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

BY

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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. Forty 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-cardial 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; Yogeeeta 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
Adriacin 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:** Forty 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 ± 5°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.
Eldakroory et al ...

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 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 tissues 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
**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 Gingko 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 ≤ 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<0.05). This decrease was significantly increased in both GB-treated group and FA-treated group compared to doxorubicin group (p<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,
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 elevated 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 cardio-

toxicity.

The heart and liver pathology was im-
proved completely and became apparent-
ly normal in Ginkgo Biloba treated group. This may be attributed to the protective ef-
fect of GB against the oxidative and apop-
totic actions of doxorubicin (Yeh et al.,
2009).

Another explanation is that Ginkgo Biloba leaves extract may act through several mechanisms including antiox-
didant effects, inhibition of platelet acti-
vating 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 pro-
tecting against capillary fragility, as anti-
oxidants, 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 proper-
ties 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 dia-
abetic rats. Dietary FA was previously found to be protective against CCl4-
induced toxicity in rat kidney and this ef-
flect was associated with increase in glu-
tathione peroxidase and superoxide dis-
mutase levels (Srinivasan etal., 2005). This result can be explained by another hypo-
thesis in the study of Bradley et al.,
(2011) who observed 16% increase in Glu-
tathione -S- transferase specific activity in rats kidney tissues compared to the con-
trol and induction of kidney Quinone re-
ductase - a marker for phase II enzyme ex-
pression-specific activity to 1.26 - fold that of the control by diet containing 1% FA.

Concerning the antioxidant status, re-
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 altera-
tions observed in antioxidant defense sys-
tems 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-transeferase 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.

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

* = significant relative to control (p<0.05). $^*$ = 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).

<table>
<thead>
<tr>
<th></th>
<th>Control mean ±SD</th>
<th>Dox mean ±SD</th>
<th>Dox+ GB mean ±SD</th>
<th>Dox + FA mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (nmol/mg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Liver</td>
<td>2.44 ± 0.67</td>
<td>4.55 ± 0.79*</td>
<td>3.27 ± 1.18</td>
<td>3.01 ± 0.45*</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.72 ± 0.52</td>
<td>3.00 ± 0.30*</td>
<td>2.26 ± 0.45*</td>
<td>1.91 ± 0.19*</td>
</tr>
<tr>
<td>Heart</td>
<td>1.68 ± 0.59</td>
<td>3.51 ± 0.45*</td>
<td>2.53 ± 0.25*</td>
<td>2.41 ± 0.27*</td>
</tr>
<tr>
<td>Serum</td>
<td>3.76 ± 0.31</td>
<td>5.57 ± 0.73*</td>
<td>4.13 ± 0.29*</td>
<td>3.67 ± 0.58*</td>
</tr>
<tr>
<td>GSH (nmol/mg)</td>
<td></td>
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<tr>
<td>Liver</td>
<td>5.46 ± 1.55</td>
<td>2.87 ± 0.66*</td>
<td>3.55 ± 0.81</td>
<td>4.30 ± 0.86*</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.49 ± 0.26</td>
<td>1.88 ± 0.22*</td>
<td>3.34 ± 0.34*</td>
<td>4.38 ± 0.36*</td>
</tr>
<tr>
<td>Heart</td>
<td>4.29 ± 0.56</td>
<td>1.96 ± 0.11*</td>
<td>3.93 ± 0.72*</td>
<td>5.58 ± 0.67*</td>
</tr>
<tr>
<td>Serum</td>
<td>3.19 ± 0.18</td>
<td>1.27 ± 0.17*</td>
<td>1.88 ± 0.37*</td>
<td>2.68 ± 0.17*</td>
</tr>
<tr>
<td>SOD (U/mg protein)</td>
<td></td>
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</tr>
<tr>
<td>Liver</td>
<td>31.14 ± 6.57</td>
<td>20.30 ± 3.59*</td>
<td>23.94 ± 3.03</td>
<td>27.19 ± 5.88*</td>
</tr>
<tr>
<td>Heart</td>
<td>26.44 ± 8.14</td>
<td>18.69 ± 3.42*</td>
<td>26.44 ± 5.83</td>
<td>27.31 ± 9.90</td>
</tr>
<tr>
<td>Serum</td>
<td>20.19 ± 5.75</td>
<td>13.85 ± 3.54*</td>
<td>15.17 ± 3.34</td>
<td>19.28 ± 2.82*</td>
</tr>
<tr>
<td>Catalase (U/ml)</td>
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<tr>
<td>Liver</td>
<td>156.04 ± 15.90</td>
<td>117.16 ±15.70*</td>
<td>152.79 ±15.86*</td>
<td>153.64 ±11.53*</td>
</tr>
<tr>
<td>Kidney</td>
<td>137.75 ± 11.87</td>
<td>111.36 ± 14.90*</td>
<td>126.19 ±11.33*</td>
<td>125.86 ± 9.48*</td>
</tr>
<tr>
<td>Heart</td>
<td>121.30 ± 10.70</td>
<td>101.13 ±14.88*</td>
<td>148.17 ±15.33*</td>
<td>141.29 ± 10.20*</td>
</tr>
<tr>
<td>Serum</td>
<td>150.33 ± 9.30</td>
<td>126.08 ± 9.55*</td>
<td>149.17 ± 9.82*</td>
<td>148.88 ± 15.33*</td>
</tr>
</tbody>
</table>

* = significant relative to control (p<0.05). $^*$ = 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.

<table>
<thead>
<tr>
<th>Organs toxicity</th>
<th>Groups</th>
<th>Dox</th>
<th></th>
<th>Dox + Gb</th>
<th></th>
<th>Dox + FA</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
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<tr>
<td><strong>Hepatotoxicity</strong></td>
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</tr>
<tr>
<td>Grade 0</td>
<td>Dox</td>
<td>0</td>
<td>0%</td>
<td>10</td>
<td>100%</td>
<td>4</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Dox + Gb</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>6</td>
<td>60%</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>Dox</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Dox + Gb</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>Dox</td>
<td>10</td>
<td>100%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>Dox + Gb</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
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<tr>
<td><strong>Renal toxicity</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>Dox</td>
<td>0</td>
<td>0%</td>
<td>1</td>
<td>10%</td>
<td>7</td>
<td>70%</td>
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Figure (1): Photomicrographs of rat livers showing: A; Control rat has normal liver morphology (H&Ex100). B, C; Rat’s 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 x 100). B: Rat heart treated with doxorubicin showing: severe congestion (H & E x 200), C: Rat heart treated with FA+ Dox showing mild edema and congestion (H & E x 200). D: Rat heart treated with Gb + Dox showing nearly normal morphology (H & E x 100).
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تقييم سمية عقار الدوكسوروبيسين ؛ هل هناك تأثير وقائي لحمض الفيرويليك مثل الجينكوبيلوبا ؟

المشكلون في البحث

أ.م.د. سهير عبد العزيز الدكروسي
أ.م.د. هالة العشوري
أ.م.د. عبد العزيز حسن

من أقسام الطب الشرعي والهيليكي، علم الأدوية، الفيسيولوجيا الطبية، والباثولوجيا

يعتبر عقار الدوكسوروبيسين من الأدوية التي تستخدم في علاج الأورام الخبيثة، ولكن بعد من استخدامها المستمر، لم يتمكن الدكروسي من البحث، في السرية المتعاونة، مع الدكتور الدكروسي. وعندما استخدم في دراسة علاج الفيرويليك، مع الدكتور الدكروسي، واستخدم الجينكوبيلوبا في مجموعة، كان هناك تأثير علاج الدوكسوروبيسين على النتائج. في مجموعتي الجينكوبيلوبا، مع الدكتور الدكروسي، وحمض الفيرويليك، علاج الفيرويليك، خاصة الكبد والقلب في مجموعة الجينكوبيلوبا، وحمض الفيرويليك، في علاج الدوكسوروبيسين.