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RESEARCH ARTICLE

Cytoprotective role of Vitamin E on the toxicity of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) chemotherapeutic regimes – An experimental animal study in albino rats

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ABSTRACT

Background: This experimental animal study was designed to evaluate the toxicity profile of two frontline chemotherapeutic regimens used in Hodgkin's lymphoma – doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and cyclophosphamide, vincristine, procarbazine, and prednisone (COPP), which are regimens commonly prescribed. We conducted this experimental animal study using albino rats, incorporating an antioxidant, Vitamin E, to assess if its cytoprotective properties could counter the free radical inducing actions of the two regimens. **Aims and Objectives:** The main objectives of our study were to document histologically, the toxic effects of chemotherapeutic agents in ABVD and COPP regimens in the various organ systems in albino rats, and to assess the protective role of the antioxidant, Vitamin E on drug-induced toxicities in albino rats. **Materials and Methods:** In this experimental animal study, 30 albino rats weighing 150 g–250 g were selected and grouped as control, chemotherapy receiving group, and cytoprotective group receiving ABVD/COPP and Vitamin E. The duration of the study was 4 weeks and hematological and histopathological studies were conducted on the models. Results: The experimental study revealed hematological and organ toxicities. Cytoprotection by Vitamin E was evident in the liver and stomach specimens on histopathology. Protection appeared minimal against hematological toxicity. **Conclusions:** The experimental animal study demonstrated a cytoprotective effect of Vitamin E against chemotherapy induced organ toxicity mainly in the stomach and liver, of the animals studied.

KEY WORDS: Cytoprotective; Vitamin E; ABVD; COPP; Albino Rats

INTRODUCTION

Our study is an experimental study on albino rats, focusing on the toxicity profile of two chemotherapeutic regimens employed in Hodgkin's lymphoma – doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and cyclophosphamide, vincristine, procarbazine, and prednisone (COPP), which are commonly prescribed frontline regimens.[1,2] Furthermore, we conducted an experimental animal study incorporating Vitamin E, an antioxidant which has received great attention the world over; to assess if its cytoprotective properties could counter the free radical inducing actions of the two regimens.

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Objectives

The objectives of the study were as follows:

- To document histologically, the toxic effects of chemotherapeutic agents in ABVD and COPP regimens in the various organ systems in albino rats
- To assess the protective role of the antioxidant, Vitamin E against these toxicities in albino rats.

MATERIALS AND METHODS

The experimental study involved 30 albino rats *(Rattus norvegicus)* maintained under identical conditions in the animal house; weighing about 150 g–250 g. The Institutional Animal Ethics Committee approval was sought before conducting the study and all experiments were conducted following the guidelines set by the Institutional Animal Ethics Committee. The animals were divided basically into three groups; Groups I, II, and III; for convenience of statistical analysis. Groups II and III were again subdivided into two [Table 1]. Hence, overall, there were five groups, with six rats in each group; maintaining the group average weight equal.

The five groups were:
1. Group I: Control
2. Group II: Anticancer drugs alone
   - II a – receiving ABVD
   - II b – receiving COPP.
3. Group III: Cytoprotective group
   - III a – receiving ABVD and Vitamin E
   - III b – receiving COPP and Vitamin E.

The duration of the study was 4 weeks. The first group, taken as control, was given distilled water. The second group and third group were given ABVD and COPP, respectively; while the fourth and fifth groups were given anticancer drugs along with Vitamin E, an antioxidant [Table 1]. The physical attributes of the five groups are given in Table 2.

The species, sex, weight, the test substance, time of injection, the dose, solvent, and the route were recorded. The dose and routes used for the administration of drugs are given in Table 3. General signs and changes in behavioral, neurological, and autonomic profile are noted[2] (Tables 4-6). Hematological investigations such as hemoglobin, total count, platelet count estimations, and measurement of weight were done during and at the end of the study.

General Signs

- Heart rate
- Respiratory rate
- Skin color.

Tail Clip Method[3,4]

This is a test for detecting neuropathy by estimating reaction time. A bulldog clamp with thin rubber sleeves is applied to the base of the rat's tail for 30 s. Control rats make continuous efforts to dislodge the clip by biting it. This is taken as the reaction time. Drug-induced neuropathy makes the affected rats indifferent to the clip.

Table 1: Study groups of the animal models

Groups	Subdivisions	*n*=6
I Control	I	Control (distilled water)
II Anticancer drugs alone	II a	ABVD
	II b	COPP
III Cytoprotective group	III a	ABVD + Vit E
	III b	COPP + Vit E

ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine,
COPP: Cyclophosphamide, vincristine, procarbazine, and prednisone

Animals were sacrificed at the end and histopathological examinations of internal organs were performed. The information and different data obtained were recorded in the pro forma sheets.

Statistics

Data were entered into statistical package Microsoft Excel and checked for data entry errors. For normally distributed continuous variables, mean, standard deviation, and analysis of variance (ANOVA) were done. For data not normally distributed, a non-parametric test such as Kruskal–Wallis was carried out. The level of significance was fixed at 5%.

RESULTS

For the purposes of statistical analysis and discussion, Groups IIa and IIIa are designated as ABVD group, and Groups IIb and IIIb are designated COPP group [Table 7].

Hematological

Hemogram: Normal values in rat (*Rattus norvegicus*)

Hb: 14.8 g% (12–17.5 g%)

TC: 14,000 cells/cu mm (5000–25,000 cells/cu mm)

Platelet count: 1,240,000 lacs/cu mm (11–13 lacs/cu mm)

By the end of the 3rd week, blood was drawn for hematological tests. Tests included estimation of hemoglobin, total count, and platelet count. The results of the laboratory tests are given in Tables 7.1 and 7.2, 8.1 and 8.2, and 9.1 and 9.2.

Table 2: Physical parameters of the animals under study

Parameter	Group I		Group II a		Group II b		Group III a		Group III b	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Weight (g)	186.66	27.32	186.61	39.88	186.49	41.312	186.60	40.33	186.53	40.12
Length (cm)	17.66	4.597	21.167	1.602	21.333	1.966	20.167	1.552	20.333	1.666
BSA (m^2)	0.033	0.0036	0.032	0.0046	0.032	0.0047	0.031	0.0046	0.030	0.0045

Table 3: Doses and routes of the drugs used[1]

Regimen	Drugs	Dose	Route
ABVD	Adriamycin	25 mg/m^2	IP
	Bleomycin	10 mg/m^2	IP
	Vinblastine	6 mg/m^2	IP
	Doxorubicin	375 mg/m^2	IP
COPP	Cyclophosphamide	650 mg/m^2	IP
	Vincristine	1.4 mg/m^2	IP
	Prednisolone	40 mg/m^2	PO
	Procarbazine	100 mg/m^2	IP
Antioxidant	Vitamin E	100mg/kg body wt.	PO

ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine, COPP: Cyclophosphamide, vincristine, procarbazine, and prednisone

Table 4: Assessment of behavioral profile of the animal models

Profile	Behavior	Interpretation
Awareness	Alert/stuporous	CNS stimulation/depression
	Virtual placing	Animal response being placed in different positions; normal or subnormal ability (motor incoordination)
	Stereotypy	Frequent mechanical repetition of a movement
	Passivity	Animal's response to being placed in unaccustomed positions. (tranquilization, central depression, myorelaxation paralysis, or anesthesia)
Mood	Grooming	Excessive indicates central excitation, stimulation
	Restlessness	Indicates central stimulation, discomfort; visceral changes
	Irritability	Extension of restlessness
	Fearfulness	Do not endure gentle manipulation
Motor activity	Spontaneous activity	Animal placed in bell jar shows moderate degree of inquisitive behavior
	Reactivity	Animal is removed from the jar and placed on a table
	Touch response	Animal is touched with a pencil or forceps at various parts (indicates presence of anesthetic activity)
	Pain response	A small artery clamp is attached to base of the tail (analgesia, sedation, and central depression)

Table 5: Assessment of neurological profile of the animal models

Profile	Behavior	Interpretation
Central excitation	Startle response	Response of the animal to a loud noise is recorded
	Straub response	Degree of elevation of tail
	Tremor	If present, is recorded
	Convulsion	If present, is recorded
Motor incoordination	Body position; limb position	If deviated much from normal; indicates neuromuscular blockade or central disturbance
	Staggering gait	Ataxia by test substance
	Abnormal gait	Muscle relaxation related to ataxia
	Somersault test	Righting reflex
Muscle tone	Limb tone	Grasping the forepaw of the animal and noting the resistance to extension of the paw
	Body tone and abdominal tone	Noting the muscle tension in comparison with control animal
Reflexes	Pinna reflex	Touching the center of the pinna with a fine instrument
	Corneal reflex	Touching the cornea with a wisp of cotton
	Ipsilateral reflex	Toe pad is compressed with a forceps which causes the animal to flex its leg in a returning movement

Table 6: Assessment of autonomic profile of the animal models

Profile	Behavior	Interpretation
Optical signs	Pupil Size	Compared before and after injection of test substance
	Palpebral opening	Compared before and after injection of test substance
Secretory signs	Micturition	Muscarinic activity or irritation of urinary tract by test substance or metabolite
	Salivation	Muscarinic activity

Table 7: Study groups of the animal models*

Groups	Subdivisions	*n*=6
I	I	Control (distilled water)
II Anticancer drugs alone	II a	ABVD
	II b	COPP
III Cytoprotective group	III a	ABVD + Vit. E
	III b	COPP + Vit. E

*For the purposes of statistical analysis and discussion, Groups IIa and IIIa are designated as ABVD group, and Groups IIb and IIIb are designated COPP group. ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine, COPP: Cyclophosphamide, vincristine, procarbazine, and prednisone

Table 7.1: ABVD group: Hemoglobin values at the 3rd week

ABVD group	Mean (g %)	Variance (g %)	SD (g %)	F/H
I	12.557	2.077	1.339	F=0.107
II a	12.093	3.664	1.864	
III a	12.402	3.917	1. 982	

Technique used: ANOVA – one-way analysis of variance. *P*=0.898862; not significant. ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine

Table 7.2: COPP group: Hemoglobin values at the 3rd week

COPP group	Mean (g %)	Variance (g %)	SD (g %)	F/H
I	12.557	2.077	1.339	F=0.103
II b	11.975	3.776	1.837	
III b	12.392	3.878	1. 853	

Technique used: ANOVA – one-way analysis of variance. *P*=0.887662; not significant. COPP: Cyclophosphamide, vincristine, procarbazine, and prednisone

Table 8.1: ABVD group: TC values at the 3rd week

ABVD group	Mean	Variance	SD	F/H
I	10.557	1.1867×10^6	1089.7	H=7.559
II a	5093	7.864×10^5	924.6	
III a	8334	5.7067×10^5	755.42	

Non-parametric technique: Kruskal–Wallis; one-way analysis of variance. *P*=0.022834; significant. ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine

Table 8.2: COPP group: TC values at the 3rd week

COPP group	Mean	Variance	SD	F/H
I	10.557	1.1867×10^6	1089.7	H=7.521
II b	6191.7	8.3642×10^5	914.6	
III b	8902	3.018×10^5	791.82	

Non-parametric technique: Kruskal–Wallis; one-way analysis of variance. *P*=0.021962; significant. COPP: Cyclophosphamide, vincristine, procarbazine, and prednisone

Table 9.1: ABVD group: PLT count values at the 3rd week

ABVD group	Mean	Variance	SD	F/H
I	1.060×10^6	6.1854×10^8	24,508.557	H=5.719
II a	1.0155×10^6	5.8441×10^8	24,571.642	
III a	1.0508×10^6	6.7456×10^8	23,755.422	

Non-parametric technique: Kruskal–Wallis; one-way analysis of variance. *P*=0.056; not significant. ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine

Table 9.2: COPP group: PLT count values at the 3rd week

COPP group	Mean	Variance	SD	F/H
I	1.060×10^6	6.1854×10^8	24,508.557	H=5.689
II b	1.0375×10^6	6.3652×10^8	28,6914.61	
III b	1.0235×10^6	6.0182×10^8	25,631.982	

Non-parametric technique: Kruskal–Wallis; one-way analysis of variance. *P*=0.05616; not significant. COPP: Cyclophosphamide, vincristine, procarbazine, and prednisone

Table 10.1: ABVD group: Weight at the 4th week

ABVD group	Mean (g)	Variance (g)	SD (g)	F/H
I	29.113	466.911	21.557	F=4.596
II a	−10.003	441.003	20.642	
III a	3.583	598.744	24.422	

Technique used: ANOVA – one-way analysis of variance. *P*=0.027751; significant. ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine

Table 10.2: COPP group: Weight at the 4th week

COPP group	Mean (g)	Variance (g)	SD (g)	F/H
I	29.113	466.911	21.557	F=4.517
II b	−10.017	446.365	20.869	
III b	3.389	586.018	23.982	

Technique used: ANOVA – one-way analysis of variance. *P*=0.026836; significant. COPP: Cyclophosphamide, vincristine, procarbazine, and prednisone

Hemogram

- The hemoglobin levels did not show much variation in all the groups studied.

Total Count

- The total count values demonstrated fall in both Groups II and III; but the decline in total count was significantly lesser in the cytoprotective group compared to Group II.

Platelet Count

- The platelet count levels did not show much variation in all the groups studied.

Weight

Weight at the 4th week-basal weight (mean difference):

There is weight loss in both groups receiving the drugs; but the loss in weight in the cytoprotective group is significantly of a much smaller magnitude than the weight loss observed in Group II.

General Assessment

Changes cannot be demonstrated in the behavioral, neurological, and autonomic profiles of the animals under study in effective doses of either ABVD or COPP regimens by blind screening methods. Effective dose failed to elicit peripheral analgesia or neuropathy in the rats under study as demonstrated by the tail clip method. There were no significant differences in reaction time in each group.

Histopathological Studies

The following tables (Tables 11–16) show the results of histopathological examination of the internal organs.

HISTOPATHOLOGICAL STUDIES

Stomach (Plate 1)

Table 11: Histopathological changes in the gastric mucosa

Gastric surface epithelial necrosis	Group
No necrosis (normal mucosa)	I
Full thickness	II
Partial thickness	III

- Microscopy of the gastric specimens revealed that a few rats in Group II showed full-thickness denudation of the gastric mucosa [Plate 1.2]. This finding was never found in the cytoprotective group, where it was merely a partial-thickness loss of the mucosa [Table 10; Plate 1.3]. In a few specimens of the cytoprotective group, even normal mucosa was also found.

Liver [Plate 2]

Table 12: Histopathological changes in the liver

Hepatic architecture	Group
Normal	I
Subcapsular hemorrhage	II
Necrosis	II
Periportal inflammation	II
Sinusoidal congestion (extensive)	II
Sinusoidal congestion (mild)	III
Fatty change (diffuse)	II
Fatty change (focal)	III
Regeneration	III

- Regarding microscopy of the hepatic specimens, toxic effects of a milder intensity were observed in the cytoprotective group in comparison to Group II [Plates 2.3A & 2.3B]. Group II specimens showed a more intense and severe manifestation of toxicity [Table 11; Plates 2.2A, B and C].
- The spleen, heart, kidneys, and lungs demonstrated toxic manifestations of similar magnitude and severity in both Groups II and III [Tables 12-16].

Spleen [Plate 3]

Table 13: Histopathological changes in the spleen

Splenic architecture	Group
Normal	I
Sinusoidal congestion	II, III
Hemorrhage	II, III

Heart [Plate 4]

Table 14: Histopathological changes in the heart

Cardiac architecture	Group
Normal	I
Congestion	II, III
Hemorrhage	II, III
Pericarditis	II, III

Kidney [Plate 5]

Table 15: Histopathological changes in the kidney

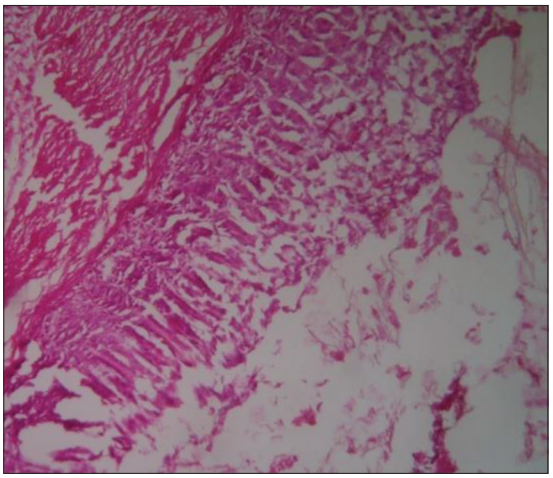
Renal architecture	Group
Normal	I
Subcapsular hemorrhage	II, III
Parenchymal hemorrhage	II, III
Tubular necrosis	II, III

Lung [Plate 6]

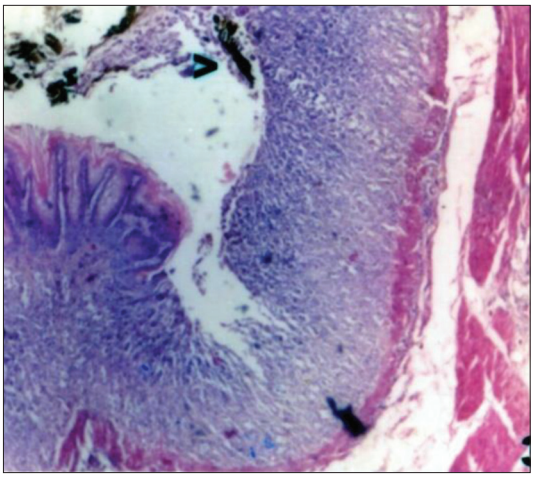
Table 16: Histopathological changes in the lung

Pulmonary architecture	Group
Normal	I
Inflammation	II, III
Collapse	II, III
Edema	II, III

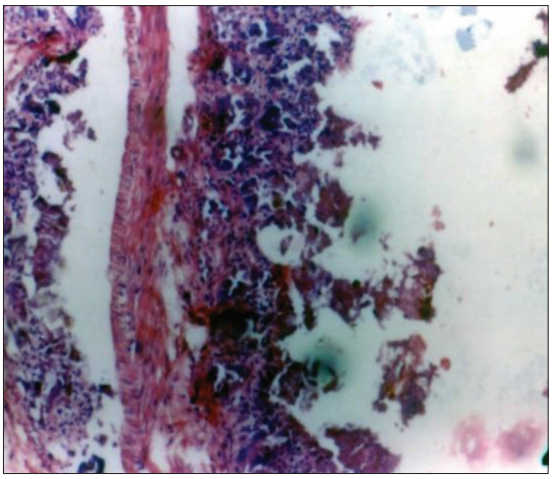
Plate 1 - Experimental animal study: Histopathology of stomach



1.1 Group I: Normal gastric mucosa

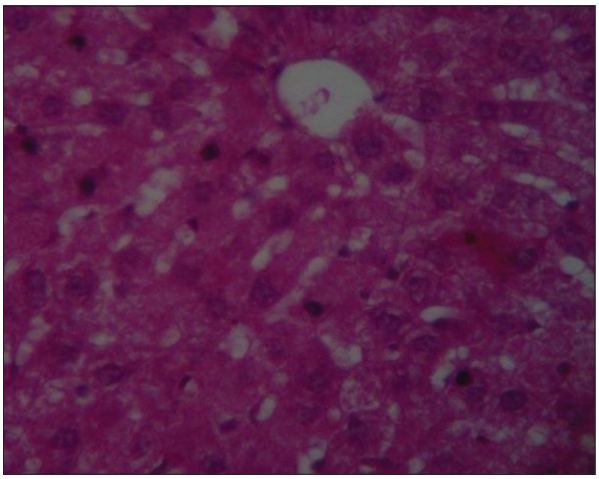


1.2 Group II: Full-thickness mucosal necrosis

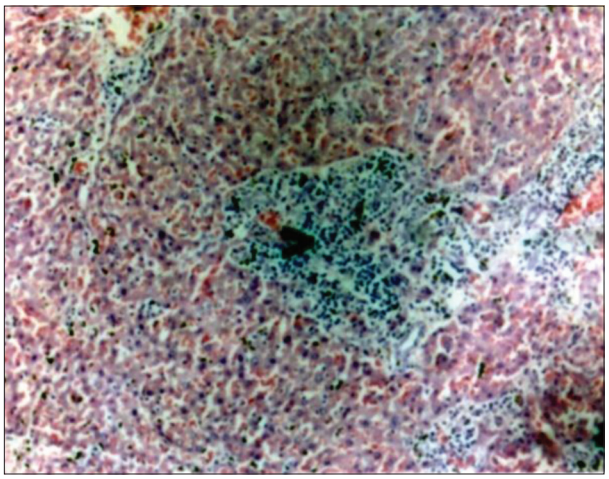


1.3 Group III: Partial-thickness mucosal necrosis

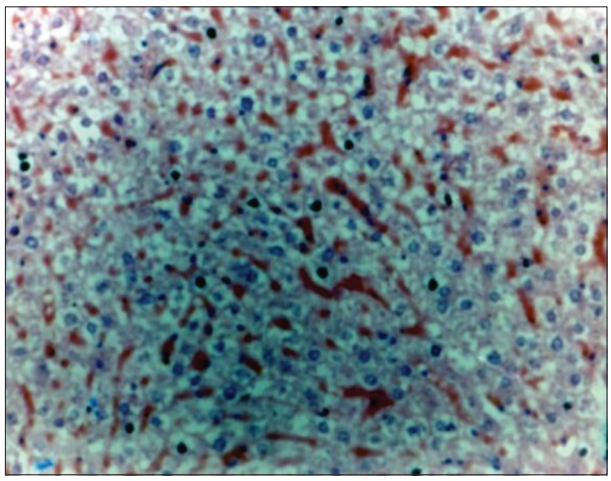
Plate 2 - Experimental animal study: Histopathology of liver



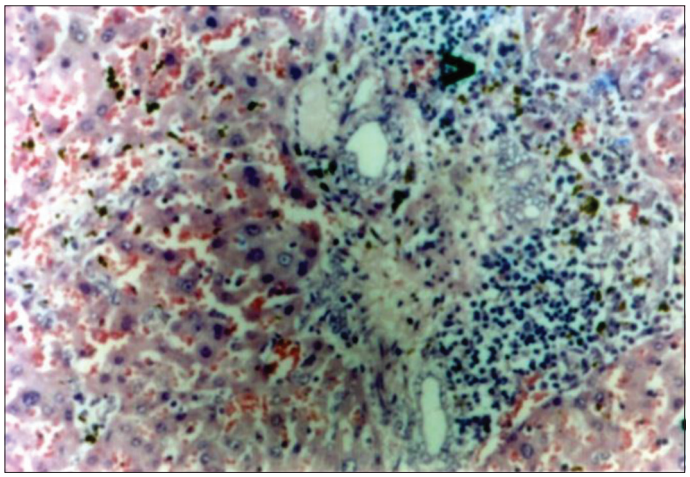
2.1 Group I: Normal liver



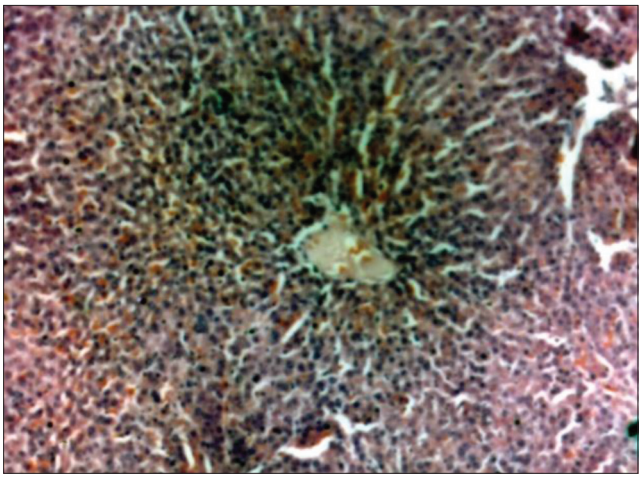
2.2A Group II: Severe congestion and hepatic necrosis



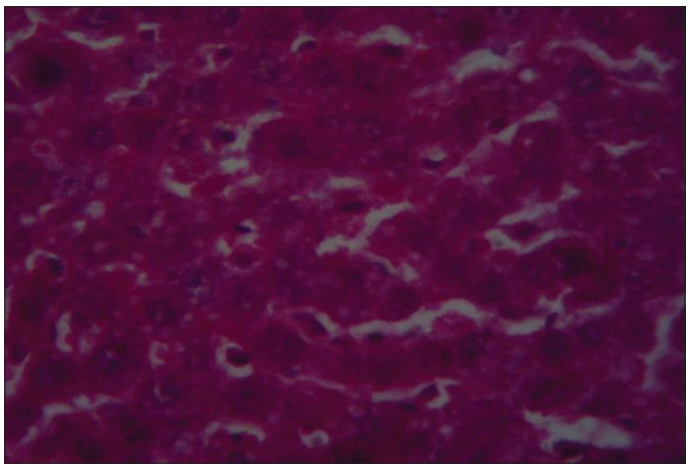
2.2B Group II: Microvesicular diffuse fatty change



2.2C Group II: Periportal inflammation

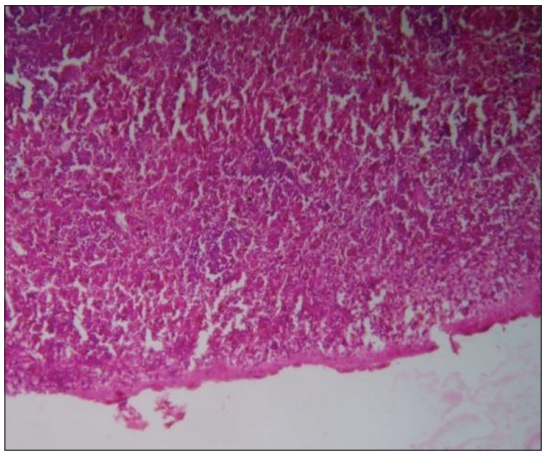


2.3A Group III: Mild congestion

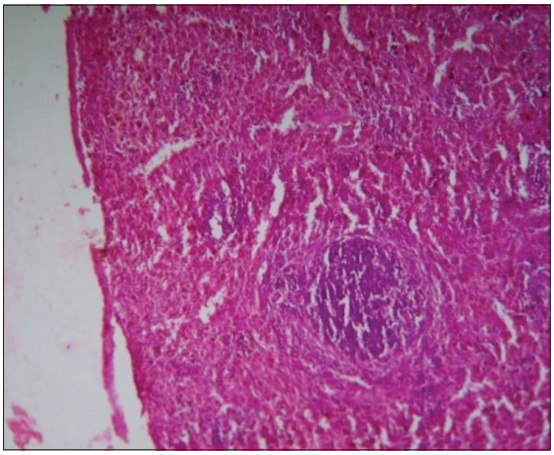


2.3B Group III: Regenerative hepatocytes

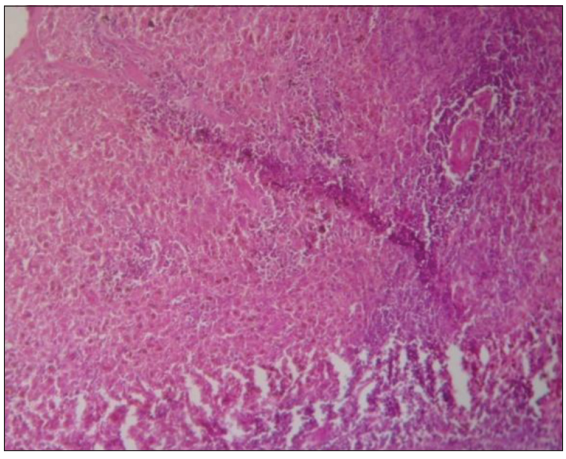
Plate 3 - Experimental animal study: Histopathology of spleen



3.1 Group I: Normal spleen

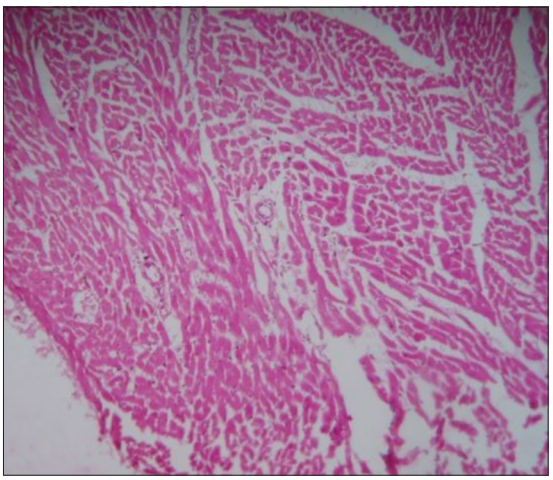


3.2 Group II: Sinusoidal congestion

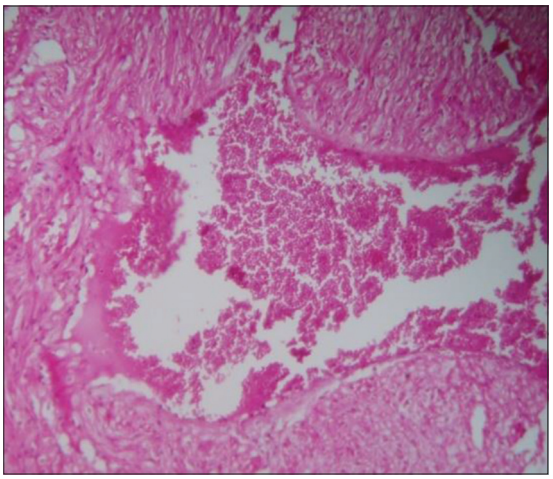


3.3 Group III: Sinusoidal congestion

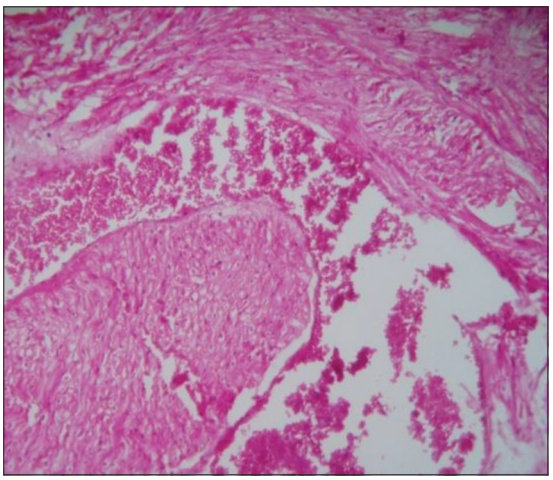
Plate 4 - Experimental animal study: Histopathology of heart



4.1 Group I: Normal heart

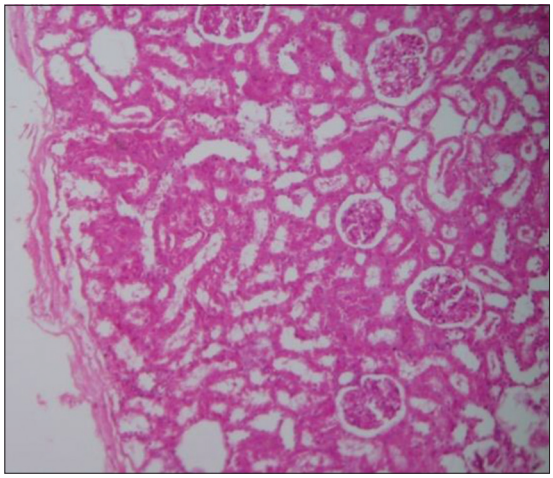


4.2 Group II: Hemorrhage

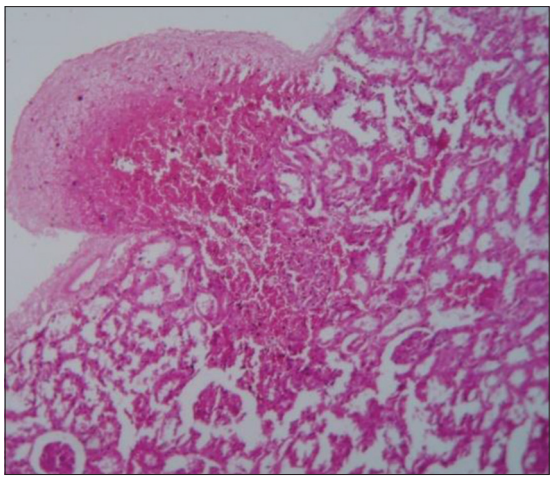


4.3 Group III: Hemorrhage

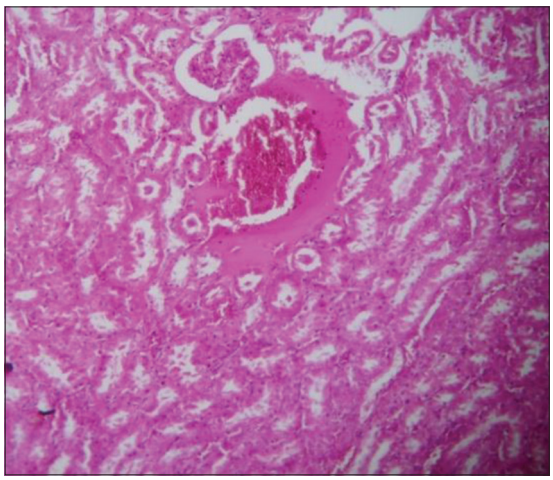
Plate 5 - Experimental animal study: Histopathology of kidney



5.1 Group I: Normal kidney

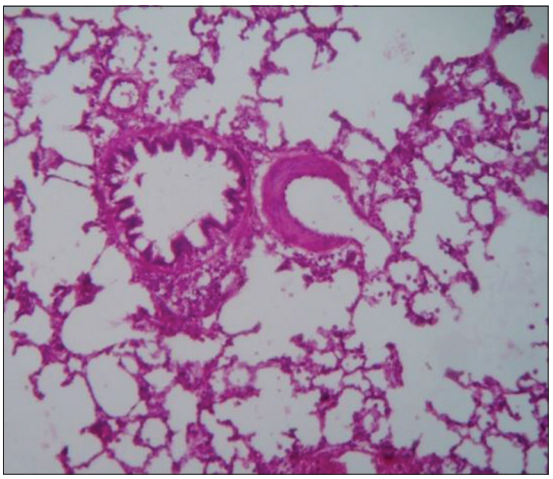


5.2 Group II: Capsular hemorrhage

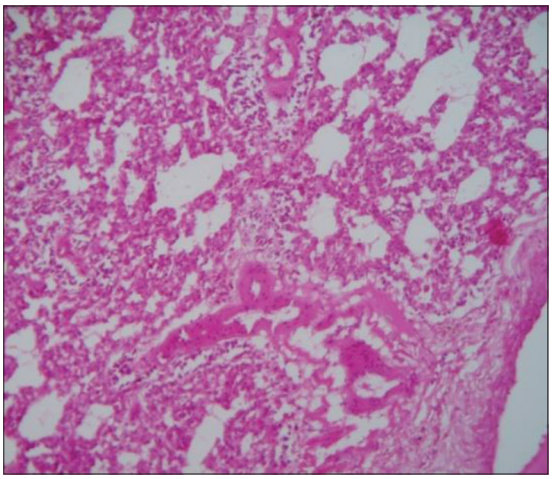


5.3 Group III: Parenchymal hemorrhage

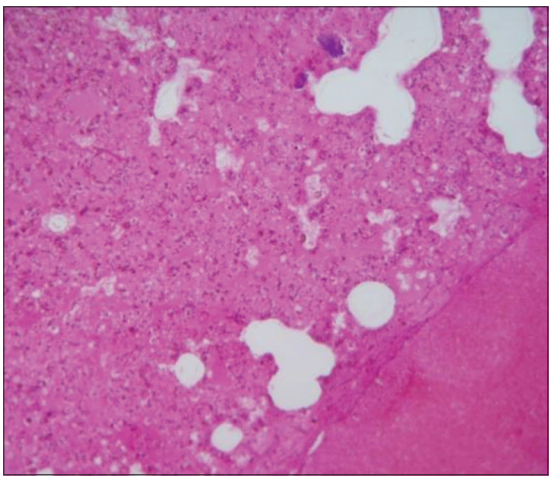
Plate 6 - Experimental animal study: Histopathology of lung



6.1 Group I: Normal lung



6.2 Group II: Inflammation and collapse



6.3 Group III: Severe collapse and edema

DISCUSSION

The main objectives of our experimental study were to study the toxicity profile of ABVD and COPP regimes in albino rats and to assess the protective role of Vitamin E, an antioxidant, on drug-induced toxicities. Mean hemoglobin of Group II (group receiving anticancer drugs alone) was less compared to Group III (cytoprotective group), but P value was insignificant ($P = 0.8988$) (Table 7.1 and 7.2), indicating only minimal protection by Vitamin E for the cytoprotective groups. Regarding total count values, there was significant difference ($P = 0.0371$, 0.021962) between the groups (Table 8.1 and 8.2), indicating a protective role by Vitamin E for Group III. Platelet count did not show much variation in the three groups studied (Tables 9.1 and 9.2). Weight of animals at the 4th week was compared to the basal values. In the 4th week, both Groups II and III demonstrated weight loss; but the weight loss in Group III was significantly ($P = 0.0277$, 0.026836) (Table 10.1 and 10.2) much less, compared to Group II which again points toward the protection afforded by Vitamin E.

Several studies suggest that supplementation with antioxidants influences the response to chemotherapy as well as the development of adverse side effects related to chemotherapy.[5-7] Administration of antineoplastic agents results in oxidative stress, that is, the production of free radicals and other reactive oxygen species (ROS). ROS cause or contribute to certain side effects that are common to many anticancer drugs, such as gastrointestinal toxicity and mutagenesis. ROS also contribute to side effects that occur only with individual agents, such as doxorubicin-induced cardiotoxicity and bleomycin-induced pulmonary fibrosis. Antioxidants detoxify ROS and can reduce or prevent many of these side effects and may enhance the anticancer effects of chemotherapy.[8]

Histopathological Examination of the Internal Organs of Albino Rats Studied

Protective role of Vitamin E on liver and stomach in rats was studied by Canturk *et al*.[9] The authors found that macroscopic and microscopic mucosal injuries were significantly greater in the control than the Vitamin E pre-treatment group. In our study, histopathological examination of the gastric mucosa revealed full-thickness surface epithelial necrosis in Group II (Plate 1.2*)* whereas Group III demonstrated only partial-thickness surface epithelial necrosis (Table 11; Plate 1.3). The necrosis could be due to the drug-induced changes in the gastric mucosa, and difference in severity in necrosis could be due to Vitamin E protection in Group III.

It was found in our study that spleen, kidney, and lungs were not protected from the toxic effects of the drugs by Vitamin E, as evidenced by the results (Tables 13, 15 and 16). In our study, the spleen showed sinusoidal congestion with hemorrhage when treated with cytotoxic chemotherapy irrespective of the use of the antioxidant Vitamin E (Plate 3). The kidney demonstrated tubular necrosis, subcapsular, and parenchymal hemorrhage in all groups except for the control (Table 15, Plate 5). The lungs showed evidence of inflammation and

edema in both Groups II and III. Some specimens showed collapse of a severe nature (Table 16, Plate 6).

A study was conducted by Legha *et al*.[10] to investigate the effects of Vitamin E on Adriamycin cardiotoxicity. The occurrence of congestive heart failure in three patients and the observation of significant pathologic changes in endomyocardial biopsies in approximately half of the patients treated with a median cumulative Adriamycin dose level of 550 mg/m_2 indicate that Vitamin E does not offer substantial protection against Adriamycin-induced cardiac toxicity. In our study, the heart was also, not found to be protected by Vitamin E from these effects (Table 14, Plate 4).

In our study, histopathological examination of the liver showed marked toxic effects in Group II (Plate 2.2A, 2.2B and 2.2C), such as severe sinusoidal congestion, hemorrhage, hepatic necrosis, periportal inflammation, and diffuse fatty change. These changes were absent or minimal in Group III, with some specimens demonstrating regenerative hepatocytes (Table 12, Plate 2.3B). This further proves the scavenging role Vitamin E plays to counter the oxidative stress the liver is exposed to, during the course of these regimens.

The limitations of this study are that the data are representative alone and do not imply that all the animals in a particular group demonstrated that particular histomorphology.

CONCLUSIONS

The experimental animal study demonstrated a cytoprotective effect of Vitamin E against chemotherapy-induced organ toxicity in the animals studied. The protective effect was most evident in the stomach and liver and these observations appear promising. In the case of hematological toxicity, protection was only minimal. However, further experimental studies and extensive randomized controlled trials are warranted before implementing Vitamin E administration along with the ABVD/COPP regimen. The prime concern of chemotherapy is drug-associated oxidative stress, which results in many side effects. Use of antioxidants can be beneficial in this respect as they minimize the burden of free reactive radicals in cells and thus can decrease the duration of chemotherapy regimens.

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