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The Protective Effect of *Emblica officinalis* on Cardiac Dysfunction in Gamma-Irradiated Male Albino Rats

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***Emblica officinalis* (EO) is a plant with diverse ethnical medicinal uses. The plant has been explored for diverse pharmacological actions. Here it was planned to screen the radio-protective activities of its fruit powder. Four groups of male albino rats were used: 1- Control: untreated group. 2- Irradiated: animals exposed to a single dose of whole-body gamma-irradiation (6Gy). 3- Eo group: given daily EO fruit powder dissolved in distilled water at a dose of 750mg/kg b.wt., for 30 days, intragastrically. 4- EO+ Irrad. group: given EO (as group 3), the last dose being 2 hours before irradiation. Blood and heart tissue samples were collected after 2hrs and 2 weeks post irradiation. Reduced glutathione (GSH) content and malondialdehyde (MDA) levels were measured in cardiac mitochondrial fraction. Xanthine oxidase (XO) and Xanthine dehydrogenase (XDH) activities and the level of advanced oxidation protein products (AOPP) were measured in the cytosolic fraction of heart tissue. Atrial natriuretic peptide (ANP) and creatine phosphokinase (CPK) activity were measured in plasma. Cardiac cytosolic glucose-6-phosphate dehydrogenase (G6 PDH) and Lactate dehydrogenase (LDH) activities were determined. It could be concluded that EO administration pre-irradiation, improved the disturbances induced in the heart by irradiation.**

Introduction

It is well known that oxidant by-products of normal metabolism such as free radicals and reactive oxygen species (ROS) in excess can cause extensive damage to DNA, proteins and lipids [1]. Exposure to ionizing radiation causes many health hazardous effects. Such exposure produces biochemical lesions that initiate a series of physiological symptoms. Overproduction of free radicals and ROS such as superoxide (O_2^-), hydroxyl radical (OH^-) and hydrogen peroxide (H_2O_2), induced by exposure to ionizing radiation, cause oxidative stress, in turn leading to lipid peroxidation in cell membrane and damage to cellular activities, leading to a number of physiological disorders and dysfunction of cells and tissues [2].

High doses of radiation applied to the heart during radiotherapy, used in breast cancer, Hodgkin's disease or childhood cancers, increase cardiovascular incidence and mortality. Epidemiological studies indicated that much lower irradiation doses typical of occupational, medical or environmental exposures also increase the risk of cardiovascular disease (CVD), several decades after the exposure [3].

Natriuretic peptides [atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)] are synthesized in cardiac tissue. Their release from the heart has the immediate biologic effect of increasing electrolyte and water excretion in the kidney, in addition to their action in cardioprotection [4].

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Emblica officinalis Gaertn (commonly known in India as Amla, Syn. *Phyllanthus emblica* L.; Family: Euphorbiaceae) is regarded as "one of the best rejuvenating herbs" in the Ayurveda: an Indian traditional medicinal science. *Emblica officinalis* (EO) primarily contains tannins, alkaloids, phenolics, aminoacids, carbohydrates and flavonoids. Vitamin C in EO accounts for approximately 45-70% of the antioxidant activity [5].

The EO fruit extract has been reported to possess many pharmacological activities for the treatment of a number of diseases, and is a constituent of many hepatoprotective formulations. Moreover, several recent reports revealed that the fruit extract of EO protects against radiation [6].

Materials and Methods

In this study, 48 adult male albino rats, weighing about 180 ± 20g, were used. They were obtained from the animal house unit of the NCRRT, Cairo. The animals were housed in plastic cages, kept under normal temperature, pressure, humidity, good ventilation and illumination conditions.

Irradiation process

Whole-body gamma irradiation was performed as a single dose level (6 Gy); using a Cesium- 137 Gamma cell-40 ventilated irradiator at the NCRRT. The dose rate was 0.708 rad /sec at the time of the experiment.

Emblica Officinalis (EO) treatment

EO fruit powder (purchased from Apex International Company, Jaipur, India) was dissolved in distilled water, and given to rats by gaveging through a stomach tube. Rats received a daily dose of 750 mg/kg body weight according to [7], daily for 30 days. The last dose being given two hours before irradiation.

Experimental design

The animals were categorized into four main groups as follows:

1- **Control Group**: non-irradiated rats.
2- **Irradiated Group**: exposed to a single dose of whole body γ- irradiation (6Gy).
3- **EO Group**: animals were administered **EO** orally daily for 30 days.
4- **EO + Irradiation Group:** animals given **EO** orally, the last dose being two hours before irradiation.

Blood and tissue sampling

All animals were ether anesthesized before blood sampling was performed by heart puncture, using heparinized syringes. Blood was centrifuged and the separated plasma was used for the determination of plasma creatine phosphokinase and plasma atrial natriuretic peptide. Heart was excised and perfused in saline. Two-time intervals were chosen for tissue (heart) sampling: after 2 hours and 14 days post irradiation or post administration of **EO**.

Isolation of mitochondrial fraction

The mitochondrial fraction of the heart tissue was isolated according to the method of [8].

Biochemical analyses

The lipid peroxidation (LPO) end product (Malondialdehyde, MDA) was assayed as a marker of oxidative stress in cardiac mitochondrial fraction according to [9], glutathione (GSH) was estimated based on the method of [10] in cardiac tissue. Xanthine oxidase (XO) and xanthine dehydrogenase (XDH) activities were assayed in cytosolic fraction of cardiac tissue as described by [11] with modification. Advanced oxidation protein products (AOPP) concentration was measured in cytosolic fraction of cardiac tissue according to [12].

Creatine phosphokinase (CPK) activity in plasma, was determined by a kinetic method according to [13], using a commercial kit. The activities of glucose-6-phosphate dehydrogenase activity (G6PDH) and lactate dehydrogenase (LDH) were determined in the cytosolic fraction of cardiac tissue, by a kinetic method according to [14] and [15] respectively, using commercial kits. Plasma rat atrial natriuretic peptide (ANP) concentrations were estimated using a microplate ELISA kit (product code: CSB-E12982r), according to [16].

Statistical analysis

The SPSS computer program (version 20) was used for the analysis of data. Data were analyzed using one-way analysis of variance (ANOVA) followed by a post Hoc, LSD test. The data were expressed as mean ± standerd error (SE).

Results and Discussion

Data of the present study revealed high levels of malondialdehyde (MDA) in cardiac mitochondrial fraction after exposure to 6 Gy gamma radiation, compared to the control.

This was accompanied by a remarkable decrease of reduced glutathione (GSH) content in cardiac mitochondrial fraction Table (1) at the two time intervals examined. Such observations reflect the extent of induced damage, represented by increased LPO and depression of the antioxidant system. These results coincide with the findings of several authors [3, 17, 18] who recorded a significant depletion in the antioxidant system, parallel to the enhancement of lipid peroxidation, after whole-body gamma irradiation.

Exposure to ionizing radiation increases the production of ROS [19], and directs the irradiated cells into a state of oxidative stress, that has been implicated in a variety of natural and pathological processes. They attributed this condition to the interaction of free radicals with polyunsaturated fatty acids in the phospholipids' portion of cellular membranes. The significant reduction in GSH content, following radiation exposure in the present study, could depend on the explanation of [20] who stated that an enhanced utilization of the antioxidant system occurs, as an attempt to detoxify the free radicals generated by radiation. This could be due to oxidation of its SH-group, resulting from a decrease in glutathione reductase activity [21].

administration of EO before irradiation significantly decreased cardiac MDA levels with elevations in GSH content, compared to the irradiated group Table (1)**.**

The anti-lipoperoxidative property of EO fruit powder, may be due to its rich flavonoids and polyphenol content. It is well known that flavonoids and polyphenols are natural anti-oxidants [22].

More recently, epidemiological studies have revealed that the intake of flavonoids is inversely associated with the risk of coronary heart disease. Thus, the antioxidative effect of EO may be due to its ability to combat the oxidative stress by quenching free radicals generated in the body as a result of ionizing radiation**.** EO may also act by triggering the secretion of the anti-oxidant enzymes: superoxide dismutase, catalase, and glutathione peroxidase, which in turn alleviate the oxidative damage [23].

Table (1): Effect of oral administration of Emblica officinalis (EO) (750mg/kg b.wt.) and/or γ-irradiation (6Gy) on cardiac mitochondrial malondialdehyde (MDA) concentration (µM/g) and glutathione (GSH) content (mg/g)

Parameter / Animal groups	MDA (µM/g)		GSH (mg/g)	
	2 hours	2 weeks	2 hours	2 weeks
Control	11.67±0.51	11.67±0.51	28.77±0.72	28.77±0.72
Irrad.	15.05±0.16 a***	19.28±0.32 a***c***	20.05±0.53 a***	16.41±0.51 a***c**
EO	5.67±0.29 a***	8.50±0.93 a***c***	31.93±1.53 a*	29.13±1.05 c*
EO+Irrad.	13.28±0.23 a**b**	16.57±0.23 a***b***c***	24.60±0.59 a**b**	22.92±1.20 a***b***

Each value represents Mean ± S.E. for 6 rats. a= significantly different from control group. b= significantly different from irradiated group c= significantly different from 2 hours of respective group
*: $p< 0.05$ **: $p< 0.01$ ***: $p< 0.001$

In the present study, whole-body gamma irradiation, at a dose level of 6 Gy, caused an increased activity of XO with a decreased XDH activity Table (2). The results are compatible with previous findings [24], that ionizing radiation induces the conversion of XDH into XO. This transformation can occur through irreversible proteolytic cleavage or reversible oxidation of sulfhydryl residues on XDH [25]. Experimental evidence [26] indicated that radiation promotes irreversible XO conversion by demonstrating that the serine protease inhibitor, phenylmethylsulfonyl fluoride, impaired radiation-induced XO activity. Also, in the present study, there was an increased level of advanced oxidation protein products (AOPP) in the cardiac mitochondrial fraction of the irradiated group Table (2), at the two time intervals examined. This result is in agreement with the finding of [27], which was suggested to be due to the interaction of proteins with ROS [28].

Results of the current study revealed that administration of EO before irradiation induced a significant decrease in cardiac XO activity with an increase in XDH activity Table (2), at the two time intervals, compared to the irradiated group**.**

These present results are consistent with other findings [29]. Elevation in xanthine oxidoreductase activity and lowering in superoxide dismutase activity, were observed in the intestine of mice exposed to whole-body gamma irradiation, which, however, reverted back to those levels of controls, when animals were fed triphala (a herbal formulation containing EO fruits) for 7 days prior to irradiation. This suggested the prevention of cellular oxidative damage, caused by whole-body radiation exposure, by feeding animals with triphala, thus, indicating its potential to develop into a novel herbal radio-protector for practical applications [30].

Also, administration of EO before irradiation showed significant decrease in cardiac AOPP concentrations at the two-time intervals examined, compared to the irradiated group Table (2)**.**

The elevation of creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) activities, represent a powerful and sensitive predictor of increased cardiac complications [17]. In the present study, whole-body gamma irradiation of rats induced a significant increase in the activity of LDH in cardiac cytosolic fraction Table (4), as well as an elevation in plasma CPK activity Table (3), throughout the two-time intervals examined. These results are consistent with those recorded in other studies [3, 31, 32].

The above results could be explained on the basis that ionizing radiation induces alterations in the dynamics of membranes' permeability, due to the excessive production of free radicals and lipid peroxides, causing cellular membrane damage and leakage of cytosolic enzymes out of the injured cells [32].

Table (2): Effect of oral administration of Emblica officinalis (EO) (750mg/kg b.wt.) and/or γ-irradiation (6Gy) on cardiac cytosolic xanthine oxidase (XO) activity (U/L) and xanthine dehydrogenase (XDH) activity (U/L) and advanced oxidation protein products (AOPP) concentration (µmol/L)

Parameter / Animal Groups	XO (U/L)		XDH (U/L)		AOPP (µmol/L)	
	2 hours	2 weeks	2 hours	2 weeks	2 hours	2 weeks
Control	0.23±0.012	0.23±0.012	0.29±0.013	0.29±0.013	148.47±2.00	148.47±2.00
Irrad.	0.39±0.015 a***	0.51±0.013 a***c***	0.18±0.013 a***	0.19±0.015 a***	163.90±1.58 a***	183.90±1.24 a***c***
EO	0.20±0.009	0.28±0.015 a*c**	0.29±0.020	0.27±0.019	139.26±1.14 a**	144.45±0.98 c*
EO+Irrad.	0.30±0.016 a***b***	0.43±0.013 a***b***c***	0.22±0.015 a***b***	0.24±0.017 a***b***	157.07±1.5 a**b**	174.71±1.4 a***b***c***

Each value represents Mean ± S.E. for 6 rats. a= significantly different from control group. b= significantly different from irradiated group. c= significantly different from 2 hours of respective group *: $p< 0.05$ **: $p< 0.01$ ***: $p< 0.001$

Table (3): Effect of oral administration of *Emblica officinalis* (EO) (750mg/kg b.wt.) and/or γ-irradiation (6Gy) on plasma creatine phosphokinase (CPK) activity (U/L) and plasma atrial natriuretic peptide (ANP) concentration (pg/ml)

Prameter / Animal Groups	CPK (U/L)		ANP (pg/ml)	
	2 hours	2 weeks	2 hours	2 weeks
Control	100.42±1.42	100.42±1.42	21.65±1.70	21.65±1.70
Irrad.	153.70±2.19 a***	167.79±2.34 a***c***	32.86±0.95 a*	56.28±1.80 a***c***
EO	95.46±2.06 a*	98.23±1.32	19.87±1.30	22.05±2.40
EO+Irrad.	140.44±1.78 a***b***	156.20±3.15 a***b***c***	28.26±1.81 a*b*	39.60±0.99 a***b***c**

Each value represents Mean ± S.E. for 6 rats. a= significantly different from control group. b= significantly different from irradiated group. c= significantly different from 2 hours of respective group *: $p< 0.05$ **: $p< 0.01$ ***: $p< 0.001$

Results of the present study showed a significant decrease in the activity of both plasma CPK Table (3) as well as cardiac cytosolic LDH Table (4), throughout the two-time intervals examined, in rats administered EO before irradiation, compared to the irradiated group**.** Earlier work [33] showed a significant decrease in serum CPK and LDH activities after EO fruit juice treatment of diabetic rats, this revealed that EO prevents the diabetes-induced myocardial dysfunction**.** Furthermore, administration of amla (100, 250 and 500 mg/kg) for 30 days showed a cardioprotective potential in isoproterenol-induced cardiotoxicity in rats, through ameliorating the levels of antioxidant enzymes, as well as CPK and LDH, reflecting antoxidant free radical-scavenging activity [34].

The current study showed significant decreases in cardiac cytosolic G6PDH activities, 2 hours and 2 weeks post-irradiation Table (4)**.** This may be due to the alterations of the redox state of cells in the irradiated rats, which result in a decreased formation of NADPH, and in turn, inactivates G6PDH [35]. The results are in agreement with other findings [36, 37].

Oral administration of EO alone and before irradiation significantly increased the activity of cardiac mitochondrial G6PDH Table (4), throughout the two-time intervals, compared to the irradiated group. An earlier study [38] showed that EO improved the activity of G6PDH when administrated after hexachlorocyclohexane (HCH)-induced oxidative stress. Those authors suggested that amla appears to mitigate the chemically-induced stress effects, by normalizing the activities of catalase, G6PDH, sodium dismutase (SOD) and gamma-glutamyl transferase (GGT)**.** Thus, leading to decreased peroxides and attenuation of the adverse effects of HCH-induced stress**.**

The present study showed an increase in ANP levels, that was more prominent 2 weeks after exposure of rats to 6 Gy gamma irradiation Table (3). Another study [39] showed an increase in BNP level, after whole-body gamma irradiation with a fractionated dose of 15 Gy. In earlier trials, elevated pressures in the left atrium and left ventricle, as well as increased secretion of ANP and BNP, were observed after thoracic irradiation [40, 41].

Data of the present study showed that EO administration before irradiation, caused significant decreases in the elevated levels of plasma ANP, observed in the irradiated group (Table 3). Phytochemical analyses indicated, as previously mentioned [22], that amla is rich in flavonoids, saponins, ascorbic acid and proteins. Furthermore, a number of plant components (such as terpenoids, tannins, fatty acids and flavonoids) are known to decrease the elevation in blood pressure [42].

Table (4): Effect of oral administration of *Emblica officinalis* (EO) (750mg/kg b.wt.) and/or γ-irradiation (6Gy) on cardiac cytosolic glucose-6-phosphate dehydrogenase (G6PDH) activity (U/L) and lactate dehydrogenase (LDH) activity (U/L)

Prameter / Animal Groups	G6PDH(U/L)		LDH (U/L)	
	2 hours	2 weeks	2 hours	2 weeks
Control	5.52±0.11	5.52±0.11	149.13±3.70	149.13±3.70
Irrad.	3.81±0.075 a***	2.09±0.08 a***c***	198.95±4.09 a***	233.69±4.05 a***c***
EO	6.25±0.09 a***	6.07±0.12 a***	143.27±3.40	154.51±2.67
EO+Irrad.	4.70±0.08 a***b***	3.06±0.07 a***b***c***	180.23±3.11 a***b***	225.10±2.93 a***b***c***

Each value represents Mean ± S.E. for 6 rats. a= significantly different from control group. b= significantly different from irradiated group. c= significantly different from 2 hours of respective group***: $p< 0.001$

Conclusion

EO exerts clear antioxidant and cardioprotective effects which were more prominent when administrated before exposure to radiation. This protective effect was brought about by protecting the cellular vital components from ROS generated by gamma radiation.

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