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RESEARCH ARTICLE

ISOLATED D-PINITOL FROM AERIAL PARTS OF SOYBEAN PLANTS PLAYS A PROTECTIVE ROLE ON DOXORUBICIN INDUCED CARDIOTOXICITY IN MICE MODEL: HISTOPATHOLOGICAL STUDIES OF HEART

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Abstract

Introduction:D-Pinitol, a polyol is a potent antioxidant agent and anti-inflammatory agent. Hence,this study was carried out to evaluate whether D-Pinitol administration prior to induction of cardiotoxicity using Doxorubicin would protect cardiac histopathological changes in an experimental mice model.

Methods: Ten groups of sixty Swiss Albino mice were taken for administration: Control, Doxorubicin (5 mg/kg), D-Pinitol (400 mg/kg, 300 mg/kg, 200 mg/kg & 100 mg/kg), and D-Pinitol (400 mg/kg, 300 mg/kg, 200 mg/kg & 100 mg/kg) + Doxorubicin (5 mg/kg). DOX-induced cardiac toxicity was characterized by the histopathological observations.

Results: Myocyte necrosis was clearly seen in the group that received just doxorubicin therapy. Administering D-Pinitol before receiving Doxorubicin minimized myocyte necrosis and degeneration of myocytes.

Conclusions: Administration of D-Pinitol to Doxorubicin-challenged rats ameliorated alterations in histological cardiac damage compared with the Doxorubicin alone treated group. As a result, D-Pinitol supplements may help lessen the cardiac damage caused by doxorubicin.

Introduction:-

Globally, the two leading causes of mortality and morbidity are heart diseases and cancer.Chemotherapy is animportant treatment modality for many different types of malignancies, including breast cancer. (Gürses I., 2014)Numerous chemotherapy medicines are used to treat a number of neoplastic illnesses. The extent and frequency of side effects at therapeutic levels is one trait that distinguishes anticancer medications from other therapies. (Remesh A., 2012)An outstanding class of chemotherapy drugs used to treat a variety of hematological and solid cancers are anthracyclines. The most potent and widely used anthracycline is doxorubicin (DOX). (Subburaman S., 2014)DOX causes an abundance of free radicals, oxidative stress, along with substantial inflammatory reactions in a number of tissues. (Cortés-Funes H, 2007) The accumulation of lipid peroxides in free-radical-induced oxidative stress brings hydrophilic moieties into the membrane's hydrophobic phase, altering membrane permeability and function in cells. (Suntres ZE., 2011) This causes myocardial structural integrity to deteriorate and cardiac function to decline, culminating in cardiotoxicity.(Quiles, JL.,2002; Woodley-Cook, J., 2006;

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Saalu, L.C., 2009) DOX also causes inflammation in the vascular and heart, which raises levels of inflammatory cytokines.(Liu, Y., 2006; Mercuro, G., 2007) Therefore, one potential treatment strategy to lessen the cardiotoxicity of DOX is to combine it with cardioprotective drugs.D-Pinitol (D-P), a polyol, is a soluble carbohydrate found in all sections of Glycine max L. Merr. (Soybean plants). (Mercuro, G., 2007; Jayasooriya, RGPT., 2015). Because of its diverse pharmacological effects, D-P has sparked a lot of attention as a natural medication. D-P possesses a range of therapeutically beneficial qualities, including cardioprotective (Sripathi, S.K., 2013).) due to its anti-inflammatory, (López-Domènech, S., 2018).) and antioxidant (Rengarajan, T., 2014) capabilities. As a result, the role of D-P in reducing undesirable effects following DOX therapy was studied in this study.

Materials And Methods:-

Ethics statement:

The Institutional Animal Ethics Committee (IAEC) ofAdhiparasakthi College of Pharmacy (Reg. No. 409/PO/Re/S/01/CPCSEA) approved the experimental protocol.The approval number was APCP/IAEC/2019-2020/1.

Materials Required:-

Hematoxylin and eosin stain (Himedia, India), Giemsa (Himedia, India), Formaldehyde (Labogens, India), Paraffin Wax (Labogens, India), Diluent for smear preparation: 5% bovine serum albumin (BSA) in Phosphate buffered saline (Himedia, India) and Microscope (Olympus Optical Co., Germany).

Experimental Animal:

Both male and female Swiss Albino mice of weight 25–30 g werekept in a 12-hour light/dark cycle. Animals were acclimatized by maintaining them in a clean environmentaccording to CPCSEA guidelines. (Yadav, A.R. 2020)

Methodology:-

Treatment Protocol:

Ten groups of animalswere utilized in this study (six mice in each group - Table 1).D-P (all doses viz, 100, 200, 300& 400 mg/kg) was given for fifteen days to mice and DOX (on 1st day, 8th day, and 15th day)(Padmanabhan, S., 2009)was administered for three days based on the treatment protocol.D-P treated 30 minutes prior to the DOX administration.

Histopathological investigations were used to detect the toxicity to cardiac tissues. For histopathological studies of the heart, the tissue was dissected. The tissue samples were fixed in formalin solution (10% V/V) and embedded in paraffin (4 mm thick). The slides were stained with hematoxylin and eosin for microscopic examination (Olympus Optical Co., Germany). (Hassan H.F.H., 2017)

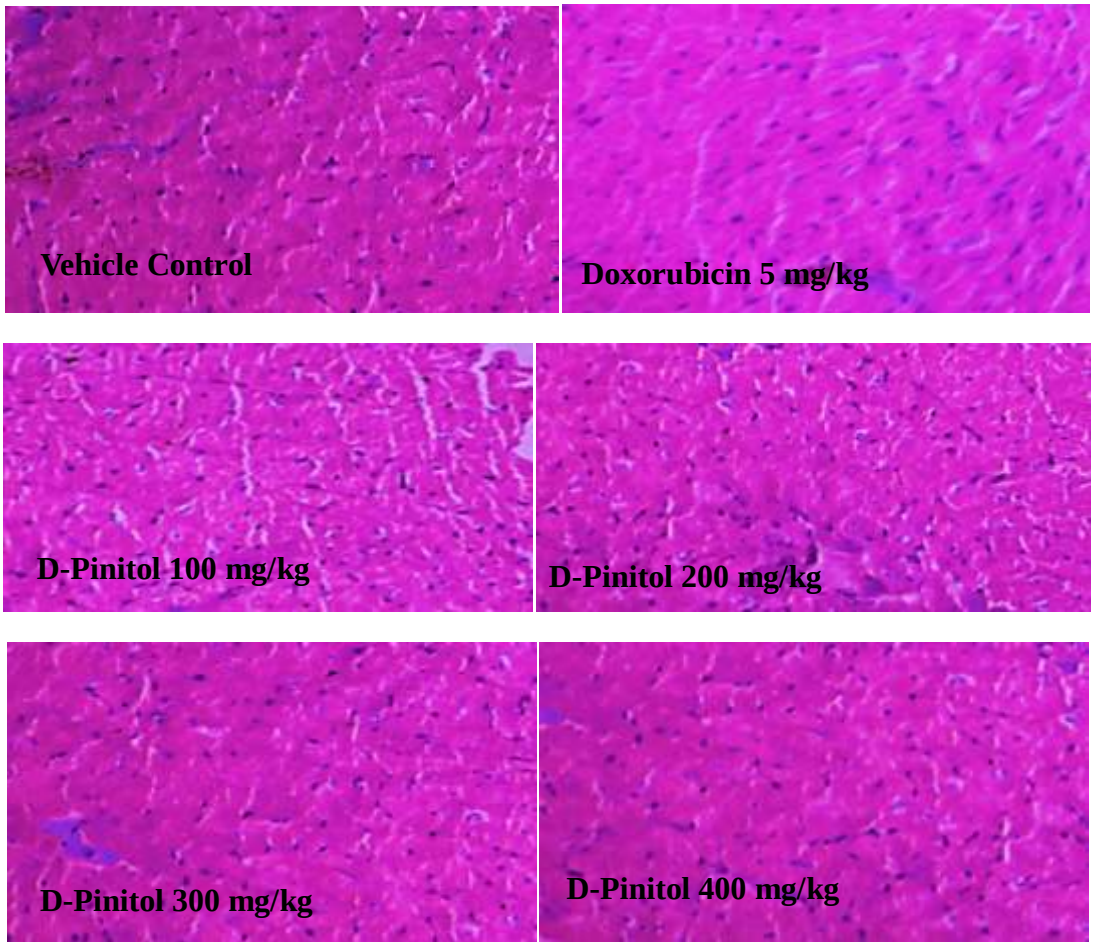
Table 1:- Treatment Protocol.

Group	Labeled	Treatment
I	Vehicle Control	0.5 ml of 0.9% normal saline
II	Positive Control	Doxorubicin (5 mg/kg), i.p. on 1st, 8th and 15th days (Positive Control)
III	Test Drugs	D-Pinitol (100 mg/kg), p.o. daily
IV		D-Pinitol (200 mg/kg), p.o. daily
V		D-Pinitol (300 mg/kg), p.o. daily
VI		D-Pinitol (400 mg/kg), p.o. daily
VII		Doxorubicin (5 mg/kg), i.p. on 1st, 8th and 15th days+ D-Pinitol (100 mg/kg), p.o. daily
VIII		Doxorubicin (5 mg/kg), i.p. 1st, 8th and 15th days + D-Pinitol (200 mg/kg), p.o. daily
IX		Doxorubicin (5 mg/kg), i.p. 1st, 8th and 15th days + D-Pinitol (300 mg/kg), p.o. daily
X		Doxorubicin (5 mg/kg), i.p. 1st, 8th and 15th days + D-Pinitol (400 mg/kg), p.o. daily

Results And Discussion:-

In the vehicle control group, the typical histological architecture of heart muscle with cylindrical branching of cardiac myocytes was seen in the histological findings. The majority of the myocytes appeared longitudinally and obliquely cut. The cardiac muscle fiber structures in all D-P alone treated groups (groups III to VI) were normal, as they were in the vehicle control group.Hence, it was revealed that D-P had no adverse effects on cardiac tissue. On the other hand, the typical properties of heart tissue were not present in DOX-treated mice. The fibers of the heart muscle were significantly disturbed. Most of the cardiac myocytes in the tissue had separated and seemed to be deteriorating. The number and severity of necrosis was prominently observed in DOX-alone treated group. When D-P was given to mice that had received DOX treatment, the toxic effects of DOX on cardiac muscle fibers were alleviated with reduction in necrosis and degeneration of myocytes, which showed the cardioprotective effect of D-P.

Prior research concluded that DOX-induced substantial degeneration in heart.(Pugazhendhi, A., 2018; Shivakumar, P., 2012)The current research also found that DOX, when administered for 15 days, caused histopathological degeneration in heart. DOX-induced ROS, oxidative stress (Deavall, D.G.,2012; Shivakumar, P., 2012))and inflammatory mediators (Hussain, M.A., 2021).) can interact with cell macromolecules to cause cytological damage.D-P has no toxic effects on organs, tissue, or bone marrow when treated alone. Because of its free radical quenching function, antioxidant activity, and anti-inflammatory property, D-P administration could successfully reverse the histological alterations in the bone, bonemarrow, and organs examined.As a result of the current research, it can be inferred that DOX caused damage to bone, bone marrow, and visceral organs damage which can be prevented by D-P.



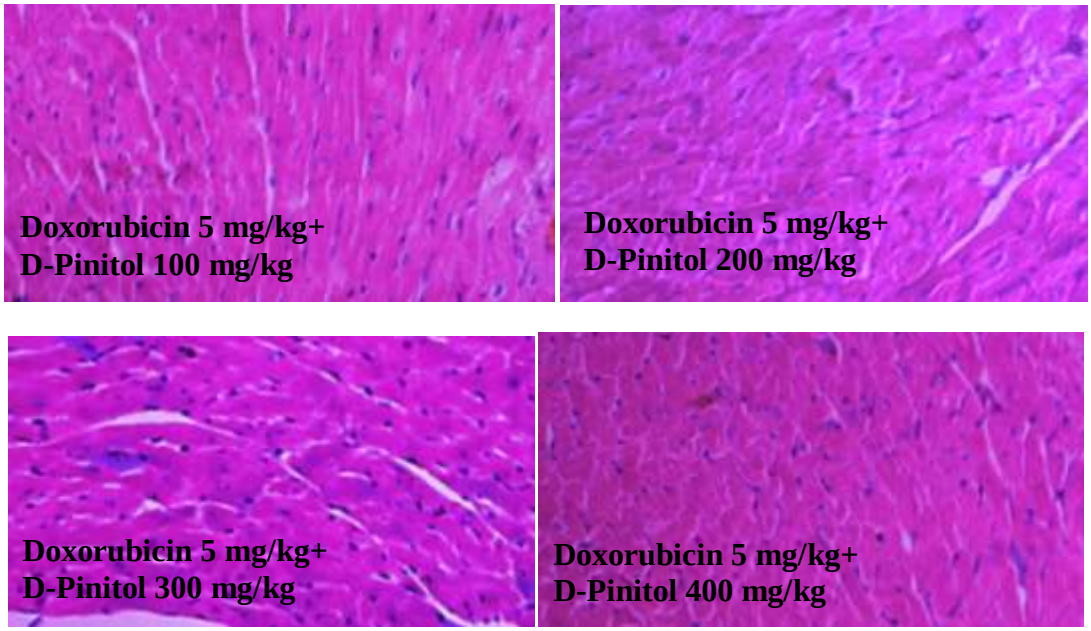


Figure 1:- Photomicrograph of a sectionof Heart.

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