

EVALUATION OF DOXORUBICIN TOXICITY; DOES FERULIC ACID HAVE A POSSIBLE PROTECTIVE EFFECT LIKE GINKGO BILOBA ?

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ABSTRACT

Doxorubicin (Dox) is an anthracycline antibiotic agent used in the treatment of solid and haematopoietic tumours, but its use is limited by its diverse toxicities. The objective of this study was to investigate the role of ferulic acid (FA), a natural antioxidant agent, and Ginkgo Biloba (GB) extract, a cytoprotective herb-derived agent, in protection against Doxorubicin-induced toxicity. Fourty albino rats weighing between 150 and 200gm were used in this study. Animals were equally divided into four groups; Group I (control group) was given 1ml/kg saline. Group II was given 2.5 mg/kg Dox intraperitoneal three times weekly for two weeks. Group III was given an GB orally in a dose of 100mg/kg/d one week before giving Dox then with Dox for two weeks; GB daily and intraperitoneal injection of 2.5mg/kg Dox three times weekly after GB by 1 hour. Group IV was given FA in a dose of 110 mg/kg/d orally for one week then with Dox for two weeks; FA daily and intraperitoneal injection of 2.5mg/kg Dox three times weekly after FA by 1 hour. Animals were sacrificed 48 hours following the last Dox dose by cervical dislocation. Intra cardiac blood sample was taken for biochemical assays of serum creatinine, serum lactate dehydrogenase, creatine phosphokinase, AST and ALT were done. Half of kidneys, heart and liver were removed for the remaining half of tissues were used to estimate levels of MDA, GSH, SOD and histological analysis catalase. The results showed that MDA was increased in all tissues and serum in Dox group; while histopathological examination, SOD and catalase activities were decreased. Overall, there was evident significant improvement of biochemical markers of Dox toxicity and decreasing the toxic histopathological effect of Dox in both GB-treated and FA treated groups especially liver and heart in GB group and kidney in FA group. The results of this study could clarify the role of a natural ultimate solution (FA) in addition to the common popular herbal drug GB in prevention of serious Dox treatment toxicity.

INTRODUCTION

Doxorubicin is one of the most effective chemotherapeutic agents for the treatment of various types of cancer. Clinical

use of this drug is, however, greatly limited by its serious adverse cardiac effects that may ultimately lead to cardiomyopathy and heart failure. Since cellular apoptosis is at least partially responsible for the

pathogenesis of doxorubicin cardiac toxicity, *in vitro* and *in vivo* studies have been conducted employing anti-apoptotic remedies to manage this devastating complication (Tsun-Jui et al., 2008).

The exact causal mechanisms of Dox induced toxicity remain unclear and various mechanisms have been proposed to interpret the toxicity, including direct interaction with the actin-myosin contractile system, anthracycline metabolite hypothesis, alterations in platelet activating factor, prostaglandin and intracellular calcium. Most of the evidences indicate that free radicals are involved (Oliveira et al., 2004; Kalender et al., 2005 ; Wang et al., 2009).

Ginkgo Biloba (GB) is one of the oldest herbal medicines that have been used as a therapeutic agent in modern pharmacology. Several constituents of Ginkgo Biloba are biologically active such as flavonoids, terpenoids and iron-superoxide dismutase (Fe-SOD) that are likely to be responsible for the wide-ranging therapeutic benefit of the plant. The antioxidant properties of GB have been examined as a potential mechanism for its beneficial action. GB extracts were shown to be potent scavengers of free radicals. By scavenging free radicals and ROS, GB inhibits lipid peroxidation and augments levels of endogenous antioxidants. They show protective effects against free radical-mediated damage in biological systems, including ischemia-

reperfusion injury of the brain, heart and retina (Ashraf et al., 2010). Utilization of the leaves of this plant as an herbal medicine for treating a variety of diseases can be traced back to thousands of years in ancient China. The leaves of Ginkgo Biloba containing ginkgo-flavone glycosides which can scavenge superoxide, hydroxyl radicals and nitric oxide (NO) and protect myocardia from ischemia reperfusion injury (Shen et al., 2011).

Ferulic acid is a hydroxycinnamic acid, a type of organic compound. It is an abundant phenolic phyto-chemical found in plant cell wall components such as arabinoxylans as covalent side chains. It is found in seeds of plants such as rice, wheat, oats, as well as coffee, apple, artichoke, peanut, orange and pineapple. It can be extracted from wheat bran and maize bran using concentrated alkali. Like many phenols, it is an antioxidant *in vitro* in the sense that it is reactive toward free radicals, quenching lipid peroxidative chains (Fereidoon and Marian, 2004; Yogeeta et al., 2006; Barone et al., 2009).

The aim of study is to evaluate the efficacy of Ferulic acid and Ginkgo Biloba in counteracting doxorubicin toxicity.

MATERIAL & METHODS

Drugs and Chemicals:

Doxorubicin : It was purchased as

Adricin vial [50mg/ml doxorubicin hydrochloride, EMC, United Pharmaceuticals, Cairo, ARE. (EUP)].

Ginkgo Biloba (GB): Was purchased as Ginkgolide powder [Fluka (st. louis, USA)]. It was dissolved in distilled water and administered to the animals via gastric gavage.

Ferulic acid: was purchased as Sodium Ferrulate powder from Sigma-Aldrich Chemical Co. (St. Louis, USA). It was dissolved in distilled water and administered to the animals via gastric gavage.

Serum CK was determined using CK NAK liquid-UV kit, Human, Germany.

Serum LDH was determined using a commercial kit purchased from Human Diagnostics, Wiesbaden, Germany.

Creatinine, MDA, GSH contents, SOD and CAT were determined using commercial diagnostic kits purchased from Biodiagnostic Company(Cairo, Egypt).

Animals : Fourty albino rats (males) weighing between 150 and 250gm were used in this study. The rats were obtained from the animal unit of the Medical Experimental Research Centre of Faculty of Medicine, Mansoura University. They were kept under standard conditions of temperature ($25 \pm 5^{\circ}\text{C}$) and with a 12 h light : 12 h

dark schedule. Prior approval of the Institutional Research Ethics Committee was taken. The animal experiments described below comply with the ethical principles and guidelines for the care and use of laboratory animals adopted by the Research Ethics Committee of the Faculty.

Methods: Animals were equally divided into four groups; ten rats in each group.

Group I : (control group): it was given 1ml/kg saline.

Group II : it was given 2.5 mg/kg Doxorubicin intraperitoneal three times weekly for two weeks (cumulative dose 15mg/kg) (Yalçin et al., 2010).

Group III: it was given Ginkgo Biloba alone in an oral dose of 100mg/kg/d (Abd-Ellah and Mariee, 2007) one week before giving doxorubicin then with doxorubicin for two weeks; GB daily and intraperitoneal injection of 2.5mg/kg doxorubicin three times weekly after it by 1 hour.

Group IV: it was given FA in a dose of 110 mg/kg/d (Zhao et al., 2004) orally for one week then with doxorubicin for two weeks; FA daily and intraperitoneal injection of 2.5mg/kg doxorubicin three times weekly after it by 1 hour.

Animals were sacrificed 48 hours following the last Doxorubicin dose by cervical dislocation. Intra-cardial blood sample was taken at the time of sacrifice. Blood samples were centrifuged at 2000 rpm for 5 minutes at 4°C and the sera were frozen at -40°C until analyzed for levels of creatinine, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), ALT (alanine transaminase) and AST (aspartate transaminase).

Heart, liver and Kidneys were removed immediately, washed in ice-cold physiological saline then each organ was sectioned; half of it was fixed in 10% formalin for histopathological examination and the remaining was homogenized separately in 10% phosphate-buffered saline at 4°C. Homogenates were centrifuged at 10,000 rpm for 30 min. and the supernatants were collected for determination of the levels of Malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (Palanisamy et al., 2012).

The tissues were fixed in 10 % formalin for 24 h, processed routinely, Four micrometer-thick paraffin sections were stained with hematoxylin and eosin for light microscope examination. Two slides from each rat were examined and assigned for severity of changes by an observer blinded to the treatments. The changes of the kidney, heart and liver tis-

ues on the light microscopy were graded according to (Cecen et al., 2011) as follows: normal (0); mild (1+); moderate (2+); severe (3+). Thus, a 1+ lesion represented an involvement of less than 25% of the tissues, 2+ lesion represented an involvement of 25% to 50% of the tissues while 3+ lesion indicated that more than 50% of the tissues are involved.

Determination of serum LDH and CPK:

LDH and CPK levels were assayed based on the method of Buhl and Jackson (1978) and Gruber (1978) respectively. LDH and CPK were calculated as units per litre.

Determination of myocardial MDA content :

MDA, a reactive aldehyde used to measure the lipid peroxidation, was determined according to the method of Draper and Hadley (1990). MDA content was expressed as nanomoles per mg.

Determination of myocardial GSH content:

GSH was determined according to the method described by Beulter et al., (1963). GSH content was expressed as nanomoles per mg.

Determination of myocardial SOD activity:

SOD activity was assessed according to

the method of Nishikimi et al., (1972). It was expressed as unit per mg.

Determination of catalase level : It was assessed according to the method of Aebi, (1984). It was expressed as unit per ml.

Determination of ALT (alanine transaminase) and AST (aspartate transaminase) : They were analyzed according to the method of Reitman & Frankel (1957). they was expressed as unit per litre.

Determination of Creatinine : It was assessed according to the method of Seeling and Wust (1969). It was expressed as mg/dl.

Statistical Analysis :

Means and standard deviations were calculated from the ten replicates per each group. One way ANOVA test with Scheffe's posthoc test were performed. P is considered significant if <0.05 .

RESULTS

Effects of Ginkgo Biloba and Ferulic acid on serum ALT, AST, creatinine, CPK and LDH:

Compared to control group, serum ALT, AST, creatinine CPK and LDH were significantly high in doxorubicin group ($p<0.05$). The increment of these parameters was significantly attenuated in both

GB-treated and FA treated group ($p<0.05$) (table 1). However, there were no statistical significant differences between GB-treated and FA treated groups.

Effects of Ginkgo Biloba and Ferulic acid on markers of oxidative stress; Malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD) and catalase:

Table (2) shows results of oxidants and antioxidants in liver, kidney, heart and serum. Compared to control group, MDA was significantly high in Dox group in liver, kidney, heart, and serum ($p<0.05$). This increase in MDA was significantly attenuated in GB-treated group and FA-treated group ($p<0.05$). Also, compared to control group, GSH was significantly decreased in serum and tissues in Dox group ($p<0.05$), and this decrease was significantly increased in ginkgo-treated and FA-treated groups ($p<0.05$) except in liver of GB-treated group which was non-significant ($P>0.05$).

Compared to control group, SOD activity was significantly decreased in Dox group in all tissues and serum except the heart which showed non-significant decrease. This decrease was significantly increased in FA-treated group in serum and liver only ($p \leq 0.05$). Whereas, the change in SOD in GB-treated group was not significant in all tissues and serum compared to Dox group ($P>0.05$).

Lastly, compared to control group, catalase enzyme was significantly decreased in Dox in tissues and serum ($p \leq 0.05$). This decrease was significantly increased in both GB-treated group and FA-treated group compared to doxorubicin group ($p \leq 0.05$).

Histopathological examination:

In histopathological examination of the livers, normal architecture was observed in control group (Figure 1a) whereas hepatic lesion including severe cloudy swelling (Figure 1b), and focal necrosis (Figure 1c) were observed in the rat livers from Dox treated animals. Hepatic lesions were improved in animals, which received GB and FA prior to Dox-treatment; the FA+Dox group showed mild cloudy swelling and inflammation (Figure 1d) in 60% of rats, whereas the hepatic sections in the GB + Dox group were apparently normal (Figure 1e), (Table 3).

As regards histopathological examination of the kidneys, normal architecture was observed in control group (Figure 2a) whereas renal lesions including moderate tubular degeneration and mild mesangial proliferation were observed (figure 2b) in the kidney of Dox treated animals. Renal lesions were improved in rats, which received GB and FA prior to Dox-treatment; the GB + Dox group shows mild tubular degeneration (Figure 2c) in 90% of rats whereas the renal sections in

the FA + Dox group were apparently normal in 70% of rats (Figure 2d), (Table 3).

In histopathological examination of the hearts, control group showed regular cell distribution and normal myocardium architecture (Figure 3a). The rat hearts from Dox treated animals revealed severe interstitial edema and congestion (Figure 3b). Cardiac lesions were improved in rats which received GB and FA prior to Dox-treatment; the FA + Dox group showed mild edema and congestion (Figure 3c) in 80% of rats whereas the cardiac sections in the GB + Dox group were apparently normal (Figure 3d) (Table 3).

DISCUSSION

Adriamycin (doxorubicin hydrochloride), an antitumor antibiotic, has been established as an effective agent against a wide range of malignant conditions. However, different organs toxicity compromises the clinical usefulness of the drug. Nevertheless, to date, no single chemical has proven to be able to reduce the deleterious action of doxorubicin. Therefore, the search for an effective and safe antagonist of doxorubicin toxicity remains a critical issue in fields of clinical toxicology and oncology (Tsun et al., 2008).

Ginkgo Biloba is one of the oldest plants in the world (Gertz and Kiefer,

2004). Ferulic acid (FA) is a polyphenol very abundant in vegetables and maize bran. It has been approved in certain countries as food additive to prevent lipid peroxidation (Sreenivasan et al., 2007). It induces a robust cell stress response through the up-regulation of cytoprotective enzymes (Barone et al., 2009).

The present study, exploring the possible counteracting effect of ferulic acid and an herbal Ginkgo Biloba extract against doxorubicin toxicity *in vivo*.

The results of the present study indicate that Dox injection induced elevation of serum LDH and CK levels. These enzymes are mostly considered as important markers of early and late cardiac injury especially during clinical follow-up of doxorubicin therapy. This finding is in agreement with that of Vijay et al. (2011); Ragavendran et al., (2012) and Saratchandran et al., (2012) who demonstrated similar elevation in cardiac enzymes activities. The increase in serum CK-MB and LDH activities following Dox injection could be attributed to Dox-induced oxidative stress and lipid peroxidation in the heart. Lipid peroxidation affects membrane permeability and leads to CK-MB and LDH release into serum (Zhang et al., 2005).

Administration of FA or GB significantly protected from Dox-induced elevat-

ed levels of LDH and CK. The levels of serum ALT and AST were also elevated in Dox treated animals and administration of FA or GB significantly attenuated the levels of these enzymes when compared to Dox alone treated animals. This protective effect might be due to stabilization of hepatocyte membranes with the consequent decrease in the leakage of liver enzymes.

Histopathological results revealed affection of kidneys, liver and heart in Dox group in different degrees. One of the most prevailing hypotheses of organs damage resulting from Dox administration is the ability of the drug to produce free radicals and reduce the antioxidant defense mechanism. Free radicals are known to damage several macromolecular and cellular components (Lai et al., 2007; Hossein et al., 2010).

These findings can be also explained by mitochondrial apoptosis pathways induction by the classic cytotoxic chemotherapeutic agents, including anthracyclines (Elliott, 2006).

There was an improvement of pathological effects of Dox in both ginkgo Biloba and ferulic acid group. This confirms the results of Saratchandran and Cherupally (2012) who deduced that FA greatly inhibited the Dox induced changes in cardiac tissue supporting the protective

action of FA against Dox induced cardiotoxicity.

The heart and liver pathology was improved completely and became apparently normal in Ginkgo Biloba treated group. This may be attributed to the protective effect of GB against the oxidative and apoptotic actions of doxorubicin (Yeh et al., 2009).

Another explanation is that Ginkgo Biloba leaves extract may act through several mechanisms including antioxidant effects, inhibition of platelet activating factor, alterations in membrane fluidity (signal transduction), and inhibition of glucocorticoid synthesis. The purported beneficial effects of GB leave extract might be channeled through combination of one or more of the basic mechanisms of action. Its flavonoids components are believed to act in protecting against capillary fragility, as antioxidants, as anti-inflammatory agents, in reducing edema caused by tissue injury, and as free radical scavengers (Chan et al., 2007).

These results could be in accord with several other researches, who reported that, compounds with antioxidant properties like gammaglutamylcysteine ethyl ester and resveratrol could ameliorate Dox-induced cardiotoxicity (Aluise, et al., 2009; Tatlidede et al., 2009).

As regards the kidney pathology, there was more improvement in Ferulic acid treated group. In a previous study by Zhao et al., (2004) elucidated that FA had some protective effect on kidneys of diabetic rats. Dietary FA was previously found to be protective against CCl₄-induced toxicity in rat kidney and this effect was associated with increase in glutathione peroxidase and superoxide dismutase levels (Srinivasan et al., 2005). This result can be explained by another hypothesis in the study of Bradley et al., (2011) who observed 16% increase in Glutathione -S- transferase specific activity in rats kidney tissues compared to the control and induction of kidney Quinone reductase - a marker for phase II enzyme expression-specific activity to 1.26 - fold that of the control by diet containing 1% FA.

Concerning the antioxidant status, results of the present study showed that MDA level was increased in all tissues and serum in Dox group consistent with the results of El-Shitany et al., (2008) and El-Sayed et al., (2011). This increase is a direct indicator for enhanced oxidative stress. On the other hand, GSH, SOD and catalase activity were decreased. This supports the findings of Hossein et al., (2010) who explained that Dox-induced oxidative stress in tissues by the alterations observed in antioxidant defense systems which is both enzymatic and non-enzymatic. In their study, Dox reduced

significantly the GSH content, besides it notably lowered the enzymatic activities of SOD and Glutathione-S-transferase associated with marked increase in lipid peroxidation as manifested by increased malondialdehyde levels in rat liver.

Regarding SOD, Dox caused a significant decrease in its activity in liver, kidney and serum. Ahmed et al., (2005) attributed his similar finding to Dox-induced free radical production in tissues accompanied by exhaustion of the antioxidant enzyme, SOD, which is responsible for scavenging the liberated, toxic free radicals.

These results are also in harmony with previous studies by Yoneko et al., (2007); Ayla et al., (2011) and Nahla, (2012) who attributed these findings to tissue damage and cell membrane destruction by free radicals resulted from Dox administration.

Results of the present study showed that there was an amelioration of biochemical oxidative stress markers induced by doxorubicin in rats which well correlated with the alleviation in the histopathological changes; a significant decrease in MDA and increase in GSH levels in both GB and FA groups. This agrees with Erdogan et al.

(2006) who reported that GB can prevent bleomycin (an anti-neoplastic) induced oxidative stress via high anti-oxidant enzyme activity together with decreased radical production. However in another different study of FA effects on age-related changes, Jung et al., (2009) found that dietary FA increased GSH in renal tissue of rats.

In our study, FA significantly attenuated SOD activity decrease in liver and serum and catalase in serum and all tissues. This agrees with Saratchandran and Cherupally (2012) who proved the efficacy of FA in improvement of enzymatic and oxidative damage extent.

The current study results proved the efficacy of FA as GB in decreasing Dox oxidative organ damage which was revealed by both biochemical and histopathological parameters.

In conclusion, the results of the present study provide adequate evidence that FA may be a promising natural adjuvant therapy, potentially ameliorating Dox toxicity in clinical practice. Overall, FA can be considered a good candidate for offering protection against the deleterious toxicity of Dox.

Table (1): Effects of Ginkgo biloba and Ferulic acid treatments on serum ALT, AST, creatinine, LDH and CPK.

	Control mean \pmSD	Dox mean \pmSD	Dox+ Gb mean \pmSD	Dox + FA mean \pmSD
ALT(alanine transaminase) (U/L)	24.3 \pm 3.2	61.02 \pm 11.9*	33.2 \pm 9.9 ^s	30.1 \pm 7.5 ^s
AST(aspartate transaminase (U/L)	66.0 \pm 17.3	150.0 \pm 33*	70.8 \pm 9.5 ^s	63.9 \pm 16.1 ^s
Creatinine (mg/dl)	0.44 \pm 0.11	3.9 \pm 0.09*	0.50 \pm 0.02 ^s	0.7 \pm 0.05 ^s
Lactic dehydrogenase (LDH) (U/L)	145.0 \pm 0.19	400.0 \pm 96.2*	120.0 \pm 23 ^s	123.0 \pm 20.8 ^s
Creatine phosphokinase (CPK) (U/L)	86.0 \pm 10.51	300.0 \pm 33.1*	101.0 \pm 21.9 ^s	95.0 \pm 30.2 ^s

*= significant relative to control (p<0.05), ^s= significant relative to Dox (p<0.05). One way ANOVA test with Tukey posthoc test. Dox = doxorubicin.

Table (2): Effects of Ginkgo Biloba and Ferulic acid treatments on the concentrations of MDA , GSH, SOD, and catalase in serum and tissues (liver, kidney, and heart).

		Control mean \pmSD	Dox mean \pmSD	Dox+ GB mean \pmSD	Dox + FA mean \pmSD
MDA nmol/mg	Liver	2.44 \pm 0.67	4.55 \pm 0.79*	3.27 \pm 1.18 ^s	3.01 \pm 0.45 ^s
	Kidney	1.72 \pm 0.52	3.00 \pm 0.30*	2.26 \pm 0.45 ^s	1.91 \pm 0.19 ^s
	Heart	1.68 \pm 0.59	3.51 \pm 0.45*	2.53 \pm 0.25 ^s	2.41 \pm 0.27 ^s
	Serum	3.76 \pm 0.31	5.57 \pm 0.73*	4.13 \pm 0.29 ^s	3.67 \pm 0.58 ^s
GSH nmol/mg	Liver	5.46 \pm 1.55	2.87 \pm 0.66*	3.55 \pm 0.81	4.30 \pm 0.86 ^s
	Kidney	3.49 \pm 0.26	1.88 \pm 0.22*	3.34 \pm 0.34 ^s	4.38 \pm 0.36 ^s
	Heart	4.29 \pm 0.56	1.96 \pm 0.11*	3.93 \pm 0.72 ^s	3.58 \pm 0.67 ^s
	Serum	3.19 \pm 0.18	1.27 \pm 0.17*	1.88 \pm 0.37 ^s	2.68 \pm 0.17 ^s
SOD(U/mg protein)	Liver	31.14 \pm 6.57	20.30 \pm 3.59*	23.94 \pm 3.03	27.19 \pm 5.88 ^s
	Kidney	24.96 \pm 6.61	18.93 \pm 2.37*	21.58 \pm 4.13	22.38 \pm 2.44
	Heart	26.44 \pm 8.14	18.69 \pm 3.42	26.44 \pm 5.83	27.31 \pm 9.90
	Serum	20.19 \pm 5.75	13.85 \pm 3.54*	15.17 \pm 3.34	19.28 \pm 2.82 ^s
Catalase (U/ml)	Liver	156.04 \pm 15.90	117.16 \pm 15.70*	152.79 \pm 15.86 ^s	153.64 \pm 11.53 ^s
	Kidney	137.75 \pm 11.87	111.36 \pm 14.90*	126.19 \pm 11.33 ^s	125.86 \pm 9.48 ^s
	Heart	121.30 \pm 10.70	101.13 \pm 14.88*	148.17 \pm 15.33 ^s	141.29 \pm 10.20 ^s
	Serum	150.33 \pm 9.30	126.08 \pm 9.55*	149.17 \pm 9.82 ^s	148.88 \pm 15.33 ^s

*= significant relative to control (p<0.05), ^s= significant relative to control (p<0.05). One way ANOVA test with Tukey's posthoc test. MDA= malondialdehyde, GSH= reduced glutathione, SOD = superoxide dismutase. Dox = doxorubicin.

Table (3): Histopathological scoring of organs toxicity in different groups.

Organs toxicity \ Groups	Dox		Dox + Gb		Dox + FA	
	No.	%	No.	%	No.	%
Hepatotoxicity						
Grade 0	0	0%	10	100%	4	40%
Grade 1(mild)	0	0%	0	0%	6	60%
Grade 2 (moderate)	0	0%	0	0%	0	0%
Grade 3(severe)	10	100%	0	0%	0	0%
Renal toxicity						
Grade 0	0	0%	1	10%	7	70%
Grade 1(mild)	0	0%	9	90%	3	30%
Grade 2 (moderate)	10	100%	0	0%	0	0%
Grade 3(severe)	0	0%	0	0%	0	0%
Cardiotoxicity						
Grade 0	0	0%	10	100%	2	20%
Grade 1(mild)	0	0%	0	0%	8	80%
Grade 2 (moderate)	0	0%	0	0%	0	0%
Grade 3(severe)	10	100%	0	0%	0	0%

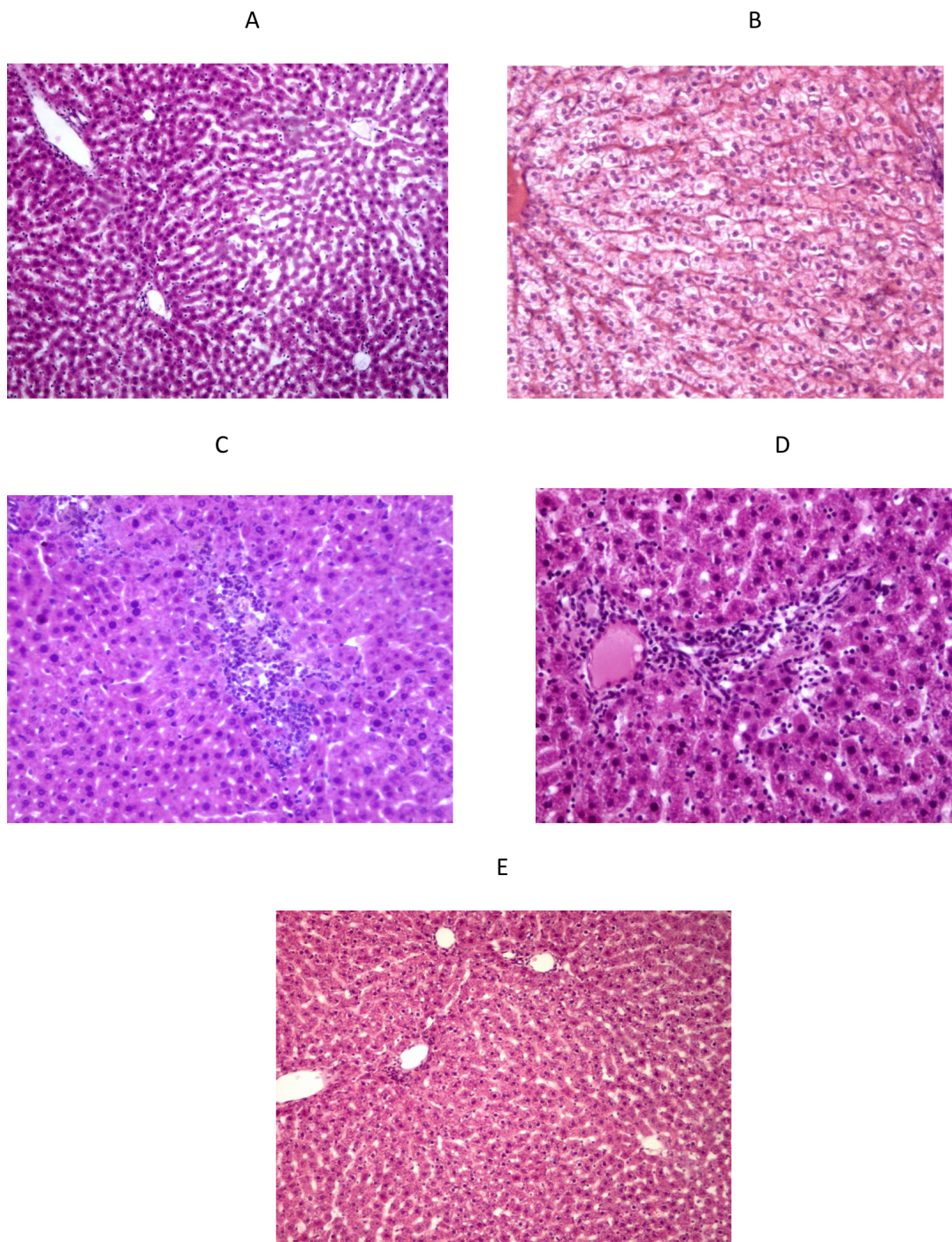


Figure (1) : Photomicrographs of rat livers showing: A; Control rat has normal liver morphology (H&Ex100). B, C; Rat´ liver treated with Dox showing: B; moderate cloudy swelling, C; focal necrosis (H&Ex200). D; Treated with FA+ Dox showing mild cloudy swelling and inflammation (H&Ex200). E; Treated with Gb + Dox showing nearly normal morphology (H&Ex100).

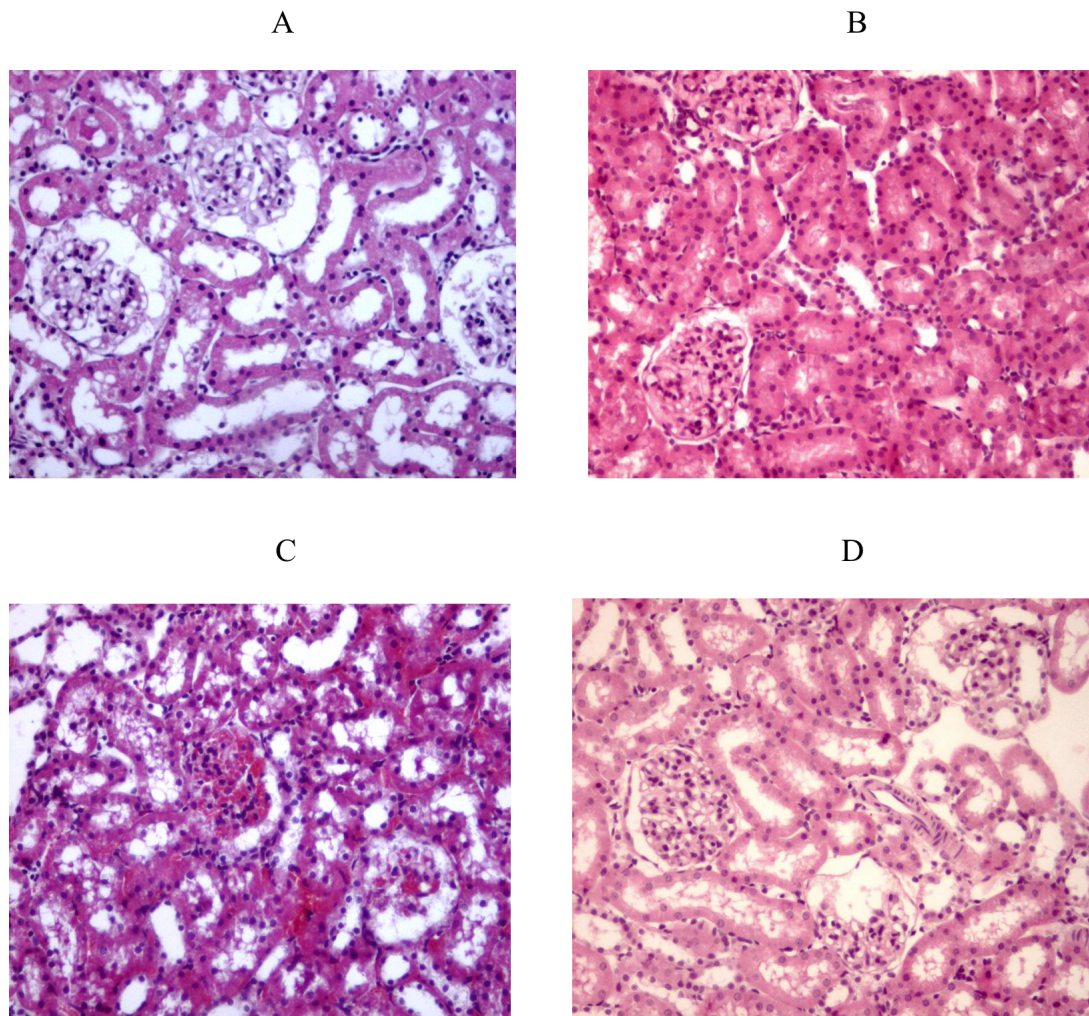


Figure (2) : Photomicrographs of rat kidney showing : A: Control rat has normal kidney morphology (H & E x 200). B: Rat´ kidney treated with Dox, showing moderate tubular degeneration and mild mesangial proliferation (H & E x 200). C: Rat´ kidney treated with Gb + Dox showing mild tubular degeneration (H & E x 200). D; Rat´ kidney treated with FA + Dox showing nearly normal morphology (H & E x 200).

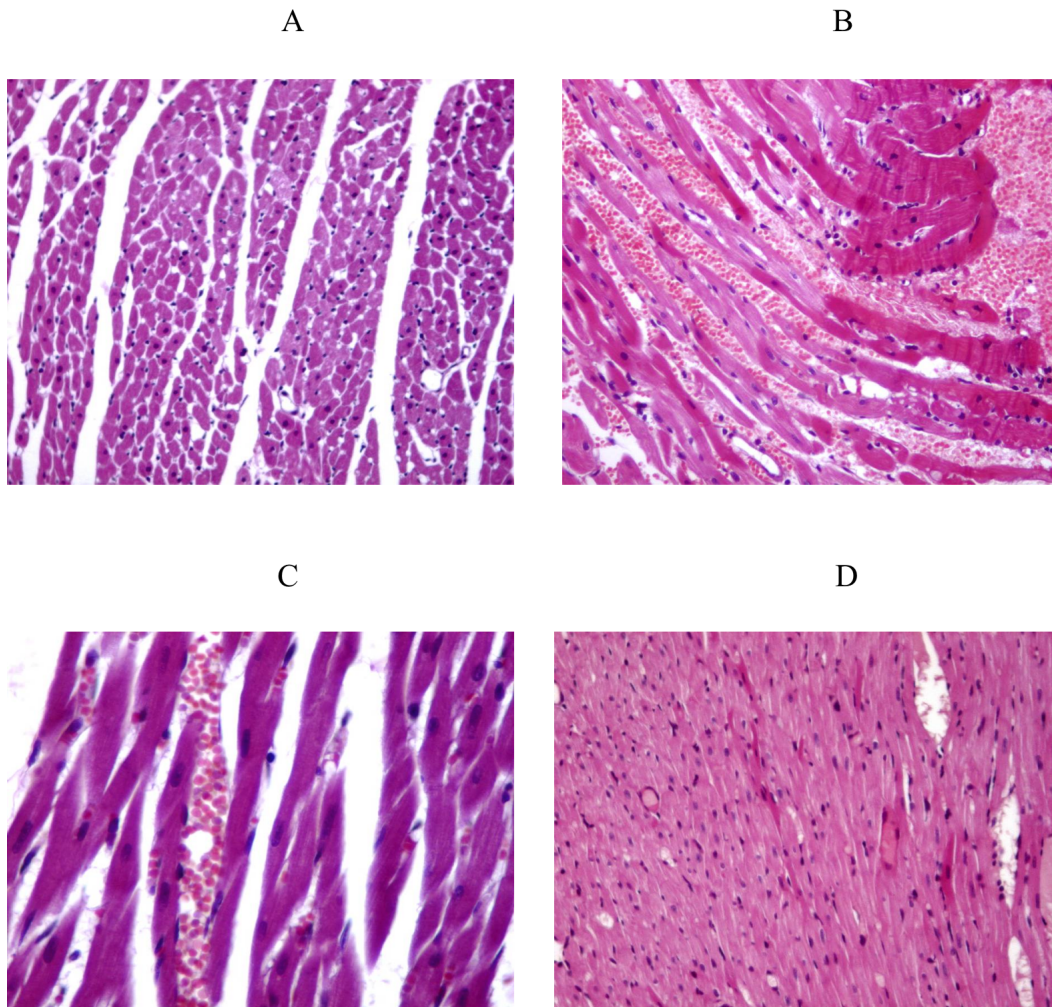


Figure (3) : Photomicrographs of rat hearts showing: A: Control rat has normal heart morphology (H & E × 100). B: Rat heart treated with doxorubicin showing: severe congestion (H & E × 200), C: Rat heart treated with FA+ Dox showing mild edema and congestion (H & E × 200). D; Rat heart treated with Gb + Dox showing nearly normal morphology (H & E × 100).

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تقييم سمية عقار الدوكسوروبيسين ؛ هل هناك تأثير وقائي لحمض الفريولييك مثل الجينكوبيلوبا ؟

المشتركون في البحث

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من أقسام الطب الشرعى والسموم الإكلينيكية، علم الأدوية*، الفسيولوجيا الطبية**، والباثولوجيا***

يعتبر عقارالدوكسوروبيسين من الأنثراسيكلين المضادات الحيوية التي تستخدم فى علاج الأورام الصلبة وأورام الدم، ولكن يحد من استخدامه السمية المتعددة له. تلعب الأكسدة دورا هاما في السمية الناتجة عن عقار الدوكسوروبيسين: الهدف من هذه الدراسة هو التحقق في دور حمض الفريولييك ، مضاد الأكسدة الطبيعي، ومستخلص الجينكوبيلوبا ، فى الحماية ضد السمية الناجمة عن الدوكسوروبيسين . استخدمت عدد ٤٠ من ذكور الجرذان البيضاء يتراوح وزنها بين ١٥٠ و ٢٠٠ جم في هذه الدراسة. تم تقسيم الحيوانات بالتساوى إلى أربع مجموعات : المجموعة الأولى (المجموعة الضابطة): أعطيت ١ مللي/كجم محلول ملحي. المجموعة الثانية: أعطيت ٢,٥ ملليجم / كجم من عقارالدوكسوروبيسين داخل الصفاق ثلاث مرات أسبوعيا لمدة أسبوعين (جرعة تراكمية ١٥ ملليجم/كجم). المجموعة الثالثة: أعطيت جينكوبيلوبا ١٠٠ ملليجم/كجم/يوميا عن طريق الفم لمدة أسبوع واحد قبل إعطاء الدوكسوروبيسين ثم مع الدوكسوروبيسين لمدة أسبوعين (٢,٥ ملليجم/كجم من الدوكسوروبيسين ثلاث مرات أسبوعيا عن طريق الحقن داخل الصفاق بعد الجينكوبيلوبا بساعة). المجموعة الرابعة: أعطيت حمض الفريولييك وحده في جرعة من ١١٠ ملليجم / كجم / يوميا عن طريق الفم لمدة أسبوع وأعطى بعد ذلك مع الدوكسوروبيسين لمدة أسبوعين (٢,٥ ملليجم /كجم الدوكسوروبيسين ثلاث مرات أسبوعيا عن طريق الحقن داخل الصفاق بعد حمض الفريولييك بساعة). ثم تم ذبح الجرذان بعد ٤٨ ساعة من جرعة الدوكسوروبيسين الأخيرة. وقد تم أخذ عينة دم من القلب لتحليل كل من لمصل الكرياتينين، لاكتات الدهيدروجيناز، الكرياتين فسفوكيناز ، وأنزيمات الكبد. وتم إزالة نصف القلب والكلى والكبد للفحص الهستوباثولوجى للأنسجة. وتم إستخلاص النصف المتبقي من الأنسجة لقياس مستويات المالوندايالدهيد، الجلوتاثيون، والكاتالاز، السوبرأوكسيد دسميوتاز. وأظهرت النتائج زيادة المالوندايالدهيد في جميع الأنسجة والدم في مجموعة الدوكسوروبيسين ، ومن ناحية أخرى، لوحظ انخفاض الجلوتاثيون ، ونشاط الكاتالاز، والسوبرأوكسيد دسميوتاز. وعموما، كان هناك تحسن ملحوظ ذو دلالة إكلينيكية في التحاليل الكيميائية، وتقليل تأثير عقار الدوكسوروبيسين علي الأنسجة في مجموعتي الجينكوبيلوبا وحمض الفريولييك المعالجة خاصة الكبد والقلب في مجموعة الجينكوبيلوبا ،والكلي في مجموعة حمض الفريولييك . ويمكن لنتائج هذه الدراسة توضيح دور حمض الفريولييك كعلاج بديلي طبيعي بالإضافة إلى الجينكوبيلوبا في الوقاية من السمية الخطيرة الناتجة عن العلاج بالدوكسوروبيسين.