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Effects of *Ficus carica* Leaf & Fruit Extracts on Cardiac Enzymes in Doxorubicin Induced Cardiotoxicity

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ABSTRACT

Introduction: Chemotherapeutic agents are associated with increased incidence of Cardiotoxicity. Many pharmacological and botanicals have been investigated to combat with this adverse effect. **Aims & Objectives:** We conducted a study to evaluate the protective effect of *Ficus carica* (Anjiir) leaf & fruit extract on elevated levels of cardiac enzymes due to Doxorubicin toxicity in rats. **Place and duration of study:** The study was conducted at PGMI, Shaikh Zayed Medical Complex, Lahore for period of 10 days. **Material & Methods:** 40 Albino rats were divided into 4 groups of 10 each. Group 1 was negative control. Groups 2 (positive control), 3 and 4 received intraperitoneal Doxorubicin 15mg/kg on day 1, following which groups 3 & 4 received oral 400mg/kg of *Ficus carica* leaf and fruit extract respectively. Blood was drawn after 10 days by cardiac puncture and serum was prepared for estimation of serum Lactate dehydrogenase (LDH) and Creatinine phosphokinase (CPK). **Results:** Administration of *Ficus carica* leaf and fruit extracts via oral route after the intraperitoneal injection of Doxorubicin produced significant decline in serum CPK and LDH levels with $p \leq 0.05$. **Conclusion:** *Ficus Carica* leaf and fruit extracts has shown to possess protective effect on cardiotoxicity of Doxorubicin by decreasing the elevated levels of cardiac enzymes.

Key words: Cardiotoxicity, Cardioprotective, *Ficus carica* leaf & fruit, Doxorubicin(Dox), Cardiac enzymes.

INTRODUCTION

Cardiotoxicity caused by chemotherapeutic drugs is the most concerned adverse effect of these agents[1,2]. Doxorubicin, an anthracyclin antibiotic is being extensively used since the late 1960's for a wide range of hematological malignancies, many types of carcinomas, and soft tissue sarcomas. It can be used as a single agent or in combination with other chemotherapeutic agents[3].

Cardiotoxicity is the major and most dangerous side effect of Doxorubicin, on which ample research work has been conducted since its discovery and use[4]. Estimates of the incidence of anthracyclin induced heart failure diagnosed within a year of treatment range from less than 5% to greater than 50% for cumulative doses of 550 to 1,000mg/m^2, respectively[5]. It has been found that cardiotoxicity can occur even after only four cycles of anthracyclin containing chemotherapy (240mg/m^2) [6].

Doxorubicin induced cardiotoxicity can present acutely in the form of transient arrhythmias, pericarditis-myocarditis syndrome or left ventricular heart failure and is related to the cumulative anthracyclin dose[7] whereas chronic cardiotoxicity occurs in the form of cardiomyopathy which occurs within one year of treatment. However the late onset cardiotoxicity usually occurs at least 1 year after the end of treatment[8].

Several hypothesis have been proposed to explain the cardiotoxicity of Doxorubicin, however free radical formation and resulting DNA or membrane damage have been suggested to play a critical role for its cardiac effects[9]. As the heart cells are rich in mitochondria and deficient in antioxidant defense system, so they are much more prone to this oxidative damage caused by free radicals[10].

Over the last two decades lot of research has been done to prevent the cardiotoxicity of doxorubicin. In

this regard many natural and synthetic pharmacological agents with antioxidant potential have been tried. Genus Ficus is an important group of trees in this regard because of its immense medicinal and religious values in many Asian countries[11]. Many species of this genus have been evaluated for their antioxidant effects.[12]

Ficus carica or 'Anjiir' is used for a number of medical illnesses. It is one of the only five plants mentioned in the Holy Quran, along with olives, grapes, pomegranate and dates[13]. Its antioxidant capacity has been evaluated but its cardioprotective effect is not studied. Because of this antioxidant potential of *Ficus carica* and other species belonging to this genus, we designed this study to evaluate its cardioprotective effect; not only by its leaves but also by its fruit, by measuring the serum levels of cardiac enzymes elevated by Dox.

MATERIAL AND METHODS

Ficus carica Leaf & Fruit Extract:

Leaves & Dried Fruits of *Ficus carica* were collected from Lahore region. They were identified and authenticated from herbarium maintained by the department of botany, Punjab University Lahore. Ethanolic extract was prepared in the chemistry department of PCSIR laboratories Lahore. Leaves & fruit of *Ficus carica* were dried under shade for three weeks. They were crushed and rinsed with hexane solution thoroughly for defattening and filteration. The filterate was immersed in ethanol for 48 hours and further purified to obtain a solution which was placed in a rotary evaporator (Labrota 401 digital. Heidolph). On evaporation of ethanol, the residue obtained was stored in a dessicator[14]. The leaf extract obtained was semisolid with greenish black color and greasy consistency.

Animals:

Male Sprague dawley albino rats, weighing 250-300g, were purchased from National Institute of Health (NIH), Islamabad. They were housed in standard polypropylene cages at controlled room temperature of 25±10ºC and relative humidity 60-70%. They were fed with standard laboratory diet with water ad libitum[15]. Four groups of 10 animals each, were used for the experiment. Duration of study was for total of 10 days. On 11th day blood was taken by intracardiac puncture for serum enzymes analysis.

Drug Administration:

Group 1: (control) The animals in this group were given standard laboratory diet for 10 days.

Group 2: On day 1 all the animals were injected with single intraperitoneal injection of doxorubicin in a dose of 15mg/kg[16].

Group 3: All animals of this group received single intraperitoneal Injection of doxorubicin 15mg/kg on day 1, immediately followed by 400mg/kg of *Ficus carica* leave extract orally. The leave extract was given in the same dose daily for up to 10 days. Required quantity of leave extract was measured on weighing scale and then dissolved in 5ml of distilled water. Solution according to weight of the animal was taken and then given via oral route with the help of nasogastric tube[17].

Group 4: All animals of this group received single intraperitoneal injection of doxorubicin 15mg/kg on day 1, immediately followed by 400mg/kg of *Ficus carica* fruit extract orally. The fruit extract was given in the same dose daily for upto 10 days. Required quantity of fruit extract was measured on weighing scale and then dissolved in 5ml of distilled water. Solution according to weight of the animal was taken and then given via oral route with the help of insulin syringe.

Blood Collection:

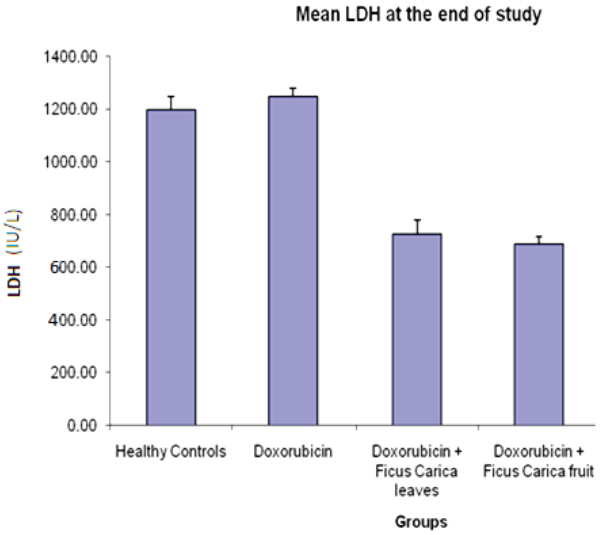
On 11th day animals were anaesthetized by using chloroform. They were then placed in dorsal recumbent position. After palpating the lower border of sternum, needle of syringe was introduced just to the left of xiphoid process blood was collected. All the syringes were labelled properly. The serum was then prepared for estimation of Creatinine phosphokinase (CPK) and Lactate dehydrogenase (LDH) on chemistry analyzer, in biochemistry Department of Shaikh Zayed hospital[18,19].

Statistical analysis:

Data was analyzed by SPSS Version 15.0. The quantitative parameters CPK and LDH were described by using Mean±SD and comparison between three groups was made by using ANOVA. A posthoc test tukey's HSD was used. A p value of ≤ 0.05 was considered as statistically significant.

RESULTS

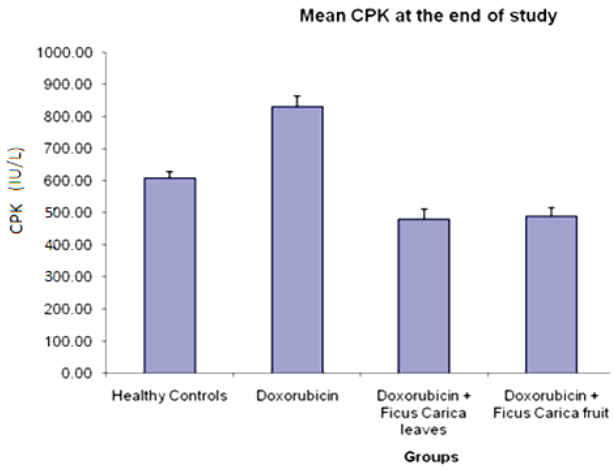
In this study single intraperitoneal injection of doxorubicin (15mg/kg) in group 2 induced severe cardiac damage. This was manifested in the form of significant elevated levels of CPK and LDH ($p \leq 0.05$) in serum. Administration of *Ficus carica* leaf and fruit extracts via oral route in animals of group 3 and group 4, after the intraperitoneal injection of Dox produced significant decline in serum CPK and LDH levels with $p \leq 0.05$ (Table-1)



Groups	CPK(IU/L)	LDH(IU/L)
Control	608.7/18.81	1197.5/50.39
Doxorubicin (Dox)	830.3/32.52	1245.0/33.49
Dox + Ficus Carica leaf extract	479.5/31.87	726.3/50.66
Dox + Ficus Carica fruit extract	489.33/25.8	688.78/27.37

P value < 0.05

Table-1: Serum Enzymes level in three groups



DISCUSSION

Doxorubicin is a well known anthracyclin used extensively for the variety of malignancies since its discovery. But the major limitation to its use is cardiotoxicity which can occur acutely or chronically[20]. Its occurrence is greatly pronounced when dose exceeds 500mg/m^2. Over the previous years effort has been directed to finding some botanical solution for anthracyclin induced cardiac damage instead of using chemical agents with more serious adverse effects. Many herbal or nutritional agents have been studied in animal models. For example a Chinese herbal medicine Schisandra Chinensis, grapefruit extracts, Ficus hispida and many other agents which have strong antioxidant potential, have been tried against Dox cardiomyopathy[21,22].

We have selected the *Ficus carica* which is found in our region and is commonly used by traditional healers for various illnesses. Although we did not evaluate its active components but biochemical studies on its sibling species showed them to be rich in tannins, flavonoid, alkaloids and polyphenols[23,24]. All of which are claimed to be excellent antioxidants. We evaluated the cardioprotective effect of its leaves and fruit. In our findings Dox increased the level of CPK by 136% in group 2 which was decreased by 58% in *Ficus Carica* leaf extract and 59% by fruit extract. LDH level was also decreased to 58% by leave extract and to 55% by fruit extract from the elevated level of 104% by Dox.These effects of *Ficus carica* were comparable to other proposed cardioprotective herbs, for example Nirengenin, which is present abundantly in grapefruit, is a flavonoid which is always claimed to

be strong antioxidants. 25mg/kg of Nirengenin administration 7 days ahead of Dox is capable of reducing the CPK level to 57% from 226% increased level by Dox. Whereas reduction in LDH level was 46% from 142% elevated level[25]. These effects of Nirengenin are almost equivalent to Ficus Carica in our rat model.

CONCLUSION

Our results showed the significant cardioprotective effects of *Ficus carica* leaf and fruit extracts on cardiac damage produced by Doxorubicin, by lowering the CPK and LDH levels. Its active constituents should be separately evaluated to have a better idea regarding its antioxidant effect. This might be able to produce some better cardioprotective agent in patients receiving doxorubicin.

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