ORIGINAL ARTICLE

SHIELDING EFFECTS OF CORN SILK EXTRACT AGAINST DOXORUBICIN INDUCED HEPATOTOXICITY IN WISTAR ALBINO RATS

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Background: Doxorubicin is a known anticancer drug. This study evaluated the protective effects of corn silk extract on hepatotoxicity induced by Doxorubicin in albino rats. **Methods:** This randomized control trial was conducted in animal house of Anatomy Department, PGMI, Lahore, for one year in 2022. Thirty healthy adult albino rats of either sex, aging 6–8 weeks with 180–220 g of weight were randomly allotted to three groups 1 (control), 2 (experimental group-1), and 3 (experimental group-2) (n=10) that were given standard rat feed and distilled water *ad libitum*. Intraperitonially 1.2 mg/Kg body weight distilled water and doxorubicin were given to group 1 and group 2+3 for 21 days respectively. Group-3 was also given corn silk extract 400 mg/Kg/body weight by oral gavage for 21 days. On 22nd day, blood was drawn for biochemical analysis of alkaline phosphatase and gamma glutamyl transpeptidase, and liver were preserved for tissue processing and histological analysis. **Results:** Serum alkaline phosphatase of group 1 was 134.70±15.18, group 2 was 328.30±18.05, and group 3 was 229.9±17.9. The serum gamma glutamyl transpeptidase of group 1 was 2.6±1.4, group 2 was 17.63±1.4, and group 3 was 9.6±1.2 (p<0.01). Histological analysis showed that group 1 rats had normal liver histology. Sinusoidal congestion and granuloma formation was observed in all rats of group 2. While in group 3, minimal sinusoidal congestion and granuloma formation was seen. **Conclusion:** Corn silk extract has protective effects against doxorubicin induced liver damage.

Keywords: Congestion, Corn silk extract, Doxorubicin, Hepatoxicity, Sinusoid

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INTRODUCTION

Global burden of cancer is increasing day by day at an alarming rate. According to the report of International Agency for Research on Cancer, more than 19 million new cancers have been reported in 2020.[1] Traditional treatment strategies for cancer include surgical resection of the mass, radiotherapy and chemotherapy. There are 100 different types of chemotherapeutic drugs that kill the cancer cells.[2] One of the most commonly used drug is Doxorubicin (Dox) an anthracycline based antibiotic with anticancer properties. It is extracted from the bacterium Streptomyces peucetius.[3] It is available in Pakistan in the form of injectables and in the dose of 10 mg, 20 mg and 50 mg. It is used in treatment of various types of cancers, e.g., breast, urinary bladder, lungs, thyroid gland, ovaries, stomach, soft tissue, bone sarcomas, neuroblastoma, Wilm's tumour, Hodgkin's and Non-Hodgkin's lymphoma, acute lymphoblastic leukaemia and acute myeloid leukaemia.[4,5] DOX is also known as the red devil, based on its bright red colour with characteristics and side-effects, including alopecia, myelosuppression, vomiting, soreness of mouth, hepatotoxicity, nephrotoxicity and cardiotoxicity.[6,7] The biochemical mechanism of action of Doxorubicin lies in its ability to intercalate into the DNA leading to inhibition of topoisomerase-II-mediated DNA replication, transcription and repair, release of free radicals and production of lipid peroxidation which damages cellular membrane and oxidative trauma which initiates the pathway of cell death or apoptosis.[3,8,9] It also induces genetic mutations which produces histological as well as biochemical changes in various organs like liver, pancreas, kidneys, heart, testes and stomach.[10,11]

Liver is the second largest and most significant organ of the body, which performs vital role in protein synthesis, storage, and metabolism of fats, carbohydrates and hormones, detoxification of drugs and toxins, excretion and metabolism of bilirubin.[12]

The administration of Dox has severe hepatotoxic effects. According to the literature the histological and biochemical changes including the presence of focal granulomatous lesion, cellular infiltrates, perivenular fibrosis and fat accumulation in liver cells and abnormal levels of liver enzymes including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT).[13–15]

Corn silk or maize silk is a yellow strand like structure that arises from the stigma of the female maize flower. It is silky soft thread, about 10 to 20 Cm in length and sweet in taste. It contains carbohydrates, strong anti-oxidants (Vit E, C and flavonoids), proteins, minerals (I, Ca, K, Mg and Na), volatile oils, alkaloids, tannins, saponins and steroids.[16] It is used as an anti-diabetic ,

anti-fungal, diuretic and uricosuric agent and hence used all over the world to treat urinary tract infections, cystitis, gout, nephritis, prostatitis, gonorrhoea, benign prostatic hyperplasia, hypertension and obesity.[17]

The natural antioxidant properties of corn silk extract eliminate free radicals and lipid peroxidation in the body. These characteristics are more obliging and less harmful than synthetic antioxidants like butylated hydroxy-anisole (BHA) and butylated hydroxytoulene (BHT).[16] Cornsilk extract is safe to use and acts on liver, pancreas, kidney, heart and fat tissues. Protective effects of corn silk extract on liver tissue are proposed to be due to its anti-oxidant properties.[18]

This study was designed to evaluate the ameliorating effects of corn silk extract against doxorubicin induced hepatotoxicity.

MATERIAL AND METHODS

It was a laboratory based randomized controlled trial conducted at the animal house and histology laboratory of Postgraduate Medical Institute Lahore in 2022. The study protocol was accepted by Advanced Studies and Research Board of University of Health Sciences, Lahore, and Ethical Committee of PGMI. Thirty, healthy adult albino rats of either sex, aging 6–8 weeks, weighing 180–220 g were taken. The animals were randomly divided into three groups of 10 each; 1 (control), 2 (experimental 1) and 3 (experimental 2). The animals were kept at 23–25 °C, 50–55% humidity, and normal photoperiod of 12–12 hours light/dark cycle and given standard rat feed and distilled water *ad libitum*, and were allowed to acclimatize for 1 week. Animals were weighed at start and end of experiment.

The rats of Group 1 (Control group) were given standard rat feed and distilled water *ad libitum* with additional distilled water I.P. in the dose of 1.2 mg/Kg/body weight every 3rd day for 21 days. The rats of Group 2 (Experimental group 1) were given Doxorubicin I.P. in the dose of 1.2 mg/Kg /body weight every 3rd day for 21 days.[19] The rats of Group 3 (Experimental group 2) were given Doxorubicin I.P. at the dose of 1.2 mg/Kg/body weight every 3rd day for 21 days and corn silk extract 400 mg/Kg/body weight orally for 21 days consecutively.[20]

After 24 hours of administration of the last dose at 22nd day, ~5 mL of blood was drawn from each rat via single intra-cardiac puncture and stored for biochemical analysis. Then animals were sacrificed and livers were removed, fixed in 10% formalin[21], and stored for tissue processing and morphological and histological study.

For serum extraction, vacutainers were centrifuged at 1300 g for 10 minutes.[22] Serum was aspirated by help of micropipette and dispensed into pre-labelled eppendorf tubes. Biochemical analysis of liver enzymes was done by colorimetric method (micro lab 300). For quantitative determination of serum ALP levels, lab kit of TRUE chemie based on IFCC method (LOT# A1322041 and linearity up to 650 U/L) was used. Whereas, for estimation of GGT, lab kit of Elabscience (Cat# E-BC-K126-M, detection range 0.88–399.4 U/L) was used. All the results we noted down for data analysis on SPSS.

For tissue processing and histological analysis, tissue samples were dehydrated and cleaned with xylene and embedded in paraffin blocks. Longitudinal sections of 5–7 micrometer thickness were obtained. Slides were stained with haematoxylin and eosin (H&E).

RESULTS

Results of biochemical parameters (serum ALP and GGT) were analysed by one-way ANOVA by using SPSS-22 and expressed as Mean±SD, (p<0.05) (Table-1). Inter group comparison was done by post Hock Tukey's HSD test and expressed in Table-2.

Table-1: Serum ALT and GGT level (Mean±SD)

Groups	ALP	GGT	*p*
Group 1	134.70±15.18	2.6±1.4	<0.05
Group 2	328.30±18. 05	17.63±1.4	<0.05
Group 3	229.90±17.984	9.6±1.2	<0.05

Table-2: Intergroup comparison by Post Hoc Tukey's HSD test

Variables	Group *vs* Group		*p*
Alkaline Phosphatase (U/L)	Group-1	Group 2	<0.001
		Group 3	
	Group 2	Group 3	
Gamma glutamyl transpeptidase (U/L)	Group 1	Group 2	<0.001
		Group 3	
	Group 2	Group 3	

Group 1 (Control group) showed normal histology of liver, i.e., typical cellular structures with preserved cytoplasm and distinct nucleus, well defined central vein, sinusoidal spaces and normal portal triad (Figure-1).

Group 2, animals administered with Doxorubicin showed multiple alterations including deranged structure of hepatocytes, dilatation and congestion of central vein and sinusoids with increased infiltration of inflammatory cells within the portal triad and oedema (Figure-2).

Group 3, animals treated with corn silk extract alongside Doxorubicin showed improvement in the hepatocyte architecture disrupted by Doxorubicin exposure. These animals exhibited significantly fewer alterations compared to the extensive liver damage observed in group 2. Corn silk extract administration effectively prevented swelling, inflammatory cells infiltration, necrosis, central vein and sinusoidal congestion (Figure-3).

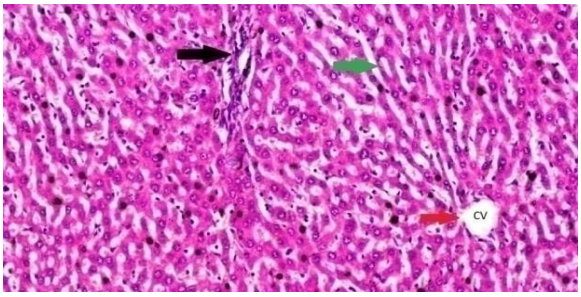

Figure-1: Photomicrograph of liver from Control group showing normal structure of hepatocytes, portal triad (black arrow), sinusoidal spaces (green arrow) and central vein (red arrow). (H&E stain, ×20)

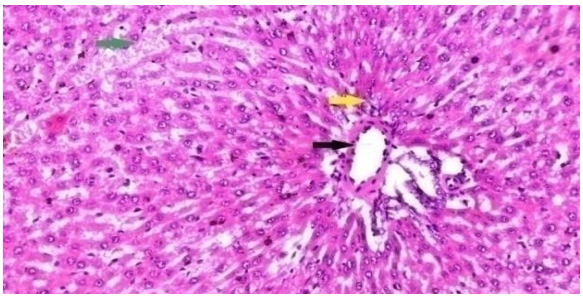

Figure-2: Photomicrograph of liver from Experimental group 2 showing deranged structure of hepatocytes including dilated and congested central vein (black arrow), infiltrate/Granuloma formation (yellow arrow) and sinusoidal congestion (green arrow). (H&E stain, ×20)

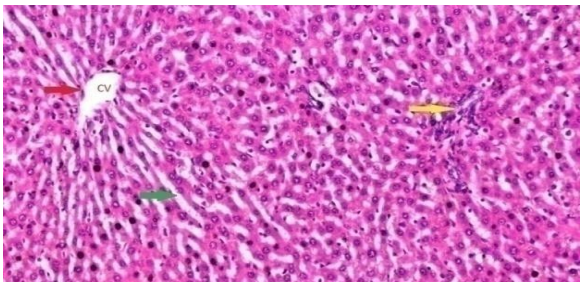

Figure-3: Experimental group 3 shows improvement compared to group 2. The central vein (red arrow) and sinusoidal congestion is reduced (green arrow) and inflammatory cell infiltration (yellow arrow) is also decreased. (H&E stain, ×20)

DISCUSSION

Rising occurrence of cancer in the developed and developing countries of the world has become a matter of concern. According to the WHO cancer data of 2019 cancer is the leading cause of mortality in more than 100 countries of the world.[1] Advancements in medical knowledge has evolved the management of cancer, e.g., same day surgery, short hospital stays, radio ablation, targeted drug therapy, personalized medication along with ambulatory home care, life style modifications and follow ups.[23]

One of the commonly used anti-cancer drug is doxorubicin which has potential side-effects on various organs of the body particularly on liver because liver is the main organ that metabolizes and detoxifies the drugs. Hence it remains exposed to the toxic metabolites of these drugs and any damage to the liver structure and function is clinically significant.[24] Hepatotoxic effects of drugs can be prevented by using natural products, i.e., crude extracts and bioactive substances.[25] One of these compounds is natural corn silk extract which is enriched with vitamins, minerals and strong anti-oxidant agents. Researches have proven its strong ameliorating effects against oxidative stress induced by various chemotherapeutic drugs like paclitaxel and cisplatin.[26,27]

Results of our study showed significant elevation of serum ALP and GGT levels, degeneration of hepatic cords, vacuolated cells with round to oval and elliptical shaped nuclei and dilated sinusoidal space, dilated and congested central vein and granuloma formation in animals of group 2. These results are in accordance with the study of Bilgic *et al*[28] in which 20 mg/Kg of DOX administered via I.P. injection for 6 days caused degenerative changes in hepatocytes, elevation of AST, ALT, and malendialdehyde levels and reduced catalase, glutathione peroxidase and super oxide dismuatase in male Sprague Dawley rats. The study of Belhan S *et al*[29] showed that single I.P. dose of 20 mg/Kg DXR reduced anti-oxidant enzymes levels and elevated malondialdehyde levels. From the results of these studies we can propose that the biochemical basis of doxorubicin induced liver damage is due to induction of free radicals and oxidative stress.

In our study the group C showed significant improvement in liver histology (significant reduction in sinusoidal congestion, granuloma formation and cellular infiltration) and reduction of serum ALP and GGT levels towards normal. These results are similar to the study of Barakat AI *et al*[26] in which corn silk extract in a dose of 400 mg/Kg given orally for 7 days restored the oxidative damage which occurred in rat lungs induced by chemotherapeutic drug paclitaxel. These properties of corn silk are due to its bioactive component flavonoids, e.g., maysin, ax-4-OH maysin, 3-methoxymaysin and vitamin ascorbic acid that have strong anticancer, anti-inflammatory, and antioxidant properties.[30]

CONCLUSION

Corn silk extract ameliorates the toxic effects of doxorubicin on the histology and biochemical functions of liver. Corn silk extract can be recommended as a protective agent against doxorubicin-induced hepatic damage due to its easy availability, low cost, rapid and safe dietary administration in cancer patients.

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Contribution of Authors:

AS: Manuscript writing, Animal dissection, Tissue processing
UZM: Blood sampling, ELISA
RE: Histological analysis of tissue
AM: Drug administration, ELISA
HAB: Dose adjustment, Statistical analysis of data
MY: Bibliography and References

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