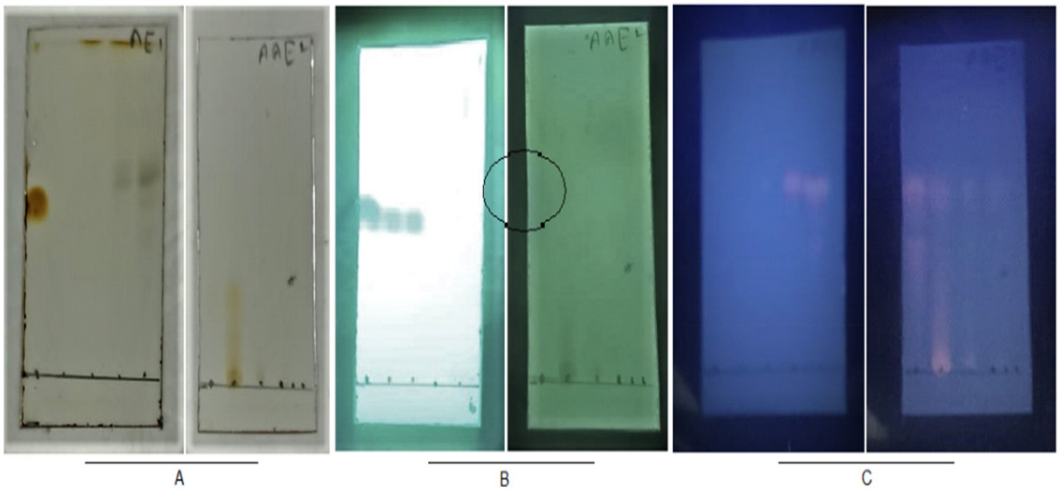

Figure 2: TLC of fractions (A) visible light (B) short UV (C) long UV.

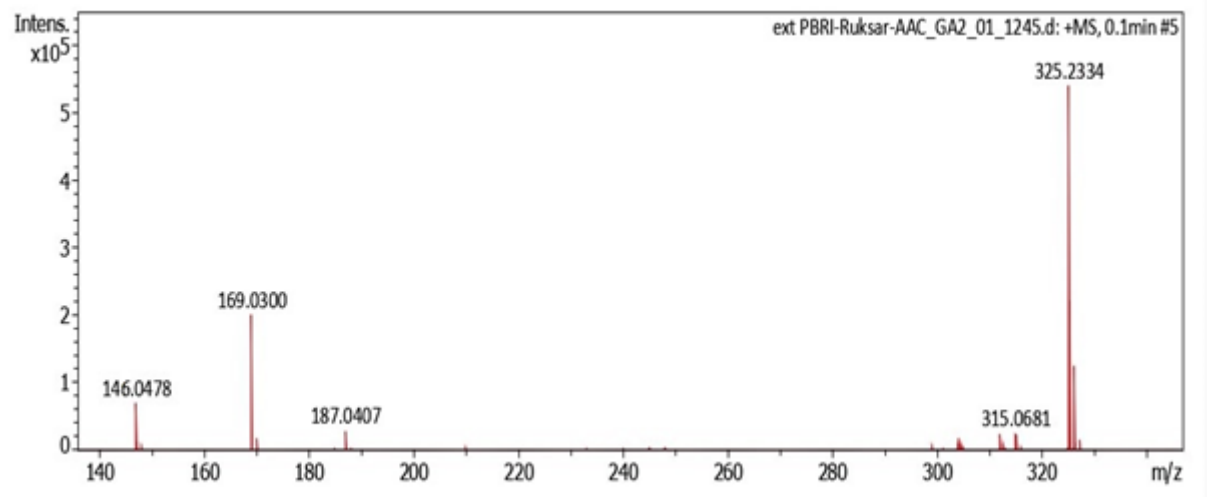

Figure 3: Mass spectra of the isolated compound (Fraction A) of AA.

Pharmacological Evaluation

The protective effect of the isolated compound from AA was studied in cisplatin induced hepto- and nephtrotoxicity in rats. The effect of the isolated product was assessed by study of various factors like body weight, organ weight, serum biomarkers and histopathological studies.

Effect on body and organ weight

The effect of the treatment on body weight of various groups of animal post the course of treatment are depicted in Table 2.

Effect on biochemical parameters of liver

The treatment groups (Group III to VI) depicted the recovery pattern on hepatic function biomarkers of serum in CP induced hepatocellular injury (Table 3).

Effect on biochemical parameters of kidney

The treatment with standard drug and the isolated compound was able to significantly reduce the BUN, creatinine, sodium, potassium and total protein levels which were elevated due to the cisplatin treatment. Cisplatin induced malfunctioning in the nephrons resulting in elevated levels of various ions and protein in serum. The pretreatment with the isolated compound was found to be non-dependent on the dose of treatment (Table 4).

Histopathological study

The liver tissue was dissected to visualize the necrosis induced by cisplatin treatment and the effect of treatment of isolated compounds was also assessed. It was found that a single dose treatment of cisplatin to the test animal resulted in gross damage to the liver tissue which was found to be prevented in the

Table 2: Effect of treatment of body and organ weight in test animal.

Treatment	Body weight	Stomach	Liver	Heart	1-Kidney	2-Kidney
Group I	71.8±2.39	11.45±0.18	4.58±0.09	0.79±0.002	0.87±0.008	0.86±0.01
Group II	145.0±5.27*	13.82±0.04*	4.98±0.01*	0.87±0.005*	0.99±0.004*	0.99±0.002*
Group III	97.7±2.11[a]	11.83±0.16 [a]	4.44±0.08 [a]	0.77±0.006 [a]	0.88±0.01 [a]	0.87±0.02 [a]
Group IV	125.0±2.56[a]	11.62±0.08 [a]	4.32±0.06 [a]	0.72±0.01 [a]	0.82±0.01 [a]	0.86±0.007 [a]
Group V	128.5±3.19	11.68±0.45[a]	4.54±0.13[a]	0.32±0.04[a]	0.76±0.06[a]	0.89±0.05[a]
Group VI	134.6±2.23	11.59±0.22[a]	4.89±0.08[a]	0.75±0.07[a]	0.78±0.09[a]	0.79±0.08[a]

Values are expressed as mean±SEM (Number of animals, n=6); *Significantly different from the normal control at $p<0.05$; [a] Significantly different from the control at $p<0.05$

Table 3: Effect of treatment of biochemical parameters of liver.

Treatment	SGOT	SGPT	Bilirubin total	Bilirubin Conjugated	Bilirubin Unconjugated
Group I	112.22±2.65	27.25±2.33	0.04±0.02	0.00±0.00	0.04±0.02
Group II	367.63±45.12	94.58±10.29	0.14±0.02	0.01±0.01	0.13±0.01
Group III	163.86±12.34	44.63±6.42	0.15±0.01	0.05±0.02	0.10±0.01
Group IV	130.14±4.44	42.33±6.66	0.16±0.01	0.05±0.01	0.08±0.02
Group V	120.26±5.25	52.44±7.45	0.05±0.00	0.19±0.15	0.05±0.00
Group VI	162.73±9.48	73.57±7.41	0.06±0.01	0.46±0.18	0.12±0.14

Value represents Mean±SEM, n=6, $p<0.05$,$p<0.01$,$p<0.001$ compared to Cisplatin group. One-way ANOVA followed by Tukey's t-test.

Table 4: Effect of treatment on biochemical markers of kidney.

Treatment	BUN	Creatinine	Sodium	Potasium	Urine total protein
Group I	18.41±4.11	0.22±0.01	128.16±1.84	5.15±0.39	16.70±1.99
Group II	37.60±2.03	0.29±0.02	157.44±0.73	7.15±0.52	73.60±6.93
Group III	28.91±4.16	0.23±0.01	137.03±6.42	6.39±0.67	67.84±2.30
Group IV	27.66±1.58	0.22±0.02	144.68±1.43	5.48±0.42	49.75±6.46
Group V	29.34±2.01	0.21±0.01	135.07±2.19	5.22±0.40	34.91±3.51
Group VI	25.21±2.17	0.23±0.01	135.39±4.16	6.56±0.31	23.34±1.00

Each value represents Mean±SEM, n=6, $p<0.05$,$p<0.01$,$p<0.001$ compared to Cisplatin group. One-way ANOVA followed by Tukey's t-test.

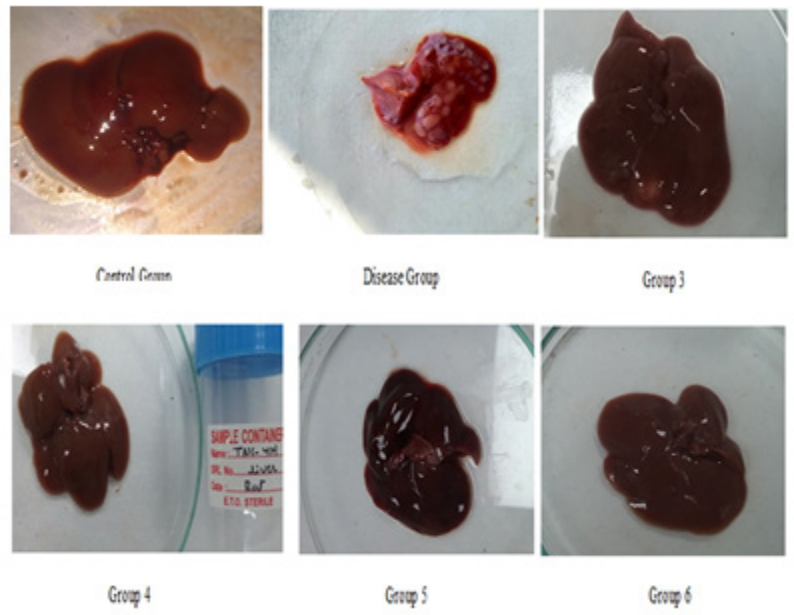

Figure 4: Gross liver necrosis in various groups.

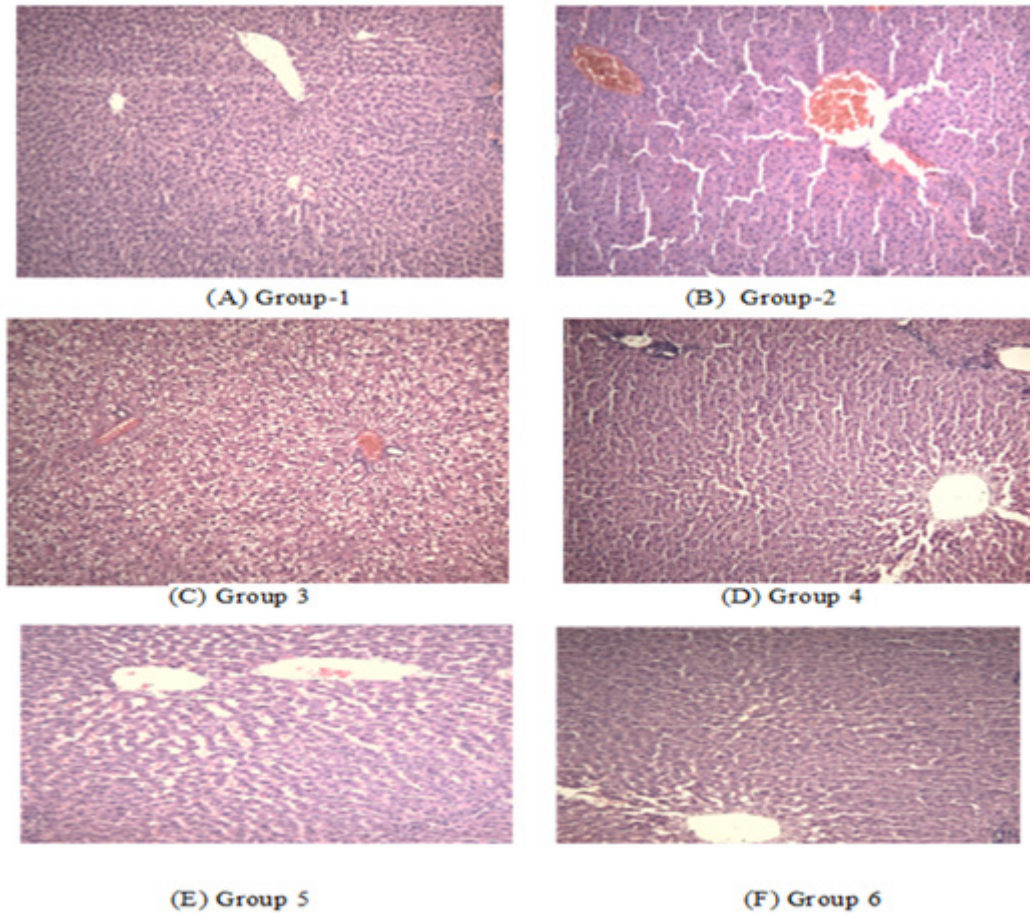

Figure 5: Histopathological examination of Liver.

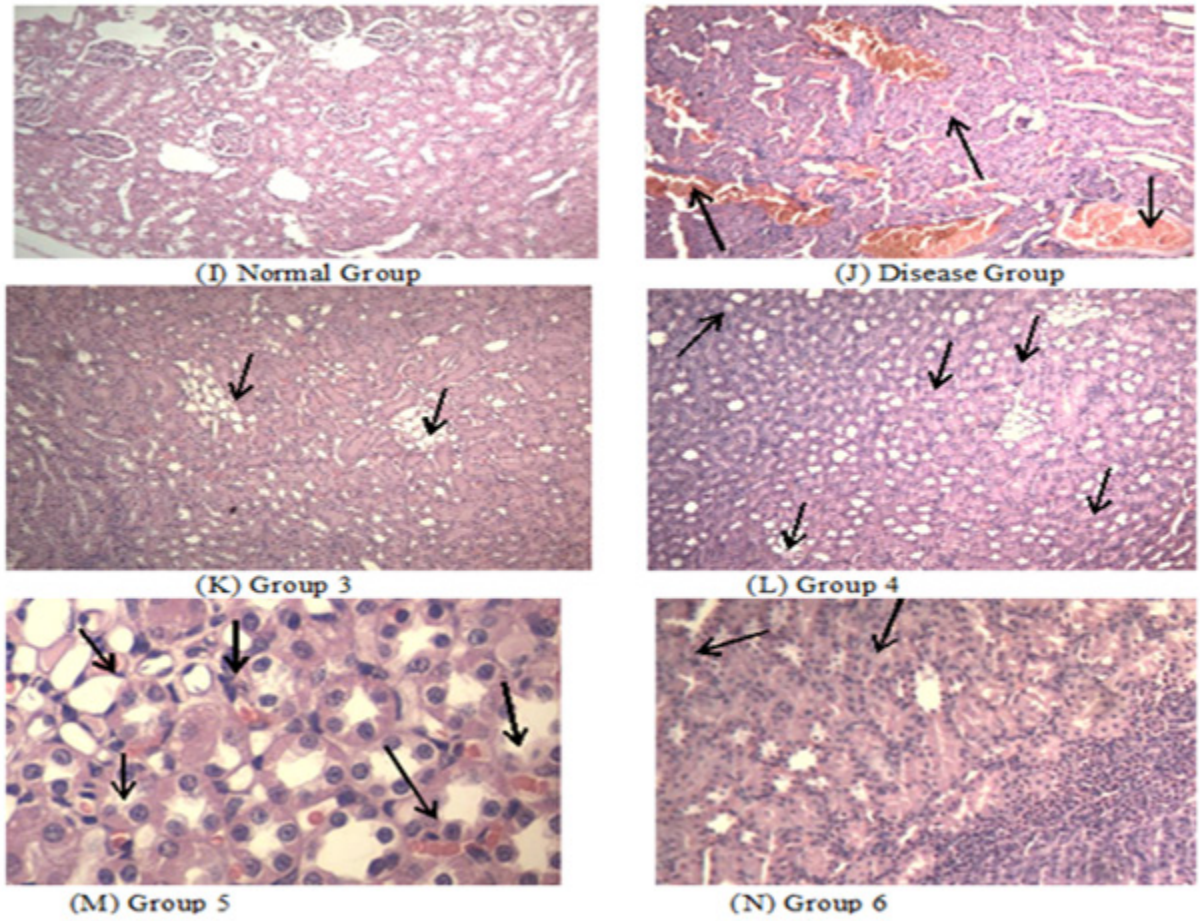

Figure 6: Histopathological examination of kidney.

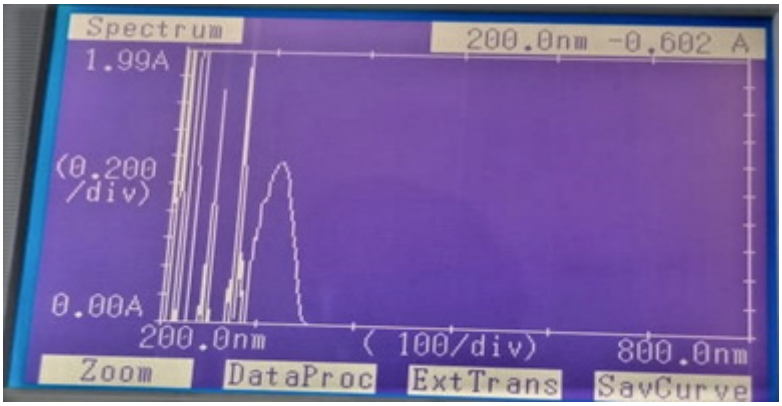

Figure 7: UV spectrum of "A" fraction of AA extract.

pretreatment with the standard as well as the test drugs (Figure 4).

The transverse section of the kidney was visualized to assess the toxicity and damage induced by cisplatin treatment and the effect of treatment by isolated compound was also assessed. It was found that a single dose treatment of cisplatin to the test animal resulted in gross damage to the liver tissue which was found to be prevented in the pretreatment with the standard as well as the test drugs (Figure 5).

As it could be seen in this figure, the histopathological section of the kidney presented nucleated and well differentiated cells whereas in the single dose cisplatin treated animal the cells were poorly differentiated and the nucleus was also found to be absent in several cells. On pre-treatment with the standard drug cystone and silymarin, the differentiation was restored. The pretreatment of coumarin led to significant reduction in the cisplatin induced damage and the cells of the kidney were found to be restored to its normal glory, well differentiated and well nucleated (Figure 6).

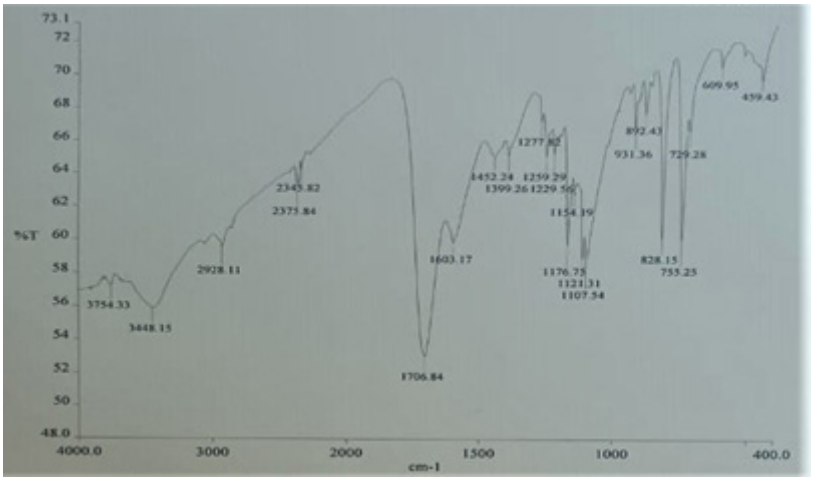

Figure 8: IR spectra of the isolated compound (Fraction A) of AA.

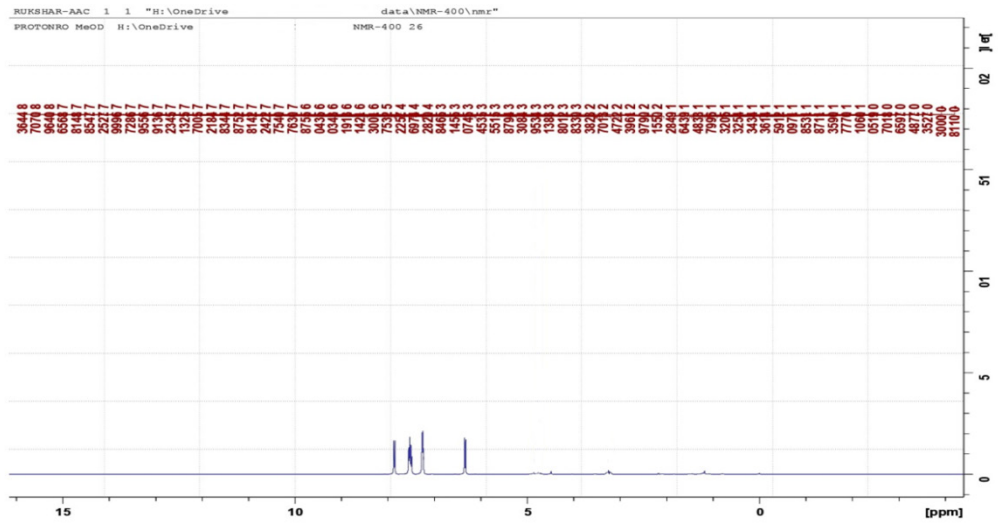

Figure 9: ^{1}H NMR spectra of the isolated Fraction (Fraction A) of AA.

DISCUSSION

The UV spectra of the isolated component exhibited absorption maximum at 322 nm (Figure 7).

The IR Spectra showed broad absorption peak at 3448.15 indicating the presence of -OH group. The peak at 2928.11 cm^{-1} indicated the presence of alkane C-H stretching. The absorption peak at 1603.17 cm^{-1} indicated the unsaturation that is C=C absorption peak (conjugated alkene) and peak at 1107.54 cm^{-1} indicated the presence of C-C stretches (Alkane). The absorption band at 1452.24 cm^{-1} indicated the presence of C=C stretching of benezne ring and absorption band at 1706.84 cm^{-1} is due to C-Ostretches of Carbonyl group. The absorption peak at 729.28 cm^{-1} is due to C-H bending for aromatic Structure (Figure 8).

The^{1}H-NMR spectra 1 proton appeared at 6.34 (d) ppm, 2 protons appeared at 7.21-7.39 ppm (7.22 (ddd), 7.24 (ddd)), 2 protons appeared at 7.63-7.88 ppm (7.69 (ddd), 7.84 (ddd)) and 1 proton appeared at 7.86 (d) ppm (Figure 9).

As visible from the results (Table 2), the treatment of cisplatin led to a significant increase the weight of the organs suggesting toxicity. The treatment of with the standard hepatoprotective drug silymarin as well as the nephroprotective drug cystone was found to reduce the organ weight. Similarly treatment with the test compound coumarin was found to have a significant control over the increased body organ weight resulting from cisplatin induced toxicity. Also it was found that the effect of the test compound was independent of dose. The results obtained at both the low and high dose were found to be almost similar to each other.

Serum biomarker enzyme estimate serves as a helpful measure for assessing liver function and all forms of hepatocellular lesions. As a result of the CP inoculation, there was a significant (p<0.001) increase in the levels of hepatic biomarkers in the serum, such as Alkaline Phosphatase (ALP), Total Serum Bilirubin (TSB), Direct Bilirubin (DB) and Amino-Transferase enzymes (ALT and AST), with ALT being a specific and important indicator of liver damage. Administration of CP markedly increased the levels of ALT, AST, ALP, TSB and DB in the serum. The increased levels

of these blood biomarkers indicate hepatic dysfunction, which may be a side effect of drug-induced liver injury that results in hepatocyte enzyme leakage. In a previous study with aqueous extract of *Lophira lanceolata* leaf, moderate protection was found against cisplatin induced hepatorenal damages.[28] Similarly, a dose-dependent hepatoprotective effect was observed in cisplatin induced liver damage using methanol extract of *Zataria multifora* Biossan.[29] This heptatoprotection was attributed to the presence of antioxidnats in the extract. In yet another study apocynin administration was reported to reverse the adverse effects of cisplatin in hepatic tissues.[30]

CONCLUSION

Cisplatin is an anticancer drug. It also used in various cancer like advanced cancer of the bladder, ovaries, or testicles. It leading to their accumulation in liver and kidney tissues resulting into oxidative stress, ER stress, infilteration of liver activates the proinflammatory cytokines and hepatic stellate cells, which leads to the liver fibrosis and nephrotoxicity. Some herbal medicines have shown potentially beneficial effects on cancer progression and may ameliorate chemotherapy-induced toxicities. In this work, coumarin has been isolated from the ethanolic extracts of *Achyranthes aspera* and the compound was assessed for its protective effect against cisplatin induced hepatic and nephron damage. The study led us to conclude that coumarin could be aptly isolated from *A. aspera* and owing to its antioxidant potential it was able to prevent the damage that could be induced by anti-cancer drug cisplatin in the liver and kidney of the treated animal. From the biochemical studies it could be concluded that the isolated coumarin exerted its effects by reducing the oxidative stress in rats as visible from improvement in the levels of biochemical parameters.

ACKNOWLEDGEMENT

This study marks the conclusion of my amazing path towards a Ph.D. in Pharmacology. I have had a lot of help and support from these folks over this time, without whom I could not have completed the assignment. It is now appropriate for me to thank everyone who has helped with the work that has been documented in this report. It gives me great pleasure to convey my sincere thanks to my supervisor, Additional Principal and Professor Dr. Udichi Kataria, Head of the Pharmaceutical Science Department at the Geetanjali Institute of Pharmacy, Udaipur, for his unwavering assistance, unreserved support and priceless ideas. I would especially want to thank Mr. Anurag Dubey for his assistance and support during my study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ALT: Alanine aminotransferase; **AST:** Aspartate amino transferase; **SGPT:** Serum glutamic pyruvic transaminase; **SGOT:** Serum glutamic oxidoacetic transaminase; **HF:** Formulation using herbs; **AAF:** *Achyranthes aspera* fraction; **AIF:** *Aesculus indica* fraction; **BUN:** Blood urea nitrogen; **SOD:** Superoxide dismutase; **GSH:** Reduced glutathione; **MDA:** Malondialdehyde; **UV:** Ultraviolet; **IR:** Infrared spectra.

SUMMARY

Owing to oxidative stress, inflammation and fibrosis, the commonly used anticancer medication cisplatin can harm the liver and kidneys. *Achyranthes aspera* is one herbal remedy that may help reduce these toxicity. Because of its antioxidant qualities, the coumarin that was extracted from *A. aspera* in this study was found to protect animals' liver and kidneys from damage caused by cisplatin.

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