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The Protective Effect of *Coriandium sativum* Extract on Hepato-renal Toxicity Induced in Irradiated Rats

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Authors' contributions

All the authors have cordially supported the work and preparation of manuscript. Authors OAG and HAF designed the study and experimental protocols. Authors HAF and NHS managed the biochemical analyses of the study. Author OAG did the computational work with interpretations of the results and prepared the first draft of the manuscript. All the authors have read and approved the final manuscript

Original Research Article

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ABSTRACT

Aim: The aim of this study was to examine the effect of ethanolic extract of coriander leaves as a potent *in vivo* antioxidant agent in an effort of finding possible sources of antioxidants for future use in food and pharmaceutical formulations.
Study Design: Randomized controlled experiment.
Place and Duration of Study: Experimental Animal Unit, Drug Radiation Research Department, National Center for Radiation Research and Technology, Cairo Egypt.
Methodology: Antioxidant activity of ethanol extract of coriander leaves was estimated by oxidative stress induced by radiation exposure with the dose of 4 Gy, Silymarin was used as a reference antioxidant drug in female albino rat.
Results: Results of experiment revealed that radiation exposure caused a significant increase in serum caspase3 (0.870± 0.086), alanine transaminase (ALT) activity (24.43± 5.02) as well as urea (42.53± 6.11) and creatinine (0.865± 0.064) levels with an increase in liver and kidney lipid peroxidation (MDA) (307.0± 29.22 & 285.5± 48.93) respectively, while decrease in serum albumin (3.003± 0.355), protein (8.66± 0.436) as well as glutathione (GSH) contents of liver and kidney tissues (63.24± 12.19 & 17.38± 1.414) were estimated respectively. In addition serum globuline level and albumin /globuline ratio

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showed no significant changes. On the other hand, the administration of coriander (600 mg/kg bw) and silymarin (70 mg/kg bw) pre-treatment effectively prevented these alterations and maintained the antioxidant status.
Conclusion: Data from present results revealed that *Coriandum Sativum* act as an antioxidant agent due to its free radical scavenging and cytoprotective activity.

Keywords: Coriandium satvium; silymarin*; Hepato-renal toxicity; MDA; albumin/ globulin ratio.*

1. INTRODUCTION

Since very old times, herbal medications have been used as a rebate of symptoms of disease [1]. Despite the great advances observed in modern medicine in recent decades, plants still make an important contribution to health care. Much interest, in medicinal plants however, emerge from their long use in folk medicines as well as their prophylactic properties, especially in developing countries. Large number of medicinal plants has been investigated for their antioxidant properties. Natural antioxidants either in the form of raw extracts or their chemical constituents are very effective to prevent the destructive processes caused by oxidative stress [2]. Although the toxicity profile of most medicinal plants have not been thoroughly evaluated, it is generally accepted that medicines derived from plant products are safer than their synthetic counterparts [3].

Coriandrum sativum L. is an important spice crop that occupies a prime position in flavouring substances. Coriander is available throughout the year providing a fragrant flavour, originated around the Mediterranean and is cultivated mainly in the tropical areas. They are used in medicine as carminative and diuretic agents. They are also used in the preparation of many house hold medicines to cure bed cold, seasonal fever, nausea, and stomach disorders. Coriander seeds contain petroselinic acid, linoleic acid, oleic acid and palmitic acid [4]. Major components of essential oil are linalool, a-pinene, camphor and geraniol [4]. Coriander oil is used in baked foods, spice and also functions as an essential ingredient in curry mixes [5].

Important evidence has accumulated and indicated key roles for reactive oxygen species (ROS) and other oxidants in causing numerous disorders and diseases. The evidence has brought the attention of scientists to an appreciation of antioxidants for prevention and treatment of diseases, and maintenance of human health [6]. Human body has an inseparable antioxidative mechanism and many of the biological functions such as the anti-mutagenic, anti-carcinogenic, and anti-aging responses originate from this property [7]. Antioxidants stabilize or deactivate free radicals, often before they attack targets in biological cells [8]. Recently interest in naturally occurring antioxidants for use in food, cosmetic and pharmaceutical products has increased considerably. This is because they possess multi-usefulness not only in their abundance but also the quantity of activity providing a massive scope in correcting imbalance [9].

Radiation is an important inducer of oxidative stress. It is commonly used for diagnostic and therapeutic purposes. The kidney is a highly susceptible organ to damage caused by ROS, due to the abundance of long-chain-polyunsaturated fatty acids. Chronic oxidative stress after total body irradiation is thought to be the cause of radiation nephropathy in rats [10]. An imbalance between ROS and the inherent antioxidant capacity of the body, directed the use of dietary and /or medicinal supplements particularly during the oxidative stress. Studies on

herbal plants, vegetables, and fruits have indicated the presence of antioxidants such as phenolics, flavonoids, tannins, and proanthocyanidins. The antioxidant contents of medicinal plants may donate the defence they offer from disease [7]. Liver and kidney damaged induced by radiation exposure remain a serious health problem. It is well known that free radicals cause cell damage through mechanisms of covalent binding and lipid peroxidation with subsequent tissue injury. Antioxidant agents of natural origin have attracted distinctive concern because of their free radical scavenging efficiency [11]. The use of medicinal plants with high level of antioxidant constituents has been suggested as an effective therapeutic tactic for hepato-renal damages [12].

The search for novel natural antioxidants of plant origin has ever since increased. It is not known which constituents of plant are associated in reducing the risk of chronic diseases, but antioxidants appear to play a major role in the protective effect of plant medicine. The present study was designed to investigate *in vivo* antioxidant activities of ethanolic extract of Coriander leaves. Results were compared to a standard antioxidant drug silymarin.

2. MATERIAL AND METHODS

2.1 Plant Collection

Coriandrum sativum leaves were kindly supplied from Medicinal and Aromatic Plants Department, National Research Centre, Cairo, Egypt

2.2 Extract Preparation

The dried and powdered leaves (200 g) were extracted successively with 70% ethanol in a soxhlet extractor for 48 hours at 60ºC. After extraction, the solvent was evaporated to dryness at 50-55ºC using a rotary evaporator. Finally, the lyophilization of the dried extract was done to yield the Coriander [13]. The extract was stored at 4°C till the analysis of different parameters.

2.3 Chemicals

The chemicals used in this experiment were obtained from Sigma Chemical (USA). Kits used in this experiments were purchased from Bio-Diagnostics (UK).

2.4 Radiation Process

A single dose whole body irradiation (4 Gy) was performed with rats, using gamma rays by Cesium 137 irradiation unit, National Center for Radiation Research and Technology (NCRRT), with the dose rate 0.7488 rad/ sec. The gamma cesium cell was calibrated by alanine dosimetry relative to a primary standard. Correction were made daily for humidity, temperature, and barometric pressure.

2.5 Animals and Treatment

Studies were carried out using female albino rats weighing 120±10 g. The animals were grouped and housed in polyacrylic cages with not more than six animals per cage and maintained under standard laboratory conditions. They had free access to standard diet and

fresh water *ad libitum*. Twenty four rats were divided randomly into four groups, each contain six animals. *Group (I)* the controls; fed with a normal diet for one week. *Group II* (induction controls) irradiated with 4 Gy single dose of gamma rays. *Group III* and *IV* received Coriander (600 mg/kg bw; orally) and silymarin (70 mg/kg, orally), as the standard reference drug, once daily for two weeks respectively and then these groups was exposed to γ-radiation in the last day of the oral administration of both treatments. Two days later, all the animals were anesthetized in an ether chamber. Blood sample was collected from heart left ventricle. Liver and kidney were removed, cleaned with normal saline solution and placed at 4°C ice cold saline for biochemical analysis. All experimental procedures involving animals were conducted in accordance with the guidelines set by the European Economic Community (EEC) regulations (Revised Directive 86/609/EEC) and approved by the Ethical Committee at the Faculty of Pharmacy, Cairo University.

2.6 Biochemical Analysis

Blood samples were centrifuged using universal 16R/ Germany centrifuge at 3000 rpm for 15 min; clear serum was collected and stored in a refrigerator. The quantitative detection of activated caspase3 is considered to be a significant marker for the apoptotic of cell death. Serum ALT activities as well as urea, creatinine, albumin, total protein and globulin levels were estimated. Liver and kidney were excised from the rat, and then homogenization was carried out using a homogenizer (universal laboratory AID type MPW- 309, Poland). Activity of caspase 3 was estimated according to the method of Chentouf and his colleagues [14]. ALT activity was done using kit according to the method of Reitman and Frankel [15]. Urea was estimated by kits according to the method of Halled and Cook [16]. Creatinine level was measured according to the method of Henery [17]. Albumin level was determined using a kit of Doumas and his colleagues [18], and the total protein was estimated by means of Gornal and his colleagues [19]. The homogenate of liver and kidney were used to analyze MDA and GSH levels. MDA content as an indication of lipid peroxidation in liver and kidney was estimated according to the method of Yoshioka and his colleagues [20], while GSH content was measured as an antioxidant indicator according to the method of Beutler and his colleagues [21].

2.7 Statistical Analysis

Data are expressed as mean ± SD from three separate observations. One way ANOVA test followed by Tukey's test ($P < 0.05$) was used to analyze the differences among the different groups. A probability of $P < 0.05$ was considered as significant.

3. RESULTS

3.1 Radiation Exposure Caused Variable Degree of Disturbance

Variable degrees of abnormal levels have been estimated in all parameters measured in the group of animals exposed to γ- irradiation as a single dose level of 4 Gy. There was a marked decrease in serum total protein (-14.7%) and albumin concentration (-22%) accompanied with non significant decrease in globulin level and albumin/ globulin ratio comparing to the control value Table 1. On the other hand, irradiation caused an increase in serum ALT activity, urea and creatinine concentrations as in Table 2, which is recorded 41%, 28% and 29% as compared to the normal control level. There was a significant increase ($p < 0.01$) in caspase-3 activity of group II that recorded 43% when compared with group I.

coriander -pre-treated groups showed resistance to radiation exposure with a significant decrease ($p<0.01$) of 25% in caspase-3 activity, when compared with group II and a non significant increase when compared with group I.

Table 1. Effect of ethanolic coriander extract (600 mg/ kg b.wt) or silymarin (70 mg/kg bwt) daily for 10 days on serum protein (g/ dl), Albumin (g/ dl), Globulin (g/ dl) levels as well as Albumin/ Globulin ratio in female irradiated rats

	Protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)	Albumin/ Globulin ratio
Group I X^-±SD	10.16± 1.32	3.847± 0.146	6.57± 1.349	0.709± 0.1555
Group II X^-±SD	8.66± 0.436*	3.003± 0.355*	5.347± 0.847	0.547± 0.1
Group III X^-±SD	8.77± 0.766	3.317± 0.74	6.052± 0.531	0.637± 0.214
Group IV X^-±SD	8.807± 0.88	3.515± 0.267	5.795± 0.541	0.612± 0.079

Each value in the table is represented as mean ± SD (n = 6). Values in the same column followed by a sample (*) is significantly different (p< 0.05) from control group, and (#) is significantly different (p< 0.05) from irradiated group.

In addition, the data represents in Table (3) shows that exposing animals to 4 Gy gamma radiation as a single dose caused a significant increase in both liver and kidney MDA. The percentage of these increases recorded were 58% and 47% respectively as compared to the normal control group.

3.2 Coriander Extract Administration Revealed A Marked Amelioration in Liver and Kidney Function

Adequate repair of liver and kidney function were noticed in the group III. Serum total protein and albumin concentration revealed a marked restoration comparing to the normal control level Table 1. Also, the activity of serum ALT as well as urea and creatinine concentration showed significant reductions comparing with irradiated group and the percentage of reduction was (-29%), (-14.55%) and (-17.23%) respectively as shown in Table 2.

On the other hand Table 3 showed that administration of coriander extract before irradiation caused a significant amelioration in liver and kidney MDA and the percentage of these amelioration was 8% for both organs comparing to the normal control level. Meanwhile, the percentage of reduction of liver and kidney MDA were -32% and -27% as compared to the induction control. According to data represent in Table 3 coriander extract showed an increase in liver and kidney GSH content, but still significantly different from normal control level (group I), however the percentage of increases were 50% and 89% respectively as compared to group II.

Table 2. Effect of ethanolic coriander extract (600 mg/kg b. wt) or silymarin (70 mg/kg bwt) daily for 10 days on serum caspase 3 ALT (U/ml), urea (mg/ dl) and creatinine (mg/dl) in female irradiated rats

	Caspase 3	ALT (U/ml)	Urea (mg/dl)	Creatinine (mg/ dl)
Group I X^{-}±SD	0.607± 0.023	17.28± 2.29	33.17± 4.24	0.704± 0.056
Group II X^{-}±SD	0.870± 0.086*	24.43± 5.02*	42.53± 6.11*	0.865± 0.064*
Group III X^{-}±SD	0.650± 0.115#	17.21± 3.10#	36.34± 4.86	0.716± 0.037#
Group IV X^{-}±SD	0.615± 0.084#	16.84± 3.14#	38.54± 3.26	0.771± 0.125

Each value in the table is represented as mean ± SD (n = 6). Values in the same column followed by a sample (*) is significantly different (p< 0.05) from control group, and (#) is significantly different (p< 0.05) from irradiated group.

Table 3. Effect of ethanolic coriander extract (600 mg/kg b. wt) or silymarin (70 mg/kg bwt) daily for 10 days on liver MDA (µM/g tissue) and GSH (mg/ g tissue) in female irradiated rats

	Liver tissue		Kidney tissue	
	MDA (µM/ g tissue)	GSH (mg/ g tissue)	MDA (µM/ g tissue)	GSH (mg/ g tissue)
Group I X^{-}±SD	194.0± 42.28	117.6± 6.986	192.4± 10.83	70.34± 14.43
Group II X^{-}±SD	307.0± 29.22*	63.24± 12.19*	285.5± 48.93*	17.38± 1.414*
Group III X^{-}±SD	209.0± 16.86#	94.66± 22.62*#	207.7± 5.21#	32.87± 6.246*#
Group IV X^{-}±SD	192.5± 42.55#	96.85± 5.774#	200.3± 26.59#	33.57± 3.727*#

Each value in the table is represented as mean ± SD (n = 6). Values in the same column followed by a sample (*) is significantly different (p< 0.05) from control group, and (#) is significantly different (p< 0.05) from irradiated group.

4. DISCUSSION

Radiation exposure induces overproduction of reactive oxygen species (ROS) and depletes the cellular antioxidant capacity that leads to a wide variety of pathological aspects. Antioxidants fight against free radicals and protect us from various diseases. They exert their action either by scavenging the reactive oxygen species or preserving the antioxidant defense mechanisms [22].

The present study has investigated the effectiveness of ethanolic coriander leaves extract, which is considered both a traditional natural medicine and an edible vegetable, against the toxicological environmental disorders induced by radiation exposure using a rat model. The evident from the current results indicated that supplementation of coriander extract before irradiation induced a protection against radiation toxicity. This evident is confirmed with the earlier report suggests the preventive effects of C*oriandrum sativum* (Chinese parsley) on

oxidative stress [23] may be due to the active ingredients in coriander possess antioxidant properties and protects against radiation exposure.

According to Henry et al. [24] the long chain alcohol and aldehydes, which are common in coriander structures, phospholipids, phytosterols, flavonoids and active phenol are found to help fighting inflammation and free radicals [25] Moreover, positive correlations were already established between total phenolic content in the extracts and antioxidant activity [26]. Flavonoids have been shown to be highly effective scavengers of most oxidizing molecules, including singlet oxygen, and various free radicals [27] implicated in several diseases [28]. Our results suggested that the antioxidant activity of coriander may be the major contributor for its phenolic acids and flavonoids constituents.

The most abundant oxidative free radicals are generated in living cells as superoxide anions and derivatives, mainly the highly reactive and damaging hydroxyl radical which induces peroxidation of cell membrane lipids [29]. Lipid peroxidation refers to the oxidative stress degradation of lipid in which malondialdehyde (MDA) is one of its end products [30]. It mostly affects polyunsaturated fatty acids causing tissue damage [31] and the elevation in MDA levels in both liver and kidney of irradiated rats as observed in our results may be due to the enrichment of cell membrane with polyunsaturated highly oxidizable fatty acids [32].

In addition a large reserve of reduced glutathione is present in living cells for detoxification of oxidative stress induced free radicals. However, oxidative stress results in toxicity when the rate of reactive oxygen species (ROS) generation exceeds the cell capacity for their removal [33]. In the current study administration of *Coriandrum sativum* caused increase in GSH content as well as decreases in MDA level in irradiated rat liver and kidney. Therefore, because of coriander antioxidant property, it is valid to consider that it might be capable of protecting the liver and kidney tissues from irradiation induced injury changes [34]. The antioxidative property of coriander is related to the large amounts of tocopherols, carotenoids and phospholipids [35], which act through different mechanisms. Carotenoids act as primary antioxidants by trapping free radicals and as secondary antioxidants by quenching singlet oxygen [36]. Tocopherols and sterols interact with oil surfaces and release hydrogen, inhibiting the propagation step of radical reactions [36].

In current findings, radiation exposure showed an elevation in serum caspase3 concentration, ALT activity and conversely decreased protein level. Caspase3 is considered as one of effectors of caspase type that cleaves other protein substrates within the cell, to trigger the apoptotic process [37]. Apoptosis inducing compounds trigger activation of the caspase cascade, which leads to the cleavage of target proteins and results in various biochemical manifestations such as GSH extrusion leading to oxidative stress [37]. According to Zhao and his colleagues [38] radiation exposure resulted in loss of mitochondrial membrane functions followed by increased caspase 3 levels. On the other hand liver enzyme such as ALT is a marker enzyme for liver function and integrity [39]. This enzyme is usually raised in acute hepatotoxicity [40]. The present available data suggest that radiation exposure exerts possible toxic effects as the increase in serum ALT due to liver damage. Since ALT is a liver enzyme, radiation exposure induced free radicals will alter the level of ALT activity by disrupting their membrane. Consequently, a discharge of the cell content into the blood stream is observed and ALT activity is also known to increase [41]. Total protein level is also a rough measure of protein status that reflects major functional changes in kidney and liver functions. Decrease of protein level as well as the increase in urea and creatinine concentration due to kidney impairment in irradiated group may be a cause of protein loss among these animals. Protein loss in irradiated animals might

decrease the level of specific proteins such as albumin, and thereby disturb the homeostasis and rate of metabolic activities, which is in agreement to results obtained in the present study.

The coriander mediated suppression of the increased ALT activity suggests the possibility of the extract to give protection against hepatic, renal injury upon radiation exposure. Pre-administration of ethanolic coriander extracts significantly increased total protein content. According to Wangensteen and his collegues [26] the large proportion of coriander antioxidant activity is attributable to the presence of phenolic compounds. The antioxidant activity is believed to play a part in the prevention of most major chronic diseases through such mechanisms as increasing endogenous protective enzymes, protecting DNA from free radical-induced structural damage, encouraging the self-destruction of aberrant cells (apoptosis) and inhibiting tumor growth.

5. CONCLUSION

In conclusion the existing study reveals that ethanolic extracts of *Coriandrum sativum* leaves can prevent or slow down the oxidative damage induced by radiation exposure. The effect of radiation induced oxidative stress on MDA and GSH levels and some biochemical variables were ameliorated by pre-treatment with plant extracts. Additional studies are needed to estimate its pharmacokinetics and toxicity outline to determine its clinical dose, isolation and explanation of bioactive components.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

COMPETING INTEREST

Authors have declared that no competing interests exist.

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