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Full Length Research Paper

Protective effect of ginger (*Zingiber officinale*) on adriamycin - induced hepatotoxicity in albino rats

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The effect of ginger (*Zingiber officinale*) upon hepatotoxicity induced in albino rats by the anticancer drug, adriamycin (ADR) was studied. Animals were divided into four groups. The first group was injected intraperitonealy with ADR at a dose level of 2 mg/kg body weight in sterile saline, once per week for 6 weeks. The second group was treated with ADR at the same dose level as those of group 1 followed by oral administration of 1 ml of final aqueous extract of ginger (24 mg/ml) 3 times weekly for 6 weeks. Animals in third group were given ginger only and those in the fourth group were served as normal controls. Injecting animals with ADR induced various histological changes in the liver. These changes include congestion of blood vessels, leucocytic infiltration, cytoplasmic vacuolization of the hepatocytes and fatty infiltration. Adriamycin caused significant elevation in serum ALT (Alanine aminotransferase) and AST (Aspartate aminotransferase) enzymes after 4 and 6 weeks of treatment. It also caused an increase in malondialdehyde (lipid peroxidation marker) and depletion of the antoxidant enzyme, superoxide dismutase. Treating animals with water extract of ginger and adriamycin led to an improvement in the histological changes induced by adriamycin together with significant decrease in ALT and AST activity. Moreover, ginger reduced the level of malondialdehyde and increased the activity of superoxide dismutase. The results of the present work indicated that ginger had protective effect against liver damage induced by adriamycin and this is due to its antioxidant activities.

Key words: Ginger, adriamycin, liver, histology, transaminases.

INTRODUCTION

Anticancer drugs are widely used against variety of human tumors. However, while they generate acceptable outcome in chemotherapy of some cancers, they also exhibit severe toxicity and undesirable side effects (Minami et al., 2010). Adriamycin (doxorubicin) is an antibiotic isolated from *Streptomyces peucetius* var Cesius. It is used as an anticancer agent in a variety of neoplastic conditions such as multiple myeloma (Alberts and Salmon, 1975), osteogenic sarcoma (Wang et al., 1971), lymphocytic leukemia (DiMarco et al., 1969) and stomach cancer (Ogawa, 1985). On the other hand, adriamycin was found to induce neoplasms in mammals (Bertazzoli et al., 1971; Sternberg et al., 1972) and amphibian (El-Mofty et al., 1991) . Extensive investigations have been conducted on the hepatotoxicity as well as general organ toxicity of adriamycin (Deepa and Varalakshmi, 2003; El-Sayyad et al., 2009).

Many medicinal plants are used today in therapy of different diseases. Ginger (*Zingiber officinale* Roscoe) is example of botanicals which is gaining popularity amongst modern physicians and its underground rhizomes are the medicinally useful part (Mascolo et al., 1989). One of the most popular uses of ginger is to relief the symptoms of nausea and vomiting associated with motion sickness, surgery and pregnancy (Gilani and Rahman, 2005). Many studies were carried out on ginger

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and its pungent constituents, fresh and dried rhizome. Among the pharmacological effects demonstrated is anti-platelet, antioxidant, anti-tumour, anti- rhinoviral, anti-hepatotoxicity and anti arthritic effect (Fisher-Rasmussen et al., 1991; Sharma et al., 1994; Kamtchouing et al., 2002). Ginger was found to have hypocholesterolaemic effects and cause decrease in body weight, blood glucose, serum total cholesterol and serum alkaline phosphatase in adult male rats (Gujral et al., 1978). The present work was conducted to study the effect of ginger on the hepatotoxicity of the anticancer drug, adriamycin in albino rats.

MATERIALS AND METHODS

Chemical

Adriablastina (ADR) (10 mg adriamycin hydrochloride), Pharmacia Italia S.P.A. Italy was used in this study.

Ginger extract

The rhizomes of Z. officinale were shade dried at room temperature and were crushed to powder. 125 g of the powder were macerated in 1000 ml of distilled water for 12 h at room temperature and were then filtered through a 5 µm filter to obtain the final aqueous extract. The concentration of the extract is 24 mg/ml equal to 120 mg/kg. In this study, each animal was orally given 1 ml of the final aqueous extract (Kamtchouing et al., 2002).

Animals and treatments

Sixty sexually mature male albino rats (Rattus norvegicus) weighting 125 ± 5 g were used. They obtained from the breeding center of experimental animals, Helwan University, Helwan, Egypt. Animals were kept in the laboratory under constant temperature (24±2°C) for at least one week before and throughout the experimental work. They were maintained on a standard diet composed of 55% corn starch, 20% casein, 15% corn oil, 5% salt mixture and 5% vitaminzed starch (Egyptian Company of Oils and Soap Kafr-Elzayat, Egypt). Water was available *ad libitum.* Animals were maintained and experimental procedures complied with the guide for care and use of laboratory animals (National Research Council, 1985). They were divided into 4 groups:

Group 1: Animals of this group (15 animals) were injected intraperitonealy with ADR at a dose level of 2 mg/kg body weight in sterile saline, once per week for 6 weeks.
Group 2: These animals (15 rats) treated with ADR at the same dose level as those of group 1 followed by oral administration of 1 ml of final aqueous extract of ginger (24 mg/ml) 3 times weekly for 6 weeks .
Group 3: Animals in this group (15 rats) were given ginger only.
Group 4: These animals (15 rats) were served as normal controls.

Histological and biochemical studies

Five animals were randomly selected from treated and control groups after 2, 4 and 6 weeks of treatment. They were sacrificed by cervical decapitation and were dissected. Liver was removed and fixed in Bouin's fluid. Fixed materials were embedded in paraffin wax and sections of 5 µ m thickness were cut. Slides were stained with haematoxylin and eosin for histological examination. The sections were graded for the degree of fatty change and inflammation. Steatosis was scored as follows: 1 when less than 25% of the cells contained fat droplets, 2 when 25 to 50%, 3 when 50 to 75%, and 4 when > 75% contained fat droplets. Inflammation was graded 0 to 3: 1 indicated the presence of scattered inflammatory cells, 2 indicated the presence of foci of inflammatory cells and 3 corresponded to diffuse inflammation (Leo and Lieber, 1983). For biochemical study, blood samples were collected from abdominal aorta into clean and dry tubes. Sera were obtained by centrifugation of the blood samples and stored at 20°C until assayed for the biochemical parameters. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured using a fully automated Hitachi 911 analyzer (Tokyo, Japan). A commercial randox kits (Randox Laboratories, LTD, Ardomre, Crumlin, United Kingdom) were used in these analyses. In hepatic tissue samples, malondialdehyde was determined by the method of Ohkawa et al. (1979) and superoxide dismutase was assayed using the method of Rest and Spitznagel (1977).

Statistical analysis

The results were expressed as mean ± SD of different groups. The differences between the mean values were evaluated by ANOVA followed by student's "t" test using Minitab 12 computer program (Minitab Inc., State Collage, PA). P>0.05 was considered significant.

RESULTS

Change in total body weight

Data showed in Figure 1 showed that treating animals with ADR for 6 weeks caused significant decrease in body weight of rats in comparison with control group. On the other hand, administration of ginger and ADR caused significant increase in body weight of rats in comparison with ADR group. When ginger was given to animals, insignificant change in body weight was recorded (P> 0.05).

Biochemical results

Table 1 showed the effect of different treatments on serum ALT activity. Non-significant difference in serum ALT activity was recorded in animals treated with ginger in comparison with control group. Animals treated with ADR showed a significant increase in serum ALT activity after 4 and 6 weeks of treatment. On the other hand, animals treated with ADR and ginger revealed a significant decrease (P<0.05) in ALT activity when compared with ADR group. Table 2 showed non-significant difference in serum AST activity in animals treated with ginger when compared with control group. Animals treated with adriamycin showed significant increase in serum AST activity while animals treated with ADR and ginger showed a significant decrease (P<0.05)

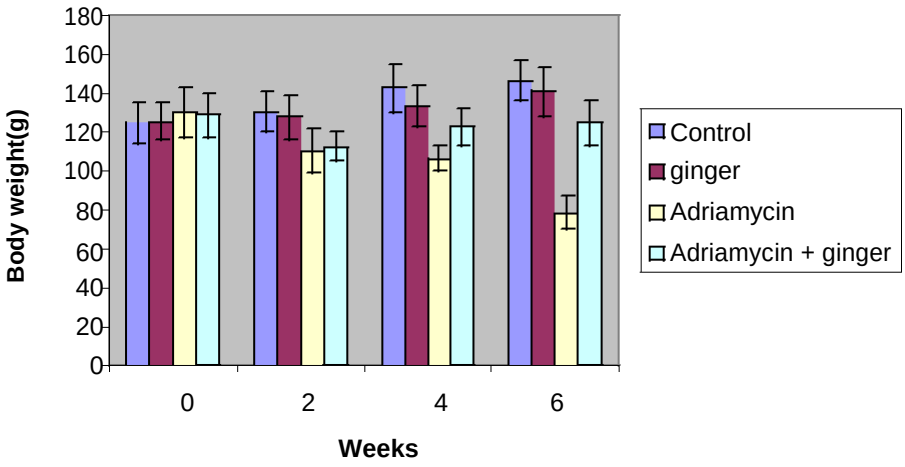

Figure 1. Effect of ginger and/or adriamycin on total body weights of rats (Mean± SD).

Table 1. Effect of different treatments on serum ALT activity.

Period of treatments (weeks)	Control	Ginger	Adriamycin	Adriamycin + ginger
2	48.6 ± 4.2	50.5 ± 5.2	67.4 ± 4.4	63.5 ± 5.5
4	50.5 ± 5.4	52.6 ± 5.5	88.5* ± 6.4	70.0 ± 2.5
6	51.5 ± 6.3	50.5 ± 6.4	106.7* ± 8.5	75.4 ±6.2

Values are expressed as mean ± SD (U/L). (*) Significant at P < 0.05.

Table 2. Effect of different treatments on serum AST activity.

Period of treatments (weeks)	Control	Ginger	Adriamycin	Adriamycin + ginger
2	98.5 ± 11.5	102.0 ± 8.5	125.6 ± 11.4	112.8 ± 9.4
4	101.0 ± 9.8	111.6 ± 10	172.6* ± 12.0	130.0 ± 13.5
6	102.5 ± 10.5	111.6 ± 12	206.0* ± 12.7	145.4 ± 12.7

Values are expressed as mean ± SD (U/L). (*) Significant at P<0.05.

Table 3. Effect of ginger and /or adriamycin on malondialdehyde level and superoxide dismutase activity in liver of rats.

Animal group	Malondialdehyde (nmol/mg)	Superoxide dismutase(/mg)
Control	1.23 ± 0.4	2.4 ± 0.80
Ginger	1.44 ± 0.33	2.1 ± 0.62
Adriamycin	2.87 ± 0.21*	1.1 ± 0.42*
Ginger+adriamycin	1.63 ± 0.18	1.88 ± 0.22

Values are expressed as mean ± SD. (*) Significant at P<0.05.

in AST activity when compared with ADR treated group.

Table 3 showed the effect of different treatments on malondialdehyde (MDA) (index of tissue lipid peroxidation) and superoxide dismutase (SOD) in liver of animals examined after 6 weeks. MDA level was increased significantly (P< 0.05) whereas SOD was found to be decreased in ADR–treated animals when compared to the control group. Treating rats with ginger and ADR altered the above changes by regulating the MDA level and SOD to nearly that of the control.

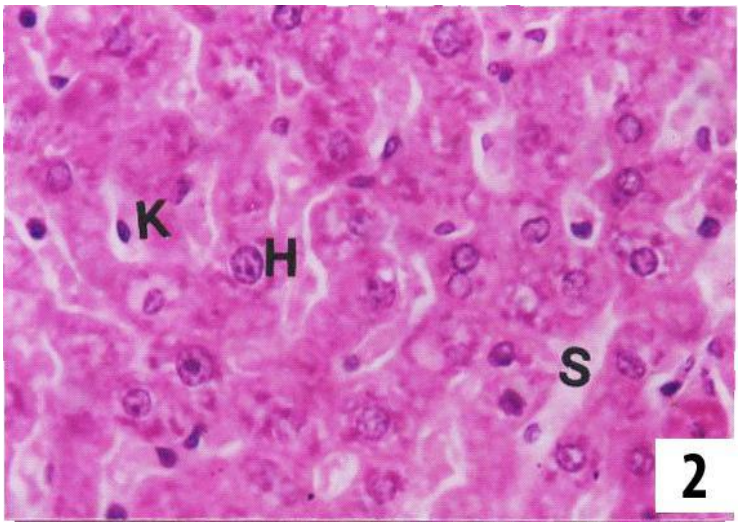

Figure 2. Liver section of a control rat showing hepatic cell (H), hepatic sinusoid (S) and Kupffer cell (K), (X 400).

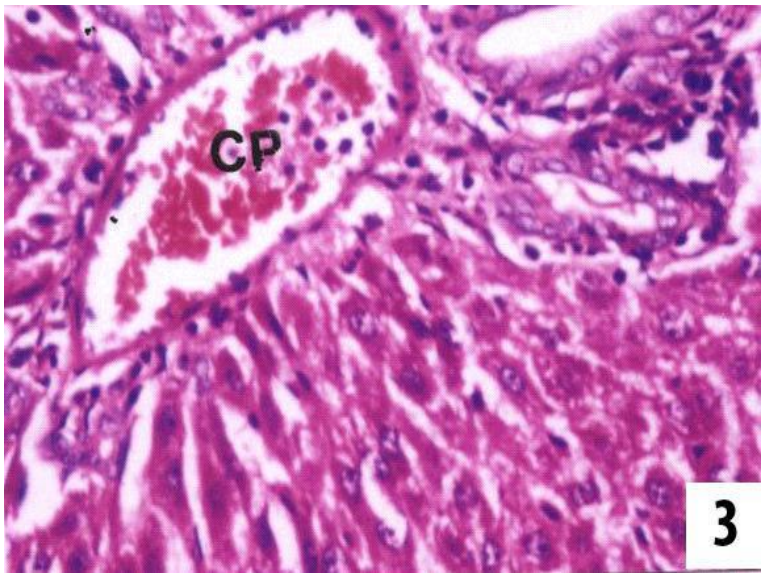

Figure 3. Section of liver of a rat treated with adriamycin for 2 weeks showing congestion of portal vein with eroded lining (CP), (X 400).

Histological results

Figure 2 showed histological structure of liver of control rat. Animals administered with ginger for 6 weeks showed the same histological observations as in the liver of control animals. Histological examination of liver of ADR-treated rats revealed many histopathological alterations which are correlated with the increase of treatment time. After two week of treatment with ADR, liver sections reflected signs of injury as indicated by congestion of intrahepatic veins, central and portal (Figure 3). Dilatation of sinusoids and infiltrations by large mass of leucocytic inflammatory cells were observed (Figure 4). After four weeks, the hepatic tissue lost its normal organization and most of the hepatocytes appeared with cytoplasmic vacuolization which is so extensive to the extent that only a very limited portion of it was left (Figure 5). The nuclei of these cells were pyknotic and the cell membranes were disrupted. Examination of liver sections of animals treated with ADR for 6 weeks reflected advanced degree of injury as indicated by fatty degeneration and activation of Kupffer cells (Figure 6) . The hepatic sinusoids were invaded with lymphocytic inflammatory cells and the blood vessels showed severe congestion. Liver sections

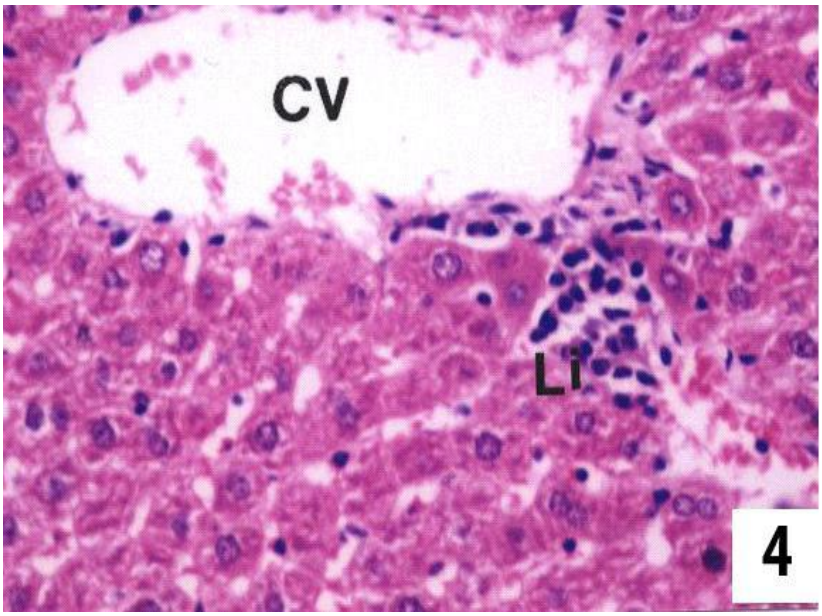

Figure 4. Specimen obtained from a rat treated with adriamycin for 2 weeks showing leucocytic infilteration (Li) and enlarged central vein (CV), (X 400).

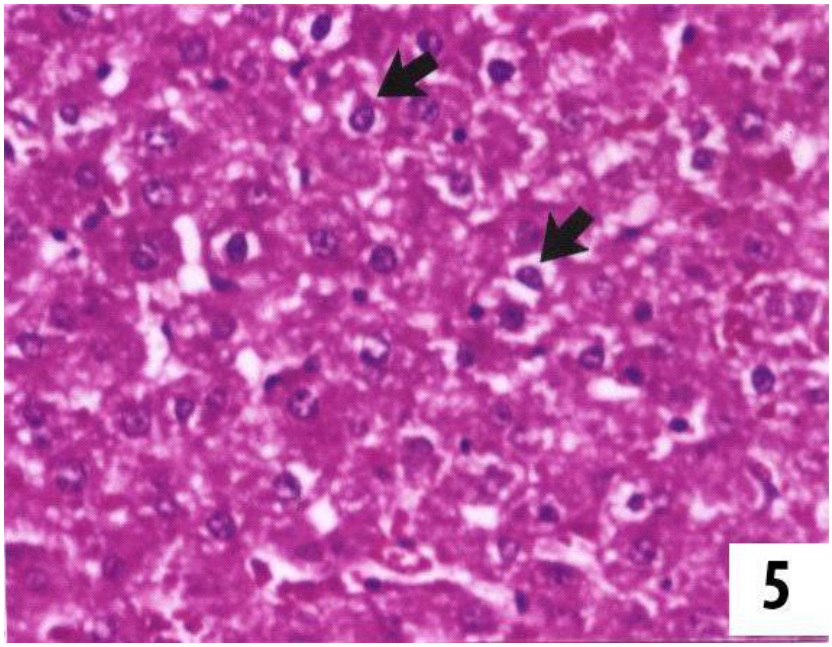

Figure 5. Specimen obtained from a rat treated with adriamycin for 4 weeks showing cytoplasmic vacuolization of the hepatocytes (arrows) with pyknotic nuclei, (X 400).

of animals treated with ADR and ginger showed that the liver tissue acquired improvement compared with adriamycin group. Slight congestion of blood vessels and few leucocytic infiltrations were recorded after 4 weeks of treatment. The repairing effects-up to certain limits were noticed after 6 weeks although few cells still appeared with cytoplasmic vacuolization and pyknotic nuclei (Figure 7). Figure 8 showed that there is reduction in inflammation and steatosis grade in liver of animals treated with ginger and ADR in comparison with those

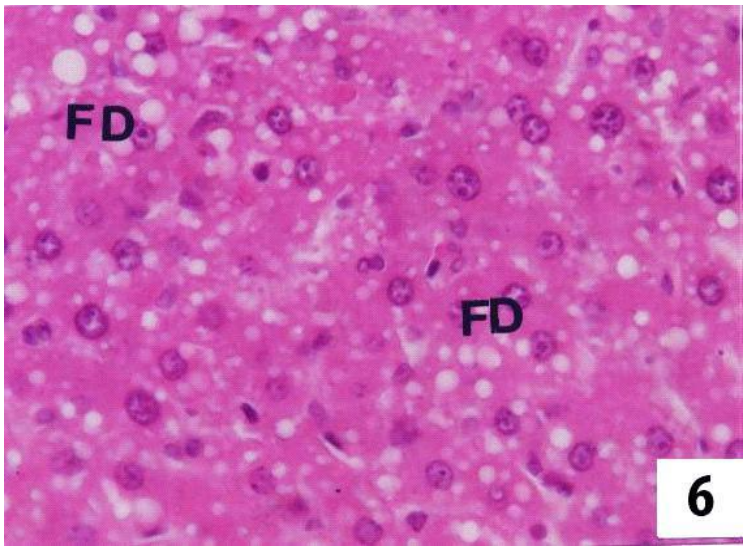

Figure 6. Section of liver of a rat treated with adriamycin for 6 weeks showing fat droplets of different sizes (FD), (X 400).

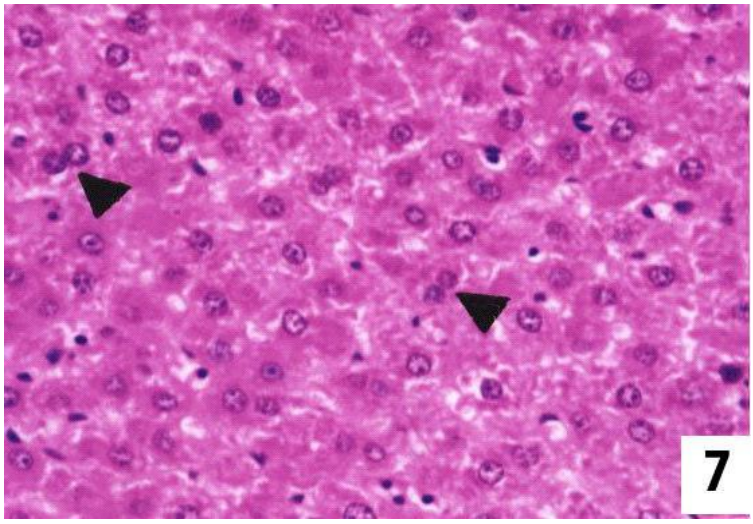

Figure 7. Liver section of a rat treated with adriamycin and ginger showing advanced degree of improvement with large number of binucleated cells (arrow heads) (X 400).

treated with ADR.

DISCUSSION

The present study indicated the adverse effect of adriamycin on hepatic tissue and its enzymatic activities. Adriamycin was found to affect serum transaminases (AST, ALT). Histopathological results showed that adriamycin induced many alterations. These are cytoplasmic vacuolization of the hepatocytes, remarkable abundance of leucocytic infiltrations, blood vessels congestion and fatty infiltrations. Similar observations were obtained by some investigators. Saad et al. (2001) reported that doxorubicin (Dox) has been shown to induce accumulation of inflammatory cells, associated with increased activities of tissue aminotransferases, LDH and ALP, indicating hepatic damage (Deepa and Varalakshmi, 2003). Gokcimen et al. (2007) reported that doxorubicin increased mononuclear cells infiltration, congestion of blood vessels and necrosis. El- Sayyad et al. (2009) detected inflammatory cells forming granulomatous lesions and periportal fibrosis in liver of rats after doxorubicin administration. Injac et al. (2008)

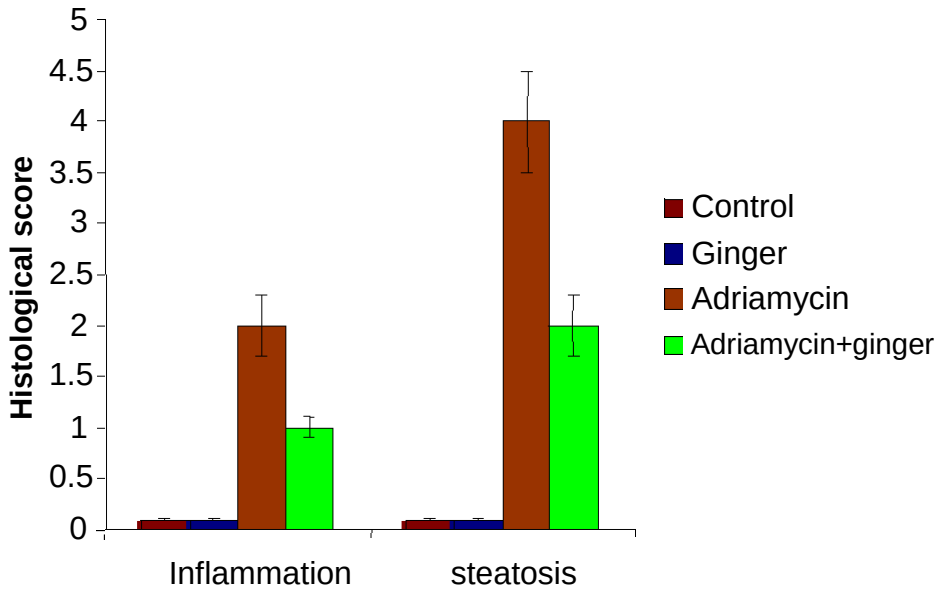

Figure 8. Histological scores of inflammation and steatosis in liver of experimental animals.

showed that treatment with doxorubicin caused significant changes in the serum levels of ALT, AST, LDH and alpha-hydroxybutyrate dehydrogenase (alpha-HBDH).

A high lipid peroxidation with a decrease in the antioxidant enzyme, SOD was recorded in liver of adriamycin-treated rats. There are several hypotheses to explain Dox-induced toxicity. Among them, the free radical hypothesis is the most thoroughly investigated (Lee et al., 1991). Dox undergoes one-electron reduction through a metabolic activation caused by NADPH-cytochrome P-450 reductase or other flavin-containing enzymes in microsomes (Bachur et al., 1978). This reduction generates Dox semiquinone free radicals. In the presence of molecular oxygen, the semiquinone rapidly reduces oxygen to superoxide, and the intact Dox remains. Superoxide spontaneously converts to hydrogen peroxide or is rapidly converted by superoxide dismutase. The effect of Dox on antioxidant enzymes was studied by many authors. Liesuy and Arnaiz (1990) reported that doxorubicin induced decreases in antioxidant enzyme levels and the mechanism of its toxicity would involve a reduction in antioxidant defenses. Kalender et al. (2005) studied the effect of doxorubicin on major enzymes participating in free radical metabolism. They found that Superoxide dismutase and catalase activity decreased while malondialdehyde levels increased in the doxorubicin-treated group compared to control.

The present results showed that treating rats with adriamycin and ginger improved the histopathological and biochemical changes induced in the liver by adriamycin. This indicated the effectiveness of ginger in prevention of adriamycin hepatotoxicity. The effect of ginger on hepatic damage was studied by some investigators. Yemitan and Izegbu (2006) tested the effect of the ethanol extract of the rhizome of *Z. officinale* against carbon tetrachloride and acetaminophen-induced liver toxicities in rats. CCl4 and acetaminophen induced many histopathological changes and increased the activities of ALT, AST, ALP, LDH and SDH in the blood serum. Ginger extract was found to have a protective effect on CCl4 and acetaminophen-induced damage as confirmed by histopathological examination of the liver. Bhandari et al. (1998) studied the effect of an ethanol extract of ginger on country-made liquor (CML)-induced liver injury in rats. Their results showed that administration of ginger ethanolic extract (200 mg/kg) orally from day 15 to 21 along with CML produced significant ($P< 0.01$) lowering of serum AST, ALT, ALP and tissue lipid peroxide levels.

Ginger treatment was found to exhibit hepatoprotective effect as recorded by enhanced activity of the antioxidant enzyme, SOD, and diminished amount of lipid peroxidation against the adriamycin-induced hepatotoxicity in rats. Many studies showed that ginger was scavenging free radical by its potent antioxidant. Siddaraju and Dharmesh (2007) reported that ginger-free phenolic and ginger hydrolysed phenolic fractions exhibited free radical scavenging, inhibition of lipid peroxidation, DNA protection and reducing power abilities indicating strong antioxidant properties. Ansari et al. (2006) showed that the ethanolic *Z. officinale* extract pretreatment for 20 days in isoproternol treated rats induced oxidative myocardial necrosis in rats, enhances the antioxidant defense (catalase, superoxide dismutase and tissue glutathione) and exhibites cardioprotection property. Ajith et al. (2007) reported that ginger ameliorated cisplatin- induced nerphrotoxicity and this

protection is mediated either by preventing the cispaltin-induced decline of renal antioxidant defense system or by their direct free radical scavenging activity. Amin and Hamza (2006) demonstrated that *Z. officinal* increased the activities of testicular antioxidant enzymes, superoxide dismutase, glutathione and catalase and reduced level of malondialdhyde. Sakr (2007) found that mancozeb fungicide induced a significant decrease in the serum antioxidant superoxide dismutase and an increase in malondialdehyde which is lipid peroxidation marker in albino rats.

The results of the present work indicated that ginger (*Z. officinale*) has protective effect against hepatoxicity induced by adriamycin and this is mediated by its antioxidant activities.

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