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Original Article

Peanut Skin Extract Attenuates Doxorubicin Induced Myocardial Infarction by Alleviating Cardiac Inflammation, Oxidative Stress and Histological Changes in Wistar Rats

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ABSTRACT

Background: Cancer treatment is a major global concern. The anticancer drugs being used are effective, but their uses are curtailed due to toxicity that they produce. Doxorubicin is one of the most efficient anti-cancer drugs, but its usage is also restricted due to cardio toxicity. Hence the demand of a drug is always there which can reduce toxicity and be used along with doxorubicin, thereby safeguarding myocardium during cancer treatment. Objectives: Thinking in the same direction we tried to evaluate Peanut Skin Extract (PSE) for its cardio protective potential in doxorubicin challenged rats. **Materials and Methods:** Seven groups of rats having six animals per group were divided into Vehicle control; Doxorubicin (DOX 2 mg/kg/48 hr)+PSE 300+DOX 2 mg/kg/48 hr; PSE 400+DOX 2 mg/kg/48 hr; Fenofibrate (FF 80)+DOX 2 mg/kg/48 hr; PSE 400 per se; and FF 80 per se. Dosing was done for 12 days. Animals were sacrificed on 13th day and biochemical parameters of oxidative stress and inflammation were estimated. Histopathological analysis was also performed to establish cardioprotective effect of peanut skin extract. **Results:** In our study it was found that peanut skin extract behaved as a potential cardioprotective candidate that attenuated DOX- induced cardiotoxicity. **Conclusion:** Thus, based on the above study we came to the conclusion that peanut skin extract protects doxorubicin-induced myocardial damage.

Keywords: Peanut skin extract, Inflammation, Doxorubicin, Myocardial infarction, Oxidative stress.

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INTRODUCTION

In the recent times cancer has emerged as the prime tenet of death in the world, with nearly 10 million deaths in 2020.[1] Tally of cancer survivor is rising because of prior noting, consciousness and refinement of remedial mediation.[2] Despite the tremendous advancement in the development of anti-cancer drugs, cardiotoxicty as a side effect of these anticancer drugs, remain a major concern.[3]

Doxorubicin is one of the most effective anti-cancer medications for treating a variety of malignancies, including cancer of the breast, solid tumors, sarcoma of soft tissues, leukemia, lung small cell carcinoma etc., but its clinical functionality is confined because of its specific cardio-toxicities.[4,5] As per published literature, there are many plausible mechanisms that causes cardio toxicity Increased ROS, direct myocardial injury,[6] diminished Na^+/K^+ ATPase,[7] vasoactive amine release,[8] increased production of pro-inflammatory cytokines, apoptotic proteins and histological aberration in cardiac tissue are often seen with the administration of DOX.[9]

Earlier studies showed that natural anti-oxidant compounds reversed the DOX- induced cardio-toxicity very well,[10] without disturbing the therapeutic efficacy. In the current time, substantial interest in the exploration of natural anti-oxidants has been developed in relation to cardiovascular related problems. The other name of peanut (family Leguminosae) is groundnut,[11] goober (US), or monkey nut (UK). Numerous health benefits related to the use of peanuts are known through many literatures, like reduction of weight[12] and prevention of definite group cancers.[13] PSE has been reported to possess antioxidant, hypolipidemic,[14] anti-inflammatory,[15] and hypoglycemic effect mainly because of the presence of rich phytoconstituent i.e., catechin. Many research works have also reported that PSE has sufficient quantity of flavanoids and phenols that are beneficial in the treatment of various skin problems.[16] The peanut consist of kernel and the safeguarding peel. The peanut skin is copious in phenolics and possibly other health advancing compounds such as A-type procyanidine dimers, catechins B-type procyanidine

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dimers, trimers, tetramers, oligomers and resveratrol.[17-19] Previous studies have further demonstrated that resveratrol and procyanidins, major components of PSE, contribute to its cardioprotective properties.[20-23] Additionally, epidemiological studies have advocated that the utilization of food having plentiful of phenols can avert chronic diseases.[24] Thus, based on published health benefit and traditional use of PSE, this study was planned to assess the cardio-protective potential of PSE against DOX-induced cardiotoxicity in Wistar rats.

MATERIALS AND METHODS

Drugs and chemicals

Doxorubicin (Adriamycin®), Batch No W67681 was acquired from Pfizer, Inc. India. PSE (Peanut skin extract) was procured from Xi'an TengYun Biotech Co., Ltd. China. The remaining chemicals of analytical grade were purchased from Sigma Chemicals located in St. Louis, Missouri, USA. Arkray Healthcare in Santacruz and Reckon Diagnostics in India were the suppliers of the LDH and CK-MB kits, respectively. cTn-T elisa kit was obtained from Krishgen Biosystems, Mumbai, India.

Experimental animals

Wistar rats weighing 200-250 g were procured from the CAHF, Jamia Hamdard, New Delhi. The Institutional Animal Ethics Committee of Jamia Hamdard permitted the experimental protocol (IAEC/JH-1522). The animals were maintained on pellet feed with free access to food and water. They were housed in polypropylene cages, maintained at 21±1°C and 12 hr light/dark cycle. The animals were split up into seven groups, each consisting of six rats. The Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) located in New Delhi, India, provided rules that were followed during the experiment.

Treatment procedure

Rats were split into seven groups (n=6) and given 12 days of treatment in accordance with Table 1. DOX at a dose of 2 mg/kg intraperitoneally, PSE at a dose of 300 mg/kg per oral, 400 mg/kg per oral, and FF at 80 mg/kg per oral, were administered to different groups. 24 hr after the last dose, body weight of rats was taken, and the rats were euthanized later on to collect the blood from the tail vein. Hearts were dislodged, cleaned by normal saline and weighed. After that 10% formalin solution was used to store a section of cardiac tissue for histopathological studies and remaining sections were preserved at -20° for biochemical estimations.[25-28]

Assessment of markers related to oxidative stress

Assessment of markers related to oxidative stress i.e., Superoxide Dismutase (SOD),[29] Catalase (CAT),[30] reduced Glutathione (GSH),[31] Malondialdehyde (MDA)[32] and Total Antioxidant Capacity (TAC)[33] all was carried out as per the earlier published method respectively.

Assessment of markers related to cardiac injury

Lactate dehydrogenase (LDH) estimation

Estimation of LDH assay was carried out as per the manufacturer's instruction. LDH assay kit (AUTOSPAN liquid gold) was purchased from Arkray Healthcare, Mumbai, India.

Creatine kinase-MB (CK-MB) estimation

Estimation of CK-MB assay was carried out as per the manufacturer's instruction. We bought the CK-MB test kit from Reckon Diagnostics Pvt. Ltd., in Baroda, India.

Cardiac Troponin T (cTn-T) estimation

Cardiac Troponin T assessment was carried out as per the earlier published literature.[34] The US-based Biocodon Technologies provided the double-antibody sandwich (ELISA) kit.

Cardiac inflammatory markers assessment

Assessment of TNF-α, IL-6 and IL-10 were completed with the help of ELISA kits according to the guidelines provided by the manufacturer. ELISA kits were acquired from Krishgen Biosystems, Worli, Mumbai, India.

Histopathology image analysis

For H and E staining, formalin (10%) was used to fasten the myocardial tissue and paraffin wax was used to implant the segmented myocardial tissue. Transversely thick sections (5 µm) were sliced in accordance with the previously established method.[35] Computer facilitated (Motic microscope) was employed to capture the photomicrographs. The images have pixel intensities in the range (0 to 250). The unlighted image color was expressed by value (0) and the lighted image color was expressed by value (250).

Statistical analysis

Statistics were represented as Mean±S.E.M. ANOVA (one-way Analysis of Variance) was used to determine statistical significance, succeeded by Tukey's Honest Significant Difference test. Values were considered statistically significant in all the tests, when $p<0.05$. Statistical assay was executed by using Prism-GraphPad version 5.06.

RESULTS

Effect of Peanut skin extract on markers related to oxidative stress

DOX intoxicated rats showed reduction in CAT, TAC, SOD and GSH level and increase in TBARS in heart tissues with reference to the control group ($p<0.001$). Oral administration of PSE 300, PSE 400 and FF 80 significantly increased CAT ($p<0.05$, $p<0.001$

and $p<0.001$ respectively), TAC ($p<0.05$, $p<0.01$ and $p<0.001$ respectively), SOD ($p<0.01$, $p<0.001$ and $p<0.001$ respectively) and GSH ($p<0.001$, $p<0.001$ and $p<0.001$ respectively) and significantly reduced TBARS level ($p<0.001$, $p<0.001$ and $p<0.001$ respectively) as compared to DOX treated rats. PSE *per se* and FF *per se* group didn't show any significant variations in these parameters with reference to the control group (Figures 1 and 2).

Result of Peanut skin extract on the level of markers related to cardiac injury

DOX intoxicated rats showed enhanced CK-MB, LDH plus cTnT with reference to the control group ($p<0.001$). Oral administration of PSE 300, PSE 400 and FF 80 considerably reduced CK-MB ($p<0.001$, $p<0.001$ and $p<0.001$ respectively), LDH ($p<0.001$, $p<0.001$ and $p<0.001$ respectively) plus cTnT ($p<0.001$, $p<0.001$ and $p<0.001$ respectively) as compared to DOX treated rats. PSE *per se* and FF *per se* group didn't show any significant variations in these parameters with reference to the control group (Table 2, Figure 2).

Result of Peanut skin extract on the level of markers related to inflammation

DOX intoxicated rats significantly enhanced TNF-α as well as IL-6 and reduced IL-10 as compared to the control ($p<0.001$). Oral administration of PSE 300, PSE 400 and FF 80 considerably decreased TNF-α ($p<0.001$, $p<0.001$ and $p<0.001$ respectively) as well as IL-6 ($p<0.001$, $p<0.001$ and $p<0.001$ respectively) and enhanced IL-10 ($p<0.001$, $p<0.001$ and $p<0.001$ respectively) as compared to DOX treated rats. PSE *per se* and FF *per se* group didn't show any significant changes in these parameters with reference to the control group (Figure 3).

Histopathological analysis by H and E staining

Histopathological analysis revealed distinct vacuolization, pyknosis, and muscular disintegration in DOX treated group. Treatment with PSE 300 and PSE 400 as well as FF 80 remarkably improved the histopathological damage cardiac tissues as shown in Figure 4.

DISCUSSION

Doxorubicin is an antibiotic which belongs to anthracycline group and is used as a chemotherapeutic drug. It is a powerful anticancer agent; however it causes cardiotoxicity via multiple mechanisms and hence becomes a model for cardiotoxicity studies.[6-9] Cancer is one of the deadliest diseases that need attention globally. The uses of anticancer drugs are curtailed due to various toxicities that they cause via different mechanisms,[36-39] Its suitability as a cardio toxic model is also increased as it mimics to those occurring in humans having MI.[40] Hence, we selected this animal model of DOX to induce cardiotoxicity and study the cardioprotective effect of our test.

Natural food items have a noteworthy impact on enhancing human health and preventing various illnesses, such as heart disease. Earlier research has indicated that consuming a diet high in natural goods, such as fruits, herbs, and spices, can help lower the risk of cardiovascular disease.[40] In many earlier reports it has been shown that Peanut skin extract has many health benefits in case of treating different ailments.[14-16] Considering this health benefit and traditional use of PSE, we planned our research to assess the cardioprotective action of PSE at the two doses 300 and 400 mg/kg against DOX mediated MI.

In the physiological system, oxidative stress is always defended by the antioxidant enzymes present in the cell. Healthy myocardium also has antioxidant enzymes i.e., reduced GSH, SOD, CAT and TAC. The key purpose of these enzymes is to maintain the cells under reduced and undamaged state. Decrease in the level of these enzymes is seen during oxidative stress. Earlier published study showed that oxidative stress causes rise of ROS and promotes peroxidation of lipids that increases permeability of membrane and as a result produces myocardium injury. These enzymes play a vital role in combating oxidative stress via removal of ROS.[40] In our study we observed that the administration of DOX at a dose of 2 mg/kg/48 hr in rats led to rise in peroxidation of lipids and caused reduction in these antioxidant enzymes. Treatment with PSE 300, PSE 400 and FF 80 significantly reversed these enzymes and lipid peroxidation towards normal indicating their significant cardioprotective role (Figures 1 and 2).

Healthy myocardium contains an abundant concentration of cellular damage markers i.e., cTnT, CK-MB and LDH that play an important role in maintenance of normal physiological condition of myocardium. Earlier published literature showed that oxidative stress promotes myocardial membrane injury that causes these cellular damage markers to ooze out in the serum indicating myocardial injury.[7-10] In our study when we administered DOX at the dose of 2 mg/kg/48 hr to the rats, as a consequence, the serum

Table 1: Detailed plan of grouping and treatment procedure.

Sl. No.	Group (n=6)	Dosage, direction and time period
1	Normal control	Normal saline orally for 12 days.
2	DOX	DOX 2 mg/kg/48 hr intraperitoneally for 12 days.
3	PSE_{300}+DOX	PSE 300 mg/kg per oral+DOX 2 mg/kg/48 hr intraperitoneally for 12 days.
4	PSE_{400}+DOX	PSE 400 mg/kg per oral+DOX 2 mg/kg/48 hr intraperitoneally for 12 days.
5	FF_{80}+DOX	FF 80 mg/kg per oral+DOX 2 mg/kg/48 hr intraperitoneally for 12 days.
6	PSE_{400} *per se*	PSE 400 mg/kg per oral, for 12 days.
7	FF_{80} *per se*	FF 80 mg/kg per oral, for 12 days.

DOX: Doxorubicin, PSE: Peanut skin extract, and FF: Fenofibrate.

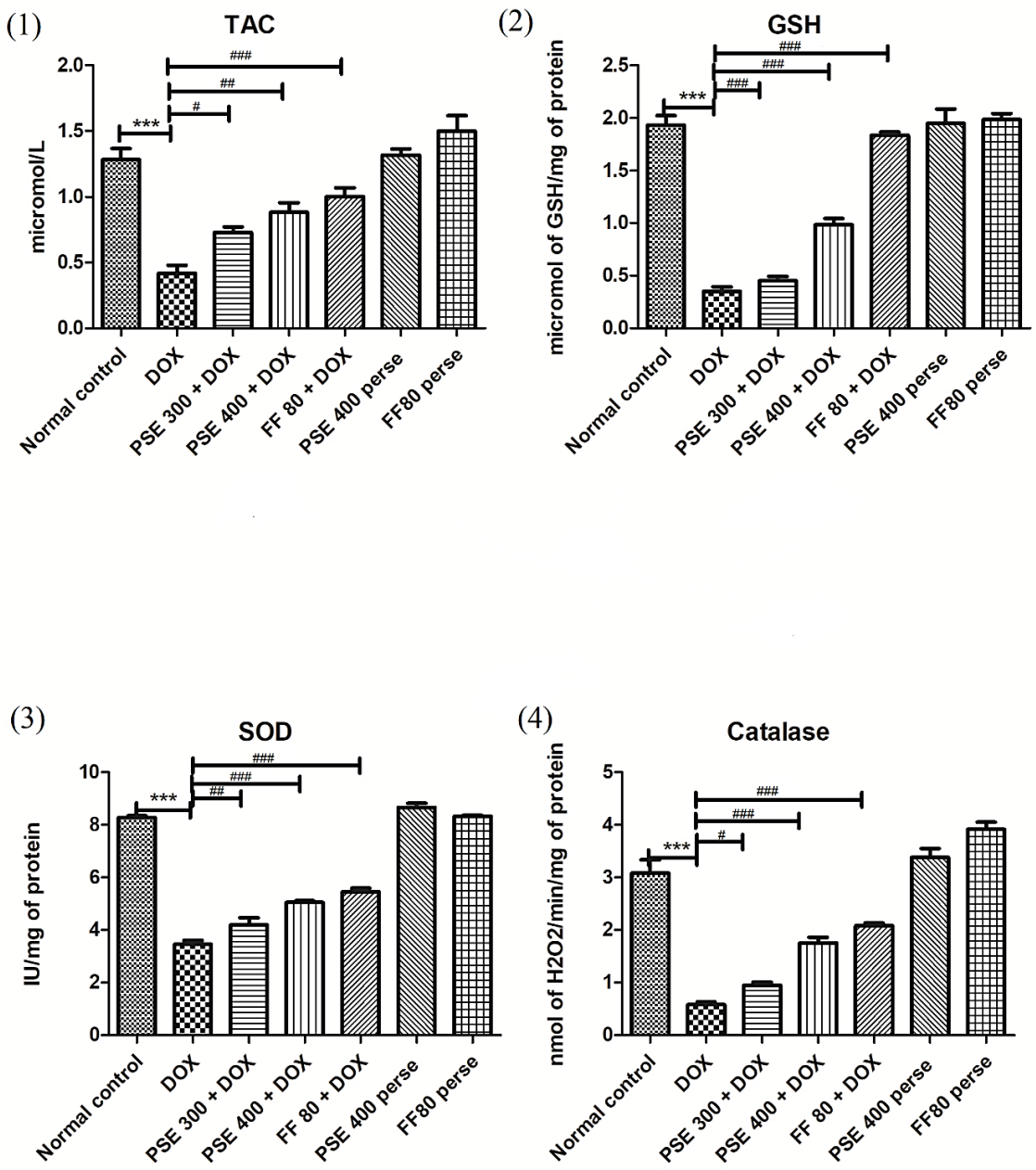

Figure 1: Effect of PSE 300, PSE 400 plus FF 80 on oxidative stress markers (1) TAC, (2) GSH, (3) SOD and (4) CAT mediated via DOX in the cardiac tissue of Wistar albino rats. DOX intoxicated rats remarkably decreased the catalytic property of TAC, CAT, SOD and GSH level in the myocardium tissue. Pretreatment with PSE 300, PSE 400 along with FF 80 enhanced the catalytic property of TAC, CAT, SOD and GSH towards normal. However PSE 400 showed the better results as compared to PSE 300. Statistics are represented as mean±S.E.M (n=6). We utilized ANOVA (one way analysis of variance) to determine statistical significance of data succeeded by Tukey's Honest Significant Difference test. $^{***}p<0.001$ significant, vs. control; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ significant vs. DOX and ns is non- significant vs. DOX.

Table 2: Comparative table showing the percentage decrease for each parameter relative to the control and DOX-treated groups.

Parameters	NC	DOX	PSE300	PSE400	DOX vs NC (%)	PSE300 vs DOX (%)	PSE400 vs DOX (%)
CK-MB (IU/L)	573	957	854	685	67.01570681	10.76280042	28.42215256
LDH (IU/L)	182	395	341	287	117.032967	13.67088608	27.34177215
cTnT (pg/ml)	0.5	4.3	3.8	3.05	760	11.62790698	29.06976744

NC: Normal control, DOX: Doxorubicin and PSE: Peanut skin extract.

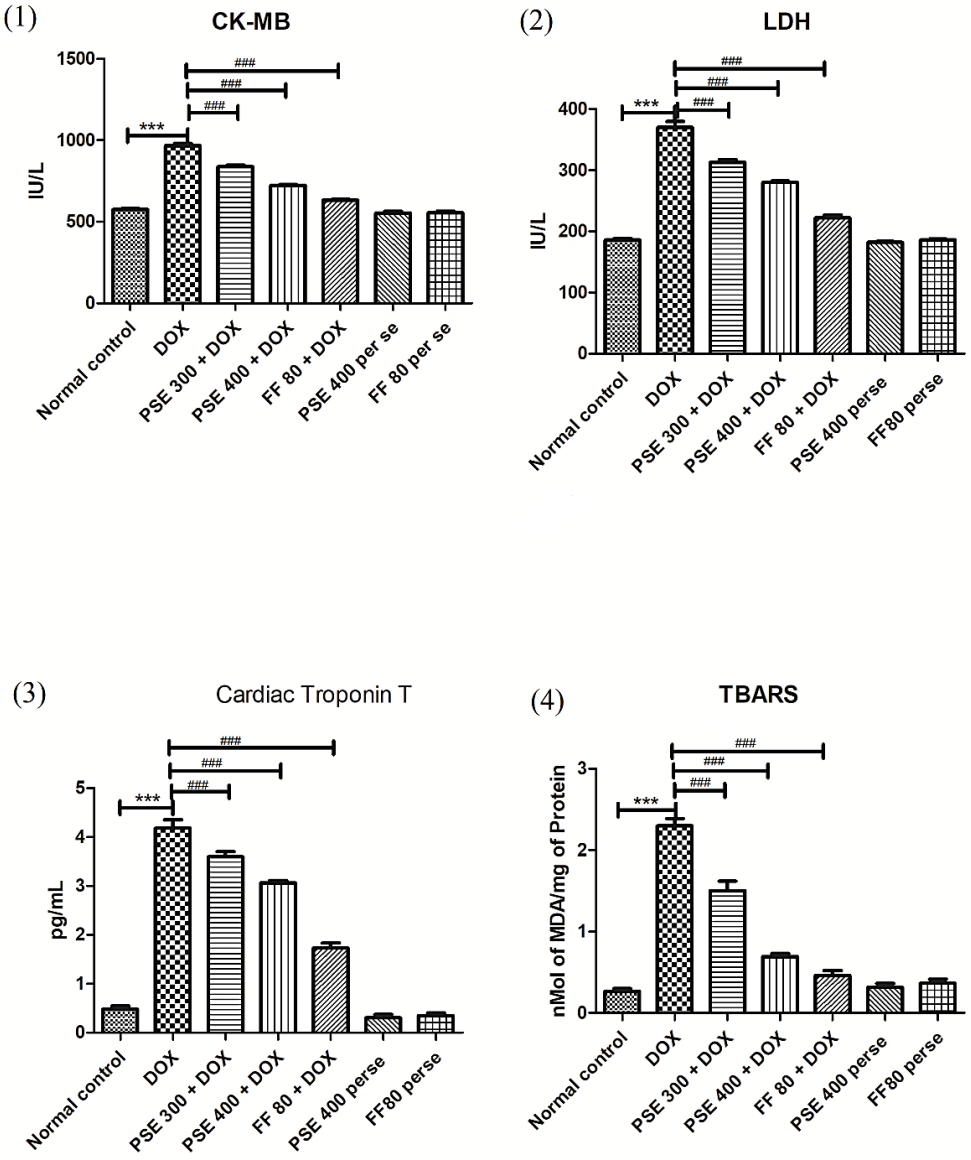

Figure 2: Effect of PSE 300, PSE 400 and FF 80 on the cardiac cellular damage markers (1) CK-MB, (2) LDH, (3) cTnT and (4) TBARS mediated by DOX in the cardiac tissue of Wistar albino rats. DOX intoxicated rats remarkably enhanced the volume of these markers. Treatment with PSE 300, PSE 400 and FF 80 decreased the volume of these cardiac cellular damage markers near to normal. However PSE 400 showed the better results as compared to PSE 300. Statistics are represented as mean±S.E.M (*n*=6). We utilized ANOVA (one way analysis of variance) to determine statistical significance of data succeeded by Tukey's Honest Significant Difference test. $^{***}p<0.001$ significant, vs. control; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ significant vs. DOX and ns is non- significant vs. DOX.

levels of cTnT, CK-MB, and LDH increased. Treatment with PSE 300, PSE 400 and FF 80 remarkably decreased level of cTnT, CK-MB and LDH in serum towards normal which indicated myocardial intactness and hence, cardio protection (Figure 2).

Cardiac toxicity beside other parameters can also be assessed by its inflammation. Inflammation can be examined by evaluating the level of various inflammatory markers like TNF- α and cytokines.[41,42] It is well known that generation of Reactive Oxygen Species (ROS) plays a key role in the formation of myocardial cytokines and apoptosis (TNF-α). The cytokines like TNF-α and IL-6 play a vital role in inflammation of cardiac tissue leading to its cellular death.[43] One of the cytokines related to inflammation is IL-10 which has been reported to neutralize numerous harmful outcomes of pro inflammatory cytokines.[44] As per our research, the DOX-treated group had elevated levels of cytokines such TNF-α and IL-6, but IL-10 levels were reduced. This conclusion is consistent with the earlier conclusion.[45] PSE 300, PSE 400 and FF 80 pretreated group showed remarkable reversal of these markers to normal (Figure 3) which showed cardio protective potential of these drugs.

Histopathological observation is one of the strongest decisive examinations to ascertain the cellular architecture. Histopathological examination of myocardium of Doxorubicin treated group was examined under 20X and the considerable damage was found in terms of disorientation of myofibrils, fibres separation, pyknosis and increased myofibril thickness along with vacuole formation. This toxicity was found reversed with the administration of our test drug i.e., Peanut skin extract (300 mg/kg and 400 mg/kg). Although both the doses showed cardioprotective but better results were obtained with 400 mg/kg potency of Peanut skin extract. Fenofibrate per se group showed no evidence of necrosis of the myocardial tissue and corresponded to the results obtained from the previous study in which myofibril damage was reduced with pre-treatment of the drug.[28]

The onset of cardiotoxicity can always be assessed by examining its oxidative enzyme status, and rise in inflammatory cytokines. This toxicity leads to various changes in the biochemical markers at the cellular and the serum level. The changes in cellular architecture can be efficiently assessed by its histopathology. We performed this study considering all these parameters and found PSE as a promising molecule that offered cardioprotection.

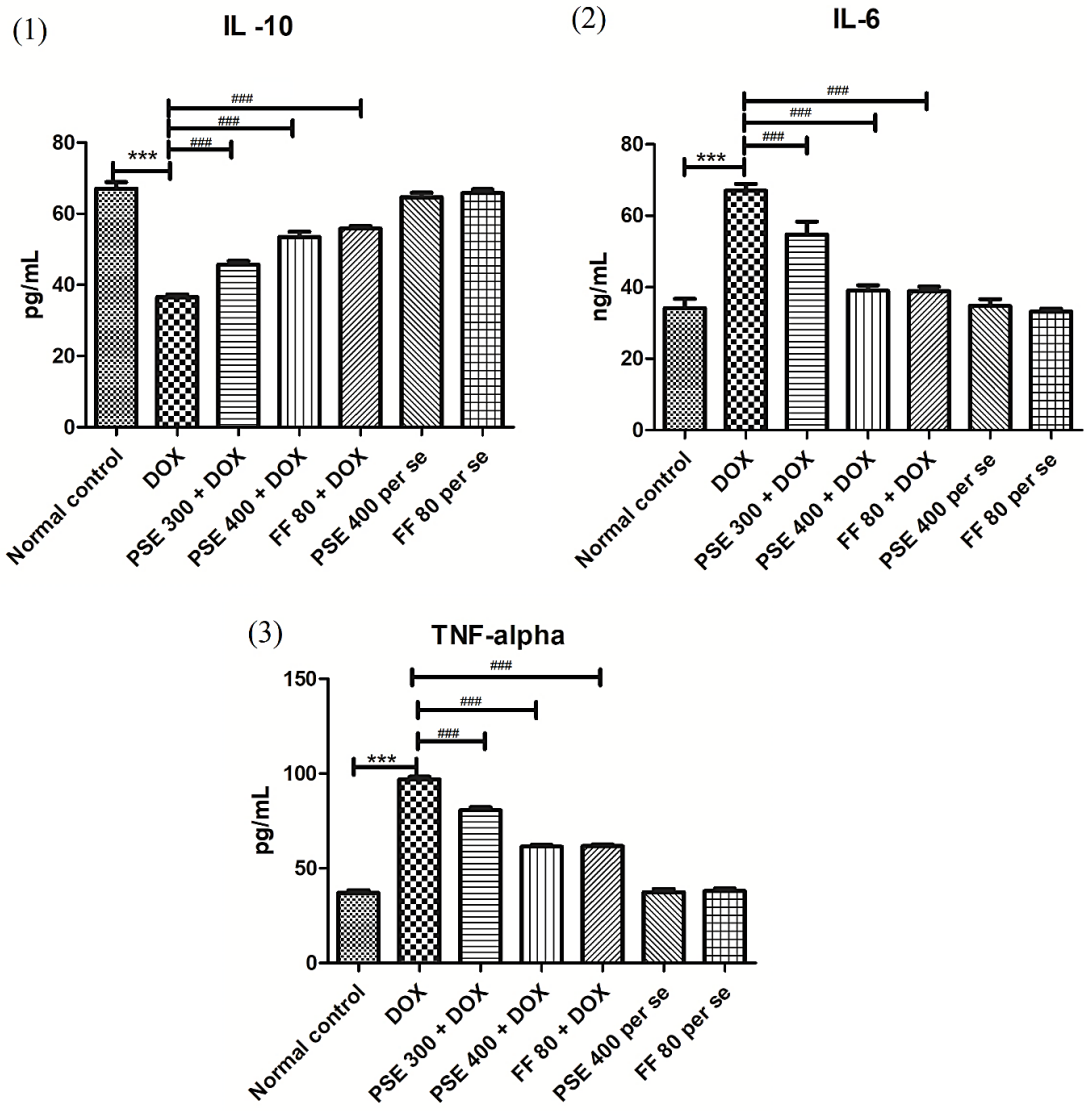

Figure 3: Effect of PSE 300, PSE 400 and FF 80 on inflammation markers (1) IL-10, (2) IL-6 and (3) TNF-α mediated via DOX in the cardiac tissue of Wistar albino rats. DOX intoxicated rats remarkably enhanced the volume of these markers. Treatment with PSE 300, PSE 400 and FF 80 decreased the volume of these inflammation markers near to normal. However PSE 400 showed the better results as compared to PSE 300. Statistics are represented as mean±S.E.M (n=6). We utilized ANOVA (one way Analysis of Variance) to determine statistical significance of data succeeded by Tukey's Honest Significant Difference test. $^{***}p<0.001$ significant, vs. control; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ significant vs. DOX and ns is non- significant vs. DOX.

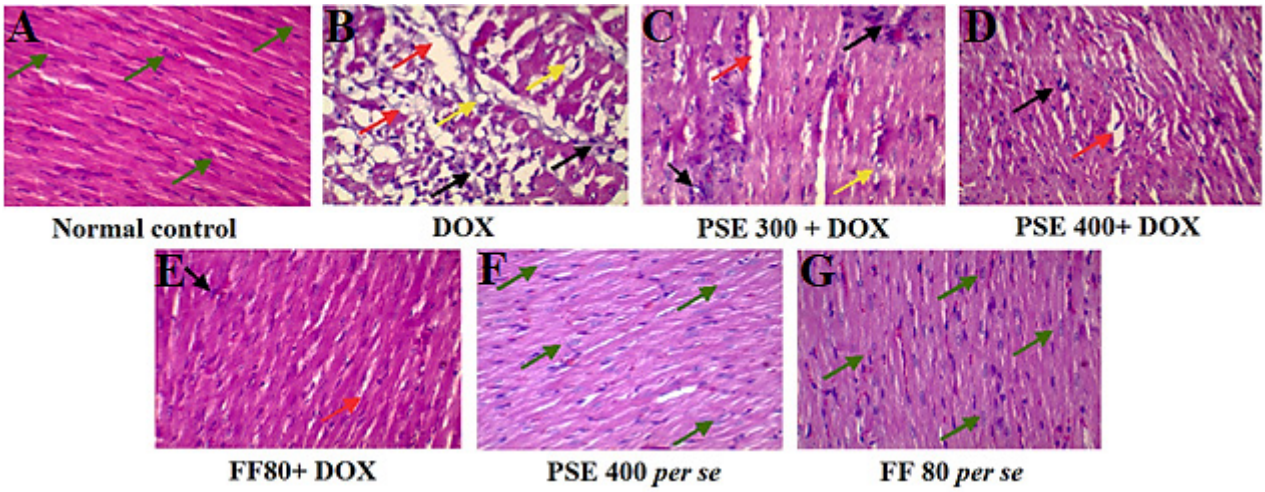

Figure 4: Images from (A-G) show the histological changes (HandE staining) of cardiac tissue in various groups (HandE, 400x, scale bar 50 µm). [A] Normal control showing normal cellular architecture, [B] DOX-treated group (Toxic group) showed a severely damaged section where there is marked cellular degeneration (red arrow), pyknotic nucleus (black arrow), and vacuolization (yellow arrow), when compared to the control group. [C] PSE 300 (Treatment 1) group showing significant reversal of toxicity when compared with the toxic group. [D] PSE 400 (Treatment 2) group showing a significant decrease in cellular disintegration, pyknotic nucleus and vacuolization as compared to the toxic group. [E] FF 80 (Standard) group also showing a significant decrease in cellular disintegration, pyknotic nucleus and vacuolization when compared with the toxic group. [F] PSE 400 *per se* group showing similar cellular architecture as that of the normal control in terms of no cellular disintegration, pyknotic nucleus and vacuolization. [G] FF 80 *per se* group also showing similar cellular architecture as that of the normal control in terms of no cellular disintegration, pyknotic nucleus and vacuolization. However PSE 400 showed the better results as compared to PSE 300.

CONCLUSION

Thus, based on the above study we came to this conclusion that peanut skin extract protects doxorubicin-induced myocardial damage. This protection was shown by both the concentration of the drug i.e. 300 mg/kg and 400 mg/kg, however 400 mg/kg was found more potent in offering cardioprotection.

Peanut skin extract being a nutraceutical can be considered as a better option for huge population suffering from cardiac and other lifestyle related diseases, as it is having no side effects, easy available, economic and shows wide range of benefits.

ACKNOWLEDGEMENT

We are thankful to Jamia Hamdard for providing the necessary facilities to perform the experimental work.

ABBREVIATIONS

PSE: Peanut skin extract; **DOX:** Doxorubicin; **ROS:** Reactive oxygen species; **LDH:** Lactate dehydrogenase; **CK-MB:** Creatine kinase-MB; **cTn-T:** Cardiac Troponin T; **SOD:** Superoxide dismutase; **CAT:** Catalase; **GSH:** Reduced glutathione; **MDA:** Malondialdehyde; **TBARS:** Thiobarbituric acid reactive substances; **TAC:** Total antioxidant capacity; **TNF-α:** Tumor necrosis factor-α; **IL-6:** Interleukin 6; **IL-10:** Interleukin 10; **H&E:** Hematoxylin and Eosin; **FF:** Fenofibrate; **IAEC:** Institutional Animal Ethics Committee; **ANOVA:** One-way analysis of variance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The experimental protocol was approved by the Institutional Animal Ethics Committee of Jamia Hamdard (IAEC/JH-1522).

SUMMARY

The present study showed that the administration of DOX 2 mg/kg/48 hr to Wistar rats produced significant cardiotoxicity, which was evident by the increased level of cardiac TBARS, serum marker enzymes (Troponin T, CK-MB, and LDH) and decreased levels of myocardial endogenous antioxidant and enzymes (GSH, SOD, and CAT). Histopathological observations also showed cardiotoxicity as evident by cytoplasmic vacuolation, pyknotic nucleus and disarrangement of myocardial fibres.

Pre-treatment with Peanut skin extract (300 mg/kg, 400 mg/kg) for 12 days showed cardio-protective effect as evident by restoration of all the biochemical parameters towards normal. Histopathological studies also confirmed reversal of cellular damage by test drug which was manifested by mild hypertrophy with few numbers of vacuoles and pyknotic nucleus.

Comparing all data obtained in relation to different concentration of PSE and Fenofibrate, the results of this study with short term oral administration of different concentration of PSE in Doxorubicin challenged rats showed that both concentration of PSE protected the myocardium against doxorubicin-induced myocardial infarction in rats.

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