



# Protective Effect of *Symplocos racemosa* Roxb Against Gamma Radiation Induced Cardiotoxicity in Male Albino Rats

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## ABSTRACT

The present study aims to evaluate the influence of the ethanol extract of *Symplocos racemosa* (EESR) on  $\gamma$ -rays-induced cardiac lesions. Thirty two male albino rats were divided into four equal groups as follows: control group, rats were administered saline (1ml/rat) orally by gastric tube for 14 days. Irradiated group (animals whole body exposed to a single shot dose  $\gamma$ -rays (10 Gy), treated group (rats received 200 mg/kg body weight EESR once daily, orally for two weeks), and treated irradiated group (rats received 200 mg/kg body weight EESR once daily, orally for two weeks, then one hour post the last treatment, were exposed to radiation. The results revealed that administration of EESR to rats pre-irradiation significantly reduced the severity of radiation-induced elevation of tumor necrosis factor  $\alpha$ , interleukin  $1\beta$ , interleukin 6 and serum creatine phosphokinase, lactate dehydrogenase and aspartate amino transferase activities, total cholesterol and low-density lipoprotein-cholesterol levels, high-density lipoprotein-cholesterol, creatine kinase-MB and cardiac troponin I. Moreover EESR treatment elevates cardiac catalase and superoxide dismutase activities while reducing malondialdehyde level compared to irradiated group. The histopathological results showed distinctive patterns of myocardial injuries in irradiated group, while in treated-irradiated group the myocardial tissues showed minimum injury. In conclusion, EESR modulates  $\gamma$ -rays induced cardiac lesions in male albino rats.

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## Authors' Contributions

AAE conceived and designed the study, and performed pathological studies. ETM and SME performed biochemical studies and analyzed the data. All authors participated in preparation of manuscript.

## Key words

Antioxidant,  
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 $\gamma$ -rays,  
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## INTRODUCTION

Radiation therapy plays an important role in the treatment of cancer. Exposure of the body to ionizing radiation produces the reactive oxygen species (ROS) which damages lipids, nucleic acids and proteins. In addition, cell lipid peroxidation is related to radiation-induced cell death, changes in membrane fluidity, and in the activities of some membrane enzymes (Riley, 1994). Total body irradiation is known to cause a marked decrease in antioxidant capacity and an excessive increase in oxidant stress (Akpolat *et al.*, 2011). ROS also negatively impact the antioxidant defense mechanisms, reduce the intracellular concentration of glutathione (GSH) and decrease the activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSHPx) (Gracy *et al.*, 1999). The final product of peroxidation is malondialdehyde (MDA), a major aldehyde product that is mutagenic in cells and could be assessed to evaluate tissue injury (Dalle-Donne *et al.*, 2006). Dyslipidemia evidenced by increased total cholesterol, triglycerides (TG), low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL) level was reported post-irradiation (Feurgard *et al.*, 1999).

Mammals are equipped with antioxidant defense systems that scavenge and decrease the formation of ROS. However, these systems are not always fully operative. So, diet derived antioxidants become particularly important in diminishing cumulative oxidative damage and a number of dietary antioxidants have been reported to decrease free radical attack on biomolecules (Varma *et al.*, 2011).

The plant *Symplocos racemosa* (Family: Symplocaceae) is a low under shrub with wide distribution, mostly found in South India and Himalayas (Kirtikar and Basu, 1998). The bark used traditionally for bowel complaints such as diarrhea, dysentery, eye diseases, liver complaints and hepatoprotective activity (Bhutani *et al.*, 2004), fever, ulcer, scorpion sting, diabetes, and liver disorders Raval *et al.* (2009), anti-inflammatory (Kambhoja and Keshava, 2004), antiulcer (Nadkarni, 2002) and an antimicrobial (Kumar *et al.*, 2007), anticancer (Arifullah *et al.*, 1986) and gynaecological disorder. The present study aimed to determine the protective effect of EESR bark extract on ionizing radiation-induced cardiac injury.

## MATERIALS AND METHODS

### Animals

Adult male Swiss albino rats (130-150g) aged 3-4 months were obtained from the Egyptian Organization for Biological Product and Vaccines, Giza, Egypt.

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Animals were kept under good ventilation and illumination condition and received standard diet and water. The animals' treatment protocol was approved by the Animal Care Committee of the National Centre for Radiation Research and Technology (NCRRT), Cairo, Egypt.

#### *Radiation processing*

It was performed by using gamma cell-40 (Cesium - 137) located at NCRRT, Cairo, Egypt. Animals were irradiated with a single dose level of (10 Gy)  $\gamma$ -ray, delivered at a dose rate of 0.46 Gy/min. at the time of experimentation. Animals were not anesthetized before irradiation.

#### *Chemicals*

The bark portion of the plant was collected from local market and authenticated by Dr. S. El-Naeimy, Faculty of agriculture Zagazig University, Egypt. The coarse powder (150 g) was packed in a Soxhlet apparatus and subjected to hot continuous percolation for 72 h by using ethanol (95% v/v) as solvent. This ethanol extract of *Symplocos racemosa* (EESR) was evaporated to dryness under reduced pressure (% yield = 6% w/w) and used (Wakchaure *et al.*, 2011).

#### *Experimental design*

Thirty two rats were divided into four groups (n = 8) and treated in parallel. Group I (control group), rats received orally by gastric tube an equivalent volume of distilled water (vehicle of EESR) during two weeks. Group II (irradiated group) received orally by gastric tube an equivalent volume of distilled water during two weeks, then whole body gamma-irradiated with an acute single dose level of 10 Gy. Group III (treated group), rats received EESR orally by gastric tube 200 mg/kg body weight once daily, for two week according to Kumar *et al.* (2013). Group IV (treated irradiated group) rats received EESR orally by gastric tube (200 mg/kg body weight) once daily, for two weeks, then one hour post the last dose of EESR, rats were whole body gamma-irradiated with an acute single dose of 10 Gy. Rats were sacrificed on the 6th day post radiation exposure.

#### *Samples collection*

After an overnight fast, rats were sacrificed. Blood samples from each rat were collected by retro-orbital puncture using blood capillary tubes. Serum was obtained immediately by centrifugation of blood samples at 3000 rpm for 10 min. Heart was directly separated after sacrifice, washed in ice-cold saline, then the heart samples were homogenized (10% W/V) using Homogenizer then the cell debris was removed by

centrifugation at 3000 rpm for 10 min. The homogenates supernatant were used for the further biochemical analysis. Tissue specimens from heart were collected and fixed in 10% buffered formalin solution followed by dehydration, clearing and embedding in paraffin. Paraffin sections of 5 $\mu$ m thickness were prepared and stained routinely with haematoxylin and eosin according to Bancroft and Stevens, (1996) and examined microscopically.

#### *Estimation of biochemical parameters*

Creative kinase-MB (CK-MB) and cardiac troponin I (cTnI), serum tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin 1 $\beta$  (IL-1 $\beta$ ) and interleukin 6 (IL-6) were performed by ELISA technique (BioSource International, Camarillo, CA, USA) according to the manufacturer's instructions. Creatine phosphokinase (CPK) level was estimated according to the method of Okinaka *et al.* (1964) and lactate dehydrogenase (LDH) was assayed depending on the method of Henery (1974). Moreover, serum total cholesterol (TC) concentration was estimated as described by Allain *et al.* (1974). HDL-C and LDL-C were determined according to the methods described by Demacker *et al.* (1980) and Marchal (1992), respectively. The activity of aspartate amino transferase (AST) was determined according to the method of Reitman and Frankel (1957). CAT activity was assayed using the method of Sinha (1972). SOD was determined according to the method described by Kakkar *et al.* (1984) and MDA level was estimated following the method reported by Buege and Aust (1978).

#### *Statistical analysis*

Data were analyzed using one way analysis of variance (ANOVA) followed by LSD as a post hoc test. The results obtained were expressed by mean  $\pm$  standard deviation. Differences were considered significant at  $P \leq 0.05$  (George and William, 1980).

## **RESULTS**

#### *Biochemical findings*

As presented in Table I, significant increases in the inflammatory markers TNF- $\alpha$ , IL-1 $\beta$  and IL-6 levels were observed in the serum of irradiated rats compared with their corresponding values of control rats. The administration of EESR before exposure to gamma irradiation significantly limits the elevation in serum TNF- $\alpha$ , IL-1 $\beta$  and IL-6 levels compared to irradiated group.

The whole body gamma-irradiation induced a significant increase in the activity of serum CPK, LDH, cholesterol and LDL-C while a significant increase in HDL-C concentration was noticed compared to control group (Table I). Pretreatment with EESR prior to gamma

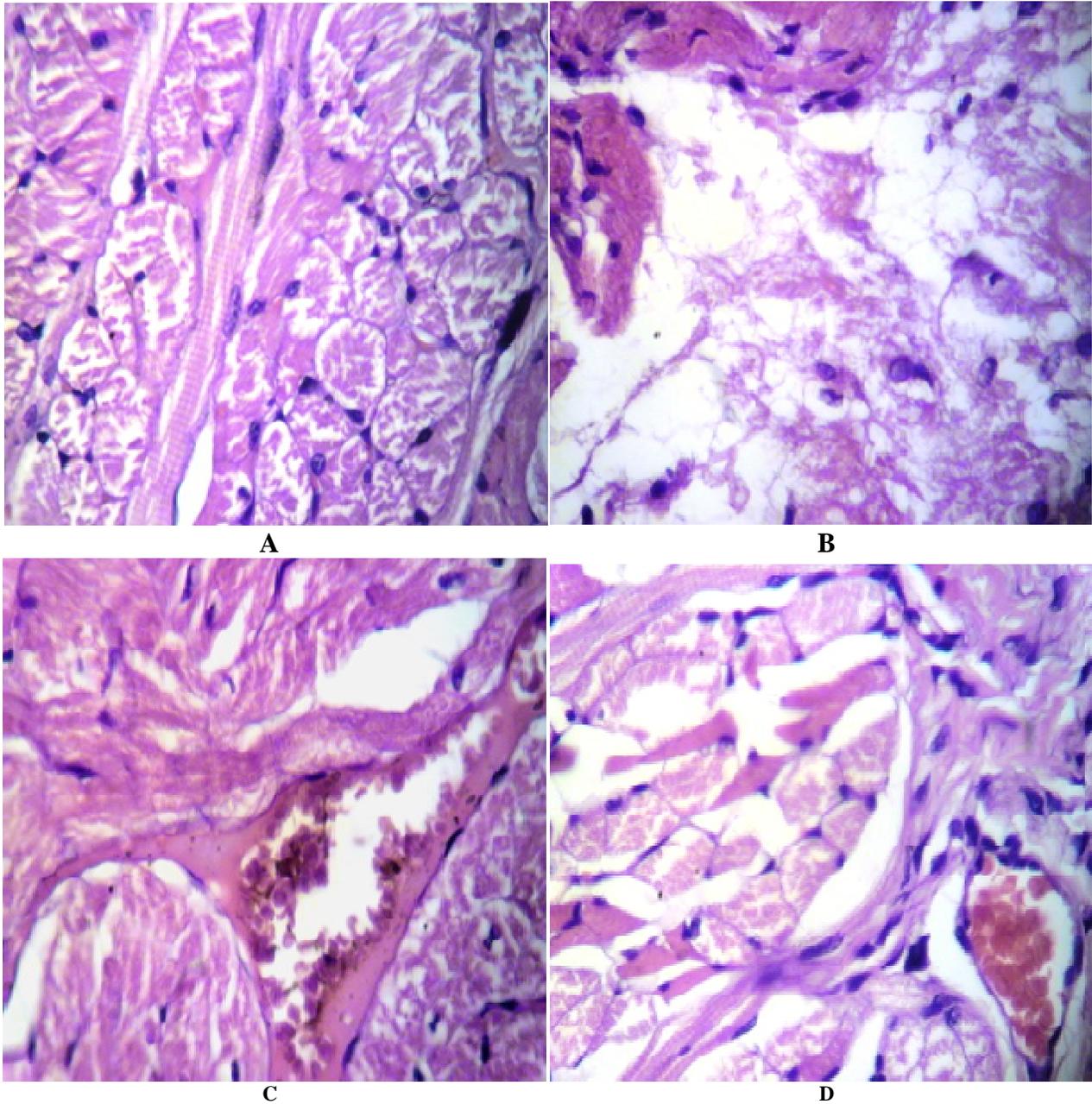


Fig. 1. Histological structure of heart of male albino rat; A, control rat showing normal structure; B,  $\gamma$ -irradiated rat showing removal necrotic myocytes by phagocytosis and edema; C,  $\gamma$ -irradiated rate showing fibrinoid necrosis in coronary vessel and widened spaces contains edema fluid; D, treated irradiated rat (group IV) showed edema and minimal architecture distructure of normal myocytes with normal endothelium of blood vessels. Stain: H & E; Magnification: 400x

irradiation was found to significantly ameliorate these radiation-induced changes. CK-MB and cTnI showed a significant increase in irradiated group. The animal group treated with EESR showed non-significant changes in the concentration of serum CPK, LDH, cholesterol, LDL-

C, HDL-C, cTnI and CK-MB compared to those of the control group.

The effects of  $\gamma$ -rays on endogenous antioxidant status are shown in Table I. Gamma-irradiation induced a significant decrease in the activity of heart CAT and SOD

**Table I.- Effect of ethanol extract of *Symplocos racemosa* (EESR) on the renal biochemical components of  $\gamma$  irradiated male albino rats.**

Parameters	Control	EESR	$\gamma$ -rays	EESR- $\gamma$ -rays
TNF- $\alpha$ (pg/mL)	39.34 $\pm$ 1.02	37.27 $\pm$ 1.87	78.53 $\pm$ 2.39 <sup>a</sup>	35.33 $\pm$ 1.92 <sup>b</sup>
IL-1 $\beta$ (pg/mL)	16.63 $\pm$ 0.74	18.10 $\pm$ 1.12	55.89 $\pm$ 2.11 <sup>a</sup>	15.28 $\pm$ 2.11 <sup>b</sup>
IL-6 (pg/mL)	85.14 $\pm$ 1.27	90.88 $\pm$ 1.41	204.31 $\pm$ 2.76 <sup>a</sup>	142.22 $\pm$ 2.32 <sup>b</sup>
CPK (U/L)	260.53 $\pm$ 6.23	259.22 $\pm$ 8.75	475.25 $\pm$ 14.54 <sup>a</sup>	320.31 $\pm$ 12.32 <sup>b</sup>
CK-MB (ng/mL)	3.21 $\pm$ 0.72	2.7 $\pm$ 0.66	7.87 $\pm$ 0.98 <sup>a</sup>	5.9 $\pm$ 0.85 <sup>b</sup>
cTnI (ng/mL)	25.74 $\pm$ 0.96	22.51 $\pm$ 1.02	75.31 $\pm$ 2.87 <sup>a</sup>	48.77 $\pm$ 1.65 <sup>b</sup>
AST (U/L)	33.22 $\pm$ 1.14	30.47 $\pm$ 1.30	73.76 $\pm$ 2.34 <sup>a</sup>	46.26 $\pm$ 1.24 <sup>b</sup>
LDH (U/ml)	228.3 $\pm$ 11.76	220.3 $\pm$ 12.76	440.4 $\pm$ 23.79 <sup>a</sup>	333.4 $\pm$ 17.88 <sup>b</sup>
Cholesterol (mg/dl)	139.26 $\pm$ 3.11	130.71 $\pm$ 3.01	260.86 $\pm$ 5.37 <sup>a</sup>	179.27 $\pm$ 3.24 <sup>b</sup>
LDL-C (mg/dl)	42.25 $\pm$ 1.23	39.12 $\pm$ 1.56	148.67 $\pm$ 4.77 <sup>a</sup>	76.92 $\pm$ 3.24 <sup>b</sup>
HDL-C (mg/dl)	48.61 $\pm$ 1.01	49.92 $\pm$ 1.54	36.41 $\pm$ 2.87 <sup>a</sup>	40.01 $\pm$ 2.21 <sup>b</sup>
SOD (U/mg protein)	3.28 $\pm$ 0.97	3.33 $\pm$ 1.15	1.42 $\pm$ 0.94 <sup>a</sup>	2.40 $\pm$ 0.88 <sup>b</sup>
CAT (U/mg protein)	2.76 $\pm$ 0.72	2.96 $\pm$ 0.83	1.21 $\pm$ 0.91 <sup>a</sup>	2.21 $\pm$ 0.98 <sup>b</sup>
MDA (nmol/g protein)	8.72 $\pm$ 1.98	9.16 $\pm$ 1.77	16.79 $\pm$ 2.54 <sup>a</sup>	12.90 $\pm$ 2.35 <sup>b</sup>

AST, aspartate amino transferase; CAT, catalase; CK-MB, Creatine kinase-MB; cTnI, Cardiac troponin I; CPK, Creatine phosphokinase; HDL, High-density lipoprotein; IL-6, Interleukin 6; IL-1 $\beta$  Interleukin 1 $\beta$ ; LDH, Lactate dehydrogenase; LDL, Low-density lipoprotein; MDA, Malondialdehyde; SOD, Superoxide dismutase; TNF- $\alpha$ , Tumor necrosis factor  $\alpha$ .

All values are expressed as mean $\pm$  SD; <sup>a</sup> Significant (P < 0.05) when compared to the control group; <sup>b</sup> Significant (P < 0.05) when compared to the irradiated group.

as well as a significant increase in the level of MDA compared to control group. Administration of EESR prior to gamma irradiation of rats restored the reduced CAT and SOD activity while it decreased the MDA level compared to irradiated group. Animal group treated with EESR alone showed no significant changes in the activity of heart CAT, SOD and MDA compared to those of control group.

#### *Histopathological findings*

Light microscopic examination of cardiac muscle of group I (controls) showed normal myocytes with one or two large oval nuclei occupying a central position. The perinuclear sarcoplasm region is distinct. The intercalated disks are irregular and wider than the normal cross-striations, and represent specialized junctions between cardiac muscle fibers (Fig. 1A). In group II (irradiated group), the myocardial muscles were necrotic and middle infiltrated with leucocytes, edema, associated with loss of striation and disappearance of nuclei, intercalated disks and removal of necrotic myocytes by phagocytosis (Fig. 1B). Moreover, in few cases in coronary vessel showed fibrinoid necrosis represented by circumferential bright pink area of necrosis with protein deposition (Fig. 1C). In group III (EESR treated rats), the cardiac muscle showed normal structure. On the other hand, most cases of group IV (treated irradiated group) myocardial muscle showed slightly preserved architecture without necrosis, with or without edema (Fig. 1D).

## DISCUSSION

Radiation plays an important role to cause oxidative modification of DNA, proteins, lipids and small cellular molecules by inducing reactive oxygen species (ROS) which cause a wide range of common diseases and age-related degenerative conditions. These include cardiovascular disease (Witztum, 1993), inflammatory conditions, and neurodegenerative diseases such as Alzheimer's disease (Richardson, 1993).

In the current study, whole body gamma irradiation of animals with 10 Gy induced a significant increase in the level of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 (Table 1). Several previous in vivo and in vitro studies have demonstrated that TNF- $\alpha$  and IL-1 $\beta$  are the most important pro-inflammatory cytokines that exert a principal role in acute and chronic inflammation. It is well known that TNF- $\alpha$  and IL-1 $\beta$  strongly promote inflammatory responses in a wide spectrum of cell types, and overproduction of these cytokines has been implicated in a variety of human diseases including atherosclerosis, autoimmune disorders, and cancer (Locksley *et al.*, 2001). Up-regulation of TNF- $\alpha$  and IL-1 $\beta$  expression was also found in lung and intestine after irradiation (Hong *et al.*, 1999) and (Linard *et al.*, 2004). IL-6 is another multifunctional pro-inflammatory cytokine that plays a major role in the mediation of the inflammatory and immune responses initiated by infection or injury (Kishimoto, 2005). Recent studies have suggested that elevated levels of IL-6,

mRNA and protein expression may be responsible for the radiation-induced inflammation in the intestine and brain (Marquette *et al.*, 2003) and Linard *et al.* (2004).

The amelioration observed in the level of inflammatory factors in the EESR-irradiated group suggested that EESR could have potent anti-inflammatory activities. Sharma *et al.* (2013) estimated the analgesic activity of ethanolic and aqueous extract of EESR bark by formalin induced paw licking and tail flick models and anti-inflammatory activity by carrageenan induced hind paw edema model. Their results revealed that the ethanolic extract was more efficient in suppressing inflammation than the aqueous extract.

In the current study a single dose (10 Gy) of whole body gamma irradiation induced a marked increase in the activity of cardiac serum enzymes (CPK and LDH activity), in addition to the increase in total cholesterol, LDL-C, HDL-C, CK-MB and cardiac troponin I (cTnI). It is well known that the magnitude of CPK and LDH activities in blood after myocardial injury reflects the extent of damage in its musculature (Preus *et al.*, 1988). The results are in accordance with previous findings reported by Elkady and Ibrahim (2014) and Khaled *et al.* (2011). The mechanism of radiation-induced cardiotoxicity has been reported to be through the formation of superoxide anions and their derivatives, particularly highly reactive and damaging hydroxyl radicals, which induces peroxidation of cell membrane lipid (Hemnani and Parihar, 1998).

A significant decrease in the activity of heart CAT and SOD in parallel to a significant increase in the level of MDA was recorded. Such results explain that the exposure to ionizing radiation increases the production of ROS and directs the irradiated cells into a state of oxidative stress that has been implicated in a variety of natural and pathological processes (Hong *et al.*, 1999). Some authors reported that injury to the heart from irradiation appears to be indirect, supporting the notion that injury to abdominal organs, principally the kidneys, is responsible for the increased risk factors for and the occurrence of cardiac disease after total body irradiation (Lenarczyk *et al.*, 2013). Renal dysfunction may be a part of the mechanism responsible for the increased risk for heart disease following total body irradiation in adults (Adams *et al.*, 2012).

The treatment of rats with EESR prior to gamma irradiation ameliorated the activity of serum CPK, LDH, as well as the level of total cholesterol, LDL-C, HDL-C, cTnI and (CK-MB). Such results indicate that EESR pretreatment protects against radiation damage. The results corroborate the findings of Hussain *et al.* (2009) who have reported the anti-angiogenic activity of (1) Symplocoside and (2) Symponoside, glycosides isolated from the bark. Their results revealed that both

isolated glycosides inhibit thymidine phosphorylase (TP) activity and associated angiogenesis. Also EESR treatment before irradiation protected against oxidative stress, evidenced by increased SOD and CAT activities and decreased MDA levels of heart tissues compared to the irradiated non treated rats (Table I), thus indicating protective role of EESR against radiation toxicity, which is substantiated by the previous findings of Devmurari, (2010a,b). The extract showed significant activities in all antioxidant assays by reducing lipid peroxidation, SOD and CAT activity. Vijayabaskaran *et al.* (2012) examines the antioxidant activity of ethanolic extract of bark by DPPH (2, 2-diphenyl-1-picrylhydrazyl), nitric oxide, hydroxyl radical and ABTS [2, 2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)] assay method. Their results indicated that the ethanolic extract showed potent antioxidant activity against ABTS assay method [2, 2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)]. Ravichandran *et al.* (2005) also mentioned that the principle constituents of *Symplocos racemosa* (salireposide and benzoylsalireposide) have potent antioxidant activity.

In the current study oxidative stress in cardiac tissues were accompanied by severe histopathological changes. The results revealed that in the irradiated group (Group II), the myocardial muscles were necrotic with leucocytes infiltration, fibrinoid necrosis in coronary vessel, edema and hyalinization of myocardial muscles were remarked which is in agreement with the previous results observed by Baker *et al.* (2009), Khaled *et al.* (2011) Elkady and Ibrahim (2014) and (Elkady and Mohamed (2016). While in treated irradiated group (Group IV) the structure of myocytes showed slightly preserved architecture without necrosis, degenerative changes or hyalinization with normal endothelium of coronary blood vessels with or without edema. Such results indicated the cardio-protective role of EESR as antioxidant agent (Vijayabaskaran *et al.*, 2012; Bhusnar *et al.*, 2014) which prevent the action of highly acute dose (10 Gy) of whole body gamma irradiation. The amelioration of the histopathological changes observed in cardiac tissues was associated with a significant improvement in oxidative stress and MDA suggesting that EESR protect cardiac tissues from radiation due to its anti-inflammatory and antioxidant activities.

## CONCLUSION

The present work documents that treatment with EESR would protect from radiation-induced cardiotoxicity probably due to its considerable antioxidant and anti-inflammatory effects.

### *Conflict of interest statement:*

The authors report no conflicts of interest. The

authors alone are responsible for the content and writing of the paper.

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