

## **Role of Cardamom (*Elettaria cardamomum*) in Ameliorating Radiation Induced Oxidative Stress In Rats**

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**Received: 2/6/2012**

**Accepted: 10/7/2012**

### **ABSTRACT**

Radiation is one of the most widespread sources of environmental stress in living environment which cause oxidative stress and metabolic changes. The present study aims to evaluate the antioxidant effect of Cardamom (*Elettaria cardamomum*) on gamma radiation-induced oxidative damage in liver and heart tissues. The study was conducted on forty (40) rats which were classified into four equal groups. Group1: Control group, Group. 2: rats given cardamom in basal diet Group3: Irradiated rats, rats were subjected to whole body gamma irradiation at 6 Gy delivered as single exposure dose. Group 4: irradiated +cardamom: rats receiving cardamom for 4 weeks and irradiated The animals were scarified 24h after irradiation. Irradiated animals had significant increase in oxidative stress markers in liver and heart tissues expressed by significant increase of malondialdehyde (MDA) content associated to significant depletion of superoxide dismutase (SOD) , catalase (CAT) activities, and reduced glutathione (GSH) content . Hepatic and cardiac changes included significant increases of serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) , total cholesterol(TC), triacylglycerol(TAG), low-density lipoprotein -cholesterol(LDL-C), and iron concentration. While, a significant decrease in high-density lipoprotein-cholesterol (HDL-C), manganese and copper were observed. Addition of cardamom to the basal diet prior to gamma radiation, improved the tested parameters. So it is a therapeutic alternative for oxidative stress, hyperlipidaemia and trace elements changes. . The data obtained in this study suggest that cardamom may prevent liver and heart from radiation-induced damage.

*Keywords: Cardamom, gamma rays, liver and heart, rats.*

### **INTRODUCTION**

Human exposure to ionizing radiation has become inevitable with its vast application in diagnosis and industry. Everyone on earth is exposed to radiation either from natural background radiation medical or dental X-ray. Radiation damage is to a large extent caused by over production of reactive oxygen species (ROS) which cause disruption of membrane lipids leading to subsequent formation of peroxide radicals <sup>(1)</sup>. Lipid peroxidation is an ubiquitous phenomenon in the body under the influence of oxidative stress <sup>(2)</sup>. Efficient defense and repair mechanisms exist in living cells to protect against oxidant species. Among the enzymes involved in antioxidative defense are superoxide dismutases (SOD), glutathione peroxidases (GSH-Px), and catalase (CAT). SOD catalyzes the

reduction of  $O_2 \bullet^-$  to  $H_2O_2$ . The majority of  $H_2O_2$  is broken down to oxygen ( $O_2$ ) and water ( $H_2O$ ) by CAT. In addition to CAT, GSH-Px can also break down  $H_2O_2$  and any peroxides that form on lipids within the body<sup>(3)</sup> and<sup>(4)</sup>. The activity of GSH-Px depends on the presence of adequate amounts of reduced glutathione (GSH). Radiation decrease in antioxidant enzymes activities such as superoxide dismutase(SOD), catalase (CAT), glutathione S-transferase (GST), and glutathione peroxidase (GPx) which acts as a free radical scavengers are conditions associated with oxidative stress<sup>(5)</sup>.

Cardamom is a sweetly aromatic spice. Cardamom spice consists of whole or ground dried fruit of *Elettaria cardamomum* (Linn.) Maton, a herbaceous perennial of the ginger family (*Zingiberaceae*): *Ellettaria*, commonly known as green cardamom, has small, light green pods; and amomum, known as black cardamom, has larger, dark brown pods. Both species of cardamom can be used in cooking and for their health benefits<sup>(6)</sup>. It has been traditionally used to treat skin condition and in digestion. Cardamom oil is also used in cosmetics because of its cooling properties and because it's pale to colorless liquid can be easily incorporated into different solutions. Cardamom has been reported to possess antioxidant properties, increase levels of glutathione<sup>(7)</sup> and reduce LDL susceptibility to oxidation<sup>(8)</sup>.

## MATERIALS AND METHODS

Male albino rats (n=40) weighing 120-130 g were used. Animals were kept under good ventilation and illumination conditions and allowed balanced diet and tap water. The whole body of the animals was exposed to 6Gy, given at a dose rate of 0.84 Gy/min from the biological irradiator Gamma Cell-40, cesium-137 source (Atomic Energy Agency, Canada), and belonging to National Center for Radiation Research and Technology (NCRRT), Cairo.

Cardamom (*Elettaria cardamomum*) purchased from local market, Cairo, Egypt, was mixed with basal diet at a ratio of 2%. The basal standard diet was prepared in accordance with AIN-93 formulation<sup>(9)</sup>(Revees et al, 1993). The basal diet contains Casein, 10%; cellulose, 5%; corn oil, 10%; corn starch, 70%; salt mixture, 4% and vitamin mixture, 1%. The animals were grouped into 4 groups each of 10 rats

**Control:** rats considered as control animals received standard diet.

**Cardamom:** rats received standard diet + 2% cardamom for 4 weeks.

**Irradiated:** rats received standard diet for 4weeks ,then whole body exposed to ? irradiation at a dose of 6 Gy.

**Cardamom +Irradiated:** rats received standard diet + 2% cardamom for 4 weeks before whole body irradiation at 6 Gy.

### Biochemical analysis :

Animals were sacrificed 24hr post irradiation. Blood samples were collected and serum were separated by centrifugation at 3000 rpm for 15 minutes and stored frozen for biochemical analysis. Tissue sample of the liver and heart were accurately weighed and homogenized using homogenizer in a 10-fold volume of ice cold (20mM) tris-HCl buffer, pH 7.4.

The lipid peroxidation products of polyunsaturated fatty acids were estimated as thiobarbituric acid reactive substances, MDA according to<sup>(10)</sup> Ohkhawa, et al., (1979). Spectrophotometric determination of SOD was carried out according to<sup>(11)</sup> Minami and Yoshikawa (1979) and Catalase

(CAT) activity was determined according to the method described by <sup>(12)</sup> Johansson and Hakan Borg (1988)., glutathione content (GSH) was determined by the method of <sup>(13)</sup> Beutler et al, (1963). Serum total cholesterol was assayed by the method of <sup>(14)</sup> Richmond, (1973). The content of triglycerides (TG) was measured according to <sup>(15)</sup> Fossati and Prencipe, (1982), low-density lipoprotein-cholesterol (LDL-c) and high density lipoprotein-cholesterol (HDL-c) were assayed according to the methods of <sup>(16)</sup> Marchal, (1992) and <sup>(17)</sup> Demacker et al. (1980), respectively. The activity of lactate dehydrogenase (LDH) was determined according to <sup>(18)</sup> Burtis and Ashwood(1994). The quantitative determination of serum ALT and AST were done using the method of <sup>(19)</sup> Reitman and Frankle,(1974). ALP activity was estimated according to the method of <sup>(20)</sup> Kind and King [1954], Serum copper, iron and magnesium are determined calorimetrically using commercial spectrum diagnostic kits (Germany)) <sup>(21)</sup> (Clegg et al., 1981).

**Statistical analysis:**

The obtained results were subjected to statistical analysis using the standard analysis of variance as outlined by <sup>(23)</sup> Snedecor and Cochran (1989).

**RESULTS**

There were no significant differences between control and rats administrated cardamom in all parameters except for MDA of the heart that showed significant decrease.

In the present study the MDA levels in liver and heart tissues were significantly (P<0.05) increased, while GSH content, SOD and CAT activity were significantly (P<0.05) decreased in irradiated rats group, when compared to control. Tissues MDA levels showed a significant (P<0.05) decrease in rats treated with cardamom post whole body gamma irradiation, when compared to irradiated group. In addition ,no significant (P<0.05) increase in the GSH content was observed whereas, significant increase in the activity of CAT and SOD were observed in liver and heart tissues in rats administrated cardamom post irradiation as compared to irradiated rats (Table 1).

**Table 1: Effect of cardamom on MDA, GSH, CAT and SOD liver and heart tissue in different rats group**

Animal groups		control	cardamom	Irradiated	Cardamom + Irradiated
MDA(u mol/g) fresh tissue	Liver	30.95±1.06	28.37±0.39 <sup>o</sup>	47.41±1.79 <sup>a</sup>	33.91±0.89 <sup>o</sup>
	Heart	21.95±1.12	17.91±0.06 <sup>ab</sup>	38.98±2.70 <sup>a</sup>	32.97±1.90 <sup>ab</sup>
GSH (mg/g) fresh tissue	Liver	71.35±1.87	69.21±2.77 <sup>b</sup>	42.35±4.81 <sup>a</sup>	51.15±3.77 <sup>a</sup>
	Heart	62.27±1.95	59.71±2.81 <sup>b</sup>	45.12±4.35 <sup>a</sup>	50.91±3.21 <sup>a</sup>
Cat(U/g)fresh tissue	Liver	73.62±4.51	76.3±4.82 <sup>b</sup>	47.2±3.42 <sup>a</sup>	62.7±3.99 <sup>b</sup>
	Heart	51.4±1.8	52.1±4.9 <sup>o</sup>	31.9±3.6 <sup>a</sup>	43.2±2.8 <sup>o</sup>
SOD (U/g) fresh tissue	Liver	14.3±0.65	13.8±0.77 <sup>b</sup>	4.2±0.34 <sup>a</sup>	10.4±0.53 <sup>b</sup>
	Heart	86.4±7.1	88.6±8.9 <sup>b</sup>	54.1±4.9 <sup>a</sup>	71.3±4.3 <sup>ab</sup>

Each value represent mean of 10 rats ±SD

- a- significantly different from control at P < 0.05
- b- Significant difference compared to the irradiated group. at P < 0.05

As shown in Table ( 2) gamma irradiation significantly altered the lipid profile. The levels of Tc, TG and LDL-c were increased significantly, but there was a significant decrease in HDL-c level in irradiated rats group when compared to lipid fractions levels of the control. The prolonged treatment of cardamom before exposure to whole body gamma irradiation has significantly lowered the alteration in the serum lipid profile levels when compared with the irradiated rats and normalized HDL-c

**Table 2: Serum lipid metabolites (mg/dl) in different animal groups**

Animal groups	Tc (mg/dl)	TG(mg/dl)	LDL.c (mg/dl)	HDL.c(mg/dl)
<b>Control</b>	53.21±1.75	43.3±1.34	27.71±0.91	28±5.78
<b>Cardamom</b>	54.21±1.85 <sup>b</sup>	44.83±1.65 <sup>b</sup>	27.11±0.79 <sup>b</sup>	27±3.93
<b>Irradiated</b>	83.58±2.37 <sup>a</sup>	73.24±1.86 <sup>a</sup>	36.93±0.85 <sup>a</sup>	22±2.28 <sup>a</sup>
<b>cardamom + Irradiated</b>	73.52±1.36 <sup>a,b</sup>	47.16±1.09 <sup>b</sup>	32.1±0.93 <sup>a,b</sup>	26±2.29

Legend as table (1)

The data of the present study revealed that exposure of rats to 6 Gy gamma radiation induced a significant increase of serum AST, ALT, ALP and LDH activities as shown in table (3), whereas cardamom treatment before irradiation significantly depressed these levels compared to the irradiated groups

**Table 3: Serum AST, ALT (U/ml), ALP and LDH (U/L) activities in different animal groups.**

Animal groups	AST (U/ml)	ALT (U/ml)	ALP (U/L)	LDH(U/L)
<b>Control</b>	43.85±1.24	29.43±0.98	78.62±2.72	173±27.01
<b>Cardamom</b>	44.92±1.08 <sup>b</sup>	28.94±0.95 <sup>b</sup>	85.97±5.01 <sup>b</sup>	169±43.20 <sup>b</sup>
<b>Irradiated</b>	63.2±2.23 <sup>a</sup>	39.16±1.34 <sup>a</sup>	153.65±6.85 <sup>a</sup>	410±48.01 <sup>a</sup>
<b>cardamom + Irradiated</b>	51.09±1.81 <sup>a,b</sup>	32.01±1.03 <sup>b</sup>	110.21±2.71 <sup>a,b</sup>	279±56.31 <sup>a,b</sup>

Legend as table (1)

The results in table (4) revealed that cardamom treatment alone induced significant increase in manganese ,whereas exposure to 6Gy irradiation significantly reduced copper and manganese and elevated iron compared to control levels. Cardamom treatment before irradiated normalized the levels of trace elements levels of metals (Cu, Mn, Ir) in serum when comparing with irradiated rats.

**Table 4-Serum Copper, Manganese and Iron of levels in different animal groups**

Animal groups	Control	Cardamom	Irradiated	Cardamom + Irradiated
<b>copper (µg /dL)</b>	88.6±1.02	90.21±1.23	83.1±2.7 <sup>a</sup>	86.1±2.3
<b>Manganese(µg/dL)</b>	2.05±0.02	2.21±0.09 <sup>o</sup>	1.54±0.07 <sup>a</sup>	1.91±0.13
<b>Iron(µg/dL)</b>	275±4.02	282±3.9 <sup>o</sup>	361±7.07 <sup>a</sup>	315±5.3

Legend as table (1)

### DISCUSSION

Exposure of mammals to ionizing radiations, leads to the development of a complex, dose-dependent series of changes, including injury to different organs which cause changes in the structure and function of cellular components, resulting in tissue damage and death. Oxidative stress with subsequent production of reactive oxygen species (ROS) has been postulated as one of the mechanisms of radiation toxicity<sup>(23)</sup>. In the present study, a significant increase (P=0.05) in the level of MDA, associated with a significant decrease (P=0.05) in the activity of SOD, CAT and in the content of GSH was recorded in the liver and heart of irradiated rats. The elevated level of TBARS might probably result from the interaction of the excess of •OH, resulting from the radiolysis of water upon exposure to ionizing radiation, with polyunsaturated fatty acids in the phospholipids portion of cellular membranes<sup>(3)</sup>. The significant decrease (P=0.05) in the activity of SOD and CAT might be, also, attributed to the excess of ROS, which interacts with the enzyme molecules causing their denaturation and partial inactivation<sup>(24)</sup>. The depletion in GSH may be due to its reaction with free radicals resulting in the formation of thyl radicals that associate to produce oxidized glutathione (GSSG). GSH can, also, react with peroxynitrite anion (ONOO-) to form S-nitrosoglutathione<sup>(25)</sup>.

In the present study, a significant increase (P=0.05) in the level of Tc, TG and LDL-C associated with a significant decrease (P=0.05) in the HDL-C was recorded in serum of irradiated rats. The hyperlipidaemic state observed after irradiation could be attributed to the mobilization of fats from the adipose tissue to the blood stream<sup>(26)</sup>, in addition to mitochondrial dysfunction<sup>(27)</sup>. Hypercholesterolaemia is an important risk factor for cardiovascular disease<sup>(28)</sup>. Oxidation of LDL-C accelerates the growth of fatty streaks in blood vessel walls and the formation of plaque<sup>(29)</sup>. Toxic aldehydes formed in lipid oxidation react with the apo lipoprotein B of the LDL particle to produce a novel epitope that is recognized by macrophage receptors, resulting in the formation of foam cells and arteriosclerotic plaques and increased risk of heart disease and stroke<sup>(30)</sup>. Irradiation induces hyperlipidemia through cell membrane destruction, enhancement of lipid metabolism, cholesterol release and triglycerides synthesis<sup>(31)</sup>. Free radicals destruct cell membranes and enhance cholesterol release and increase lipid peroxidation<sup>(32)</sup>.

Increased triglycerides after irradiation might result from inhibition of lipoprotein lipase activity leading to reduction in uptake of triglycerides by adipose cells<sup>(33)</sup>. The hypercholesterolemia and hypertriglyceridemia might be attributed to an increase in the activity of 3-hydroxyl methyl glutaryl COA, as an early reaction necessary for the restoration of biomembranes<sup>(34)</sup>.

In the present study, a significant increase (P=0.05) of AST, ALT, ALP and LDH activities, were recorded in the serum of Irradiated rats. The increase of LDH indicate the severity of radiation

induced necrotic damage of the myocardial membrane and the release of LDH enzyme from damaged heart tissue into the blood stream and alterations in dynamic permeability of cardiac cell membranes due to the excessive production of free radicals and lipid peroxides that caused cellular membrane damage and leakage of cytosolic enzymes<sup>(35)</sup>. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) as reported, are specific liver enzymes that increase in hepatic diseases and toxic damage of liver cells<sup>(36)</sup>. In the present study, their increased levels could be referred to the destruction of the radiosensitive tissues of the hepatocytes<sup>(37)</sup>.

In the present study the decrease in Copper and Manganese and the increase in iron level in irradiated rats may be due to oxidative stress inducing proteolytic modification of ferritin and transferrin<sup>(38)</sup>. Iron overload is associated with liver damage characterized by massive iron deposition in hepatic parenchymal cells, leading to fibrosis and eventually to hepatic cirrhosis. Accumulation of iron induced hepatotoxicity might be attributed to its role in enhancing lipid peroxidation. Free iron or low molecular iron or chelatable iron pool facilitates the decomposition of lipid hydroperoxides resulting in lipid peroxidation and induces the generation of •OH radicals and also accelerates the non enzymatic oxidation of glutathione to form O<sub>2</sub> • radicals<sup>(39)</sup>. Copper is absorbed into the intestine and transported by albumin to the liver. Copper is carried mostly in the blood stream on a plasma protein called ceruloplasmin.. The decrease of metals level might result from diarrhea due to the radiation injuries of intestinal mucosal membrane<sup>(40)</sup>.

Natural antioxidants that are present in herbs and spices are responsible for inhibiting or preventing the deleterious consequences of oxidative stress. Spices and herbs contain free radical scavengers like polyphenols, flavonoids and phenolic compounds. Free radical scavenger activity is elicited to cardamom (*Elettaria cardamomum* (Linn.) Maton,<sup>(41)</sup>. The present study demonstrates that administration of cardamom protected against the oxidative stress and tissue damage produced by gamma radiation. Antioxidants have great potential in preventing the oxidative diseases such as chronic fatigue, premature ageing symptoms, degenerative cardiovascular and neurovascular diseases associated with ageing<sup>(42)</sup>. The 1,8-cineol oil and alpha-terpineol, protocatechualdehyde and protocatechuic acid present in the seeds of cardamom showed antioxidant activity<sup>(43)</sup> and has potential health benefits by inhibiting lipid peroxidation<sup>(44)</sup>. The seed possess antioxidant properties attributed to their ability to activate antioxidant enzymes<sup>(45)</sup>.

The modulation of oxidative stress by cardamom is expressed in its ability to suppress lipid peroxidation due to the presence of polyphenol content<sup>(46)</sup>, and increase antioxidant enzyme activities<sup>(7)</sup>. The results are consistent with the finding of<sup>(47)</sup> that cardamom inhibits lipid peroxidation via its strong reducing power and superoxide radical scavenging activity.

The hepatoprotective effect of cardamom in irradiated animals was reflected by the significantly lower level of liver enzymes. Serum lipid profile, and, MDA, in addition elevated levels of SOD, CAT and GSH.

The decrease of serum triglyceride and cholesterol levels in rats receiving cardamom in their diet might be attributed to the inhibition of hepatic –HMG-CoA reductase activity, resulting in lowering hepatic and serum cholesterol levels<sup>(48)</sup>. In addition to its effectiveness in reducing LDL-c susceptibility to oxidation<sup>(49)</sup>,<sup>(50)</sup>,<sup>(8)</sup> and<sup>(51)</sup>.

*Elettaria cardamomum* was reported to exert a protective effect against acute or severe stress induced myocardial damages<sup>(45)</sup>. Regular consumption of greater cardamom may therefore be useful in treatment of patients with Ischemic Heart Disease (IHD), facing regular stressful conditions.

In the present study, cardamom significantly lowered the radiation induced elevation in the levels of AST, ALT, ALP and LDH enzyme. These results are in agreement with<sup>(8)</sup>. Moreover<sup>(52)</sup> found that treatments with the extract of *Elettaria cardamomum* seeds significantly reduced AST, ALT and, ALP levels indicating their hepatoprotective activity.

Pretreatment with cardamom improved the trace elements (copper, manganese and iron) contents of serum.<sup>(53)</sup> reported that cardamom seeds contain copper (7.4 mg kg<sup>-1</sup>) and iron (111.2 mg kg<sup>-1</sup>). The elements in cardamom improved nutrient status and appetite, enhanced the metabolism of elements, phytochemicals and phenolic antioxidant compounds which increased the activity or the synthesis of endogenous antioxidant enzymes<sup>(54)</sup> and<sup>(55)</sup>.

In conclusion, cardamoms exert radioprotective effects against ionizing radiation induced oxidative stress and organ injury in the liver and heart.

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