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Modulatory Effect of *Cicer arietinum* Extract against γ-Irradiation-Induced some Biochemical Disorders in Rats.

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ABSTRACT

Ionized radiations associated with risks of serious adverse effects. Administration of natural agents has been suggested to protect against ionizing radiation-induced tissue injury. Thus, the present study was oriented to study the *in vivo* ameliorative effect of *Cicer arietinum* extract (CAE) against whole body γ-irradiation induced biochemical alterations in male albino rats. Rats (n=24) were divided into control, CAE and γ-irradiated rats; the last exposed to a dose of 6Gy ^{137}Cs and subdivided into two groups. (1) γ-irradiated group received vehicle, (2) γ-irradiated group treated with CAE. γ-irradiation (6Gy) exposure induces significant increase in serum liver function markers, kidney function markers parallel with significant decline in the trace elements of rats. On the other hand, CAE (500 mg/kg b.wt, p.o) administration for 21 days to γ-irradiated rats resulted in an obvious improvement of the hazardous effects induced by γ-irradiation which was evident by the improved status of most of the abovementioned parameters. In conclusion, the present findings suggested that CAE has remarkable radioprotective effect against radiation induced biochemical alterations and this effect may be due to its bioactive chemical contents.

Keywords: γ-irradiation; *Cicer arietinum* extract; Liver function; Kidney markers; Trace elements.

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INTRODUCTION

Radiation is present in all around us, whether it is naturally or man-made due to its usage in diagnosis, industry and the energy sector which necessitates a safeguard to human being. Depending on the intensity and duration type, radiation exposure can pose a serious threat to human being. Although the ionizing radiation (IR) has great benefits, it also has harmful hazards for human beings [1]. IR consists of energetic particles and electromagnetic radiation, which can penetrate living tissue and consequently transfer the radiation energy to the biological material. This resulted in breakage in chemical bonds and ionization of different biologically important macromolecules, including water nucleic acids, membrane lipids and proteins [2]. Thus, the destructive effect of radiation that destroys the tumor cells can extends to the healthy tissues and causing damage in the areas which are being treated. IR interacts with the living tissues and produce free radicals or reactive oxygen species (ROS), which lead to deleterious effects on normal cells by attacking DNA, proteins and membrane lipids [3]. Thereby, the whole body exposure to IR may trigger multiple organ dysfunctions including liver and kidney. Sinha et al. [4] reported that liver is sensitive to IR as the possibility of liver cell regeneration decreased after radiation exposure, and the detoxification function of the liver is affected significantly.

Further, exposure of healthy tissues to low doses of IR causing alteration of some of physiological processes that depend on trace metals such as iron (Fe), copper (Cu), zinc (Zn), magnesium (Mg) and calcium (Ca) and lead to their accumulation or release from the body [5]. These transition metals are vital for living organisms as they have various biological roles in the structural and catalytic cofactors [6]. Therefore, control of radiation hazards is important challenge to protect our lives from radiation risks. Nowadays, there are many anti-radiation drugs including the sulfhydryl–ammonia compounds, cytokine and hormone. However, all are clinically inadequate due to their limited treatment range, toxic side effects and high cost [1].

Biologic modifiers effectively scavenging oxidative damage is thought to be potential strategies for protection against radiation injury [3]. Recently, a wide variety of synthetic and natural compounds have shown promise to be radioprotective agents in laboratory studies. However, most of them failed even before reaching the preclinical stage due to their toxicity and side effects and this limit their application in medicine. Therefore, searching for new low/non-toxic and effective radioprotective compounds, especially from natural origin to boost antioxidant defense, is relevant as they may reduce the biological disorders caused by IR. Dietary antioxidants considered effective nutrients in the protection against free radicals and prevention of the oxidative stress (OxS) related diseases [7]. Extracts of several plants and their phytochemical contents are reported to be modifiers of radiation effects in a variety of biological system [8].

Most of the previous studies neglect the radioprotective effect of the legumes. The chickpea (*Cicer arietinum*) is a member of the Fabaceae (Leguminosae) family and it is a widespread and inexpensive rather than there is no record to our knowledge about its effect against γ-irradiation. Thus, the present study aimed to investigate the effect of γ-irradiation (6Gy) on liver, kidney function markers and certain essential metals. Additionally, this study was conducted to evaluate whether three weeks prolonged oral administration of *Cicer arietinum* extract (CAE) has any effect against biochemical disorders in rats exposed to γ-irradiation as a pilot study.

MATERIALS AND METHODS

Preparation of crude *Cicer arietinum* extract (CAE)

Mature *Cicer arietinum* seeds were purchased from a local market, cleaned and ground to fine powder. One gram of the dried powder was soaked in 4 ml methanol, incubated at 60°C for 1 h. The resulting extract was centrifuged at 10000 rpm, 5°C for 20 min. The resulting supernatant was filtered through filter paper (Whatman number 1), then concentrated by evaporating its liquid contents following by lyophilization by LABCONCO lyophilizer (shell, freeze system, England, UK). The prepared CAE was stored in desiccator until use [9]. The prepared extract (CAE) was re-suspended in distilled water just before oral administration in rats.

Experimental Animals

Adult male Wistar albino rats (*Rattus norvegicus*), weighing 150-170 g were purchased from the animal house of the National Research Center (NRC), Egypt. All animals were provided with a standard diet and clean drinking water. The rats were maintained for one week for acclimatization. The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC) (CUFS/S/PHY/35/14) of the Faculty of Science, Cairo University, Egypt.

Irradiation procedure

Rats were placed in the irradiation chamber and the whole body was radiated with 6Gy γ-irradiation [10]. γ-irradiation was performed using a Canadian Gamma Cell-40 ^{137}Cs (137Cesium) apparatus at the gamma irradiation unit of the National Center for Radiation Research and Technology (NCRRT), Cairo, Egypt.

Experimental Design

Animals (24 rats) were randomly divided into four groups each of six rats as follows:

Control group: Rats neither exposed to radiation nor treated with CAE, but received distilled water as a vehicle.

CAE group: Rats received orally CAE (500 mg/kg b.wt) during 21 successive days.

Irradiated group: Rats were exposed to whole body gamma radiation (6Gy) and received vehicle for 21 days.

Irradiated+CAE group: Rats were exposed to whole body gamma radiation (6Gy) and after exposure; they administered CAE (500 mg/kg b.wt) for 21 consecutive days.

At the end of the experiment, animals were euthanized 24 h after the last dose of treatment. Blood samples were collected through heart puncture after light anesthesia. Blood samples were allowed to coagulate and centrifuged to obtain serum for biochemical analyses.

Biochemical analyses

Evaluation of the effect of irradiation and/or CAE on liver function markers

The activities of aspartate amino transferase (AST), alanine amino transferase (ALT), Gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) were measured according to the Biodiagnostic kits procedure [11-13].

Evaluation of the effect of irradiation and/or CAE on kidney function markers

Creatinine, urea and uric acid concentrations were assayed in serum using Biodiagnostic kits according to the methods described by Bartles et al. [14], Fawcett and Scott [15] and Barham and Trinder [16], respectively.

Evaluation of the effect of irradiation and/or CAE on metals concentration

Serum phosphorus level was determined using Biodiagnostic kit according to the methods adopted by El-Mezabani et al. [17]. The other metals were performed using simultaneous inductively coupled plasma emission spectrometer (720 ICP-OES, Agilent Technologies).

Statistical analysis

All results were expressed as mean ± SEM (n = 6). Experimental data were analyzed using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test to determine significant differences

between means. Statistical analysis was performed using Statistical Packages for Social Science (SPSS/PC) computer program. Differences between means were considered statistically significant at P<0.05.

RESULTS

Effect of irradiation and/or CAE on liver function markers

Administration of CAE (500 mg/kg b.wt) to rats for 21 days did not show significant changes in liver function markers which indicating that the extract did not affect the liver functions. The data presented in table (1) revealed that γ-irradiated rats had a significant increase (P<0.05) in the serum AST, ALT, GGT, and ALP activities as compared with control rats. Whereas, γ-irradiated rats treated with CAE had a significant decrease (P<0.05) in the levels of abovementioned enzymes comparing to those of the γ-irradiated group.

Table (1): Effect of irradiation and/or CAE on AST, ALT, GGT and ALP activities.

Marker / Group	AST (IU/L)	ALT (IU/L)	GGT (U/L)	ALP (IU/L)
Control	7.421±0.335 ^{a}	3.433±0.044 ^{a}	8.854±1.182 ^{a}	272.508±24.704 ^{a}
CAE (500 mg/kg b.wt)	8.211±0.173 ^{a}	3.766±0.008 ^{a}	10.229±2.357 ^{a}	275.566±16.185 ^{a}
Irradiated	10.098±0.359 ^{b}	4.888±0.168 ^{b}	25.184±5.138 ^{b}	340.466±24.183 ^{b}
Irradiated+CAE	9.115±0.295 ^{c}	3.695±0.161 ^{a}	15.052±1.811 ^{a}	268.020±5.723 ^{a}

Values are means ± SEM (n=6). Values in the same column with different superscripts are differing significantly at P<0.05.

Effect of irradiation and/or CAE on kidney function markers

Table (2) exhibited that rats administered CAE did not have drastic changes in kidney function parameters. Rats exposed to γ-irradiation had a significant increase (P<0.05) in the concentrations of creatinine, urea and uric acid, as compared with control group. However, administration of CAE after γ-irradiation exposure showed an ameliorative effect; since it significantly reduced (P<0.05) the elevations in creatinine and uric acid levels induced by γ-irradiation as depicted in table 2.

Table (2): Effect of irradiation and/or CAE on creatinine, urea and uric acid concentrations.

Marker / Group	Creatinine (mg/dl)	Urea (mg/dl)	Uric Acid (mg/dl)
Control	1.098±0.044 ^{a}	29.255±2.436 ^{a}	2.535±0.122 ^{a}
CAE (500 mg/kg b.wt)	1.186±0.112 ^{a}	31.471±1.402 ^{a}	2.698±0.270 ^{a}
Irradiated	2.306±0.066 ^{b}	37.750±0.883 ^{b}	4.273±0.475 ^{b}
Irradiated+CAE	0.730±0.016 ^{c}	33.070±1.654 ^{ab}	3.145±0.128 ^{a}

Values are means ± SEM (n=6). Values in the same column with different superscripts are differing significantly at P<0.05.

Effect of irradiation and/or CAE on essential trace elements

CAE administration (500 mg/kg b.wt) did not induce marked alteration in Ca, Mg, Zn, Fe and Cu levels, while it increase Ph concentration significantly as compared with control group. Gamma irradiation (6Gy) induced a significant decrease (P<0.05) in serum Ca, Ph, Mg, Fe and Cu concentrations as compared with control group. However, γ-irradiation decreased the Zn level but statistically this decrease is not significant in

comparison with control level. Conversely, CAE treatment post γ-irradiation almost ameliorate the altered serum Ca, Ph, Mg, Zn, Fe and Cu concentrations of γ-irradiated rats and restored these levels to control values.

Table (3): Effect of irradiation and/or CAE on essential trace elements.

Marker / Group	Calcium (mg/dl)	Phosphorus (mg/dl)	Magnesium (mg/dl)	Zinc (mg/dl)	Iron (mg/dl)	Copper (mg/dl)
Control	12.883±1.115 ^{a}	95.116±3.494 ^{a}	2.656±0.293 ^{a}	0.150±0.010 ^{ab}	1.100±0.054 ^{a}	0.281±0.038 ^{a}
CAE (500 mg/kg b.wt)	9.103±0.755 ^{a}	116.200±7.518 ^{b}	2.091±0.193 ^{a}	0.236±0.103 ^{a}	1.268±0.123 ^{a}	0.094±0.005 ^{b}
Irradiated	8.608±1.228 ^{b}	75.583±10.628 ^{c}	1.299±0.301 ^{b}	0.039±0.012 ^{b}	0.720±0.138 ^{b}	0.143±0.040 ^{b}
Irradiated+CAE	13.701±1.582 ^{a}	112.166±8.494 ^{ab}	2.103±0.164 ^{a}	0.138±0.012 ^{ab}	0.981±0.127 ^{ab}	0.271±0.050 ^{a}

Values are means ± SEM (n=6). Values in the same column with different superscripts are differing significantly at P<0.05.

DISCUSSION

Nowadays, the advances of technological revolution boost the using of electronic equipment which leading to more serious irradiation pollution. Ionizing irradiation including γ-irradiation resulted in chemical and biological alterations in living tissues. When radiation is absorbed by a living cell, ionization and excitation of the atoms resulted in deterioration in the cellular and subcellular structures causing damage of cellular essential components, and results in a visible biological lesion [18]. Several synthetic compounds have potent radioprotective efficacy; but they exhibit severe toxicity at their effective doses which limit their clinical application [19]. As human beings consume nutritive agents daily, which may better than other chemical agents, the present study try to mimic this fact through the usage of a common dietary pulse. Based on this, the aim of the present study was to evaluate the effects of γ-irradiation on the liver, kidney, and trace elements and assesses the radioprotective action afforded by CAE.

The present study demonstrated that administration of CAE for 21 days did not show any adverse symptoms of toxicity and mortality at 500 mg/kg b.wt and this reflect the safety of CAE at such dose. On the other hand, the present finding revealed that whole body γ-irradiation of rats was accompanied by a significant increase in the activities of AST, ALT, GGT and ALP. These results are in accordance with those found by El Shahat [20] and Karabulut et al. [21]. This finding reflects the hepatocellular damage via γ-irradiation as these enzymes are considered as reliable biomarkers of hepatic dysfunction and hepatocellular damage [22]. The current work supposed that the elevation in aminotransferases enzymes by radiation may be attributed to the hepatocytes cell membrane impairment which increase its permeability; and hence facilitates the leakage of cytoplasmic enzymes (aminotransferases) out of the cells leading to increase their levels in the serum. This suggestion is matching with the report of Ramadan et al. [23]. Moreover, the elevated level of GGT confirms the liver damage as is known that the higher the GGT level, the greater the liver damage. This is due to the fact that GGT found in cell membranes of many tissues, one of them is the liver, and this emphasizes that when the cell membrane interrupted; the GGT level increase. The increased activity of ALP assures the disintegrity of liver cell membrane. As ALP assess the integrity of plasma membrane [24], since it is predominantly localized in the microvilli of the bile canaliculi, found in the plasma membrane. Therefore, any alteration in the serum enzyme level than control or normal level may expect impairment to the external boundary of the cell plasma membrane [25]. In this study, its elevation may indicate that following γ-irradiation, the functional activity of ALP increased, which consequently leads to *de novo* synthesis of the enzyme molecules. However, administration of CAE to γ-irradiated rats resulted in an obvious reduction in the activity of AST, ALT, GGT and ALP than the untreated rats. This restoration manifests the anti-hepatotoxicity of CAE against IR which may be through the ability of CAE to stabilize the hepatocellular membrane consequently diminishing enzymes outflow into the blood. The current results are in line with the postulation that transaminases level restored to normal level if the hepatic parenchyma becomes healed and the hepatocytes regenerated [26]. This effect may be related to the phenolic compounds of the CAE beside its isoflavones constituents that revealed earlier [27]. Since, flavonoids and isoflavones have hepatoprotective role [28,29]. Xiao and Högger [30] clarified that

flavonoids metabolized in liver and the metabolite products may boost the desirable ameliorative effects of the dietary bioactive constituents.

Regarding the effect of irradiation and/or CAE on kidney function, the current study found that γ-irradiation provokes renal injury in rats. This evidenced by a significant increment in serum creatinine, urea and uric acid in rats exposed to γ-irradiation as a measurement of renal function is a reliable marker for renal function/dysfunction. Consequently, elevations of the serum concentrations of renal markers are indicative for renal injury occurrence. Parallel to the present study, Osman and Hamza et al. [8] found significant increase in renal function markers. The present renal deterioration may be related to an impairment of glomerular selective properties triggered by irradiation as Berry et al. [31] explained. The present work speculated the raising level of serum creatinine post-irradiation due to the back-leakage of the filtered creatinine through the tubular epithelium that may impaired by radiation as Nada et al. [2] reported. The current investigation expected that the rising of urea in the γ-irradiated rats may be due to either an increase in ammonia production during deamination of amino acids which converted to urea or increased breakdown in nitrogenous bases of nucleic acids as Osman and Hamza et al. [8] justified. Further, the ongoing work attributes the elevated levels of uric acid in untreated γ-irradiated rats to the catabolism of purines into uric acid. Since, irradiation may cause destruction of DNA molecules and their bases (purines) which finally catabolized into uric acid [32]. However, administration of CAE reversed the renotoxicity of γ-irradiation. This finding suggesting that the CAE bioactive compounds, evidenced by Fahmy et al. [27], have the regenerative and reparative properties that can preserve the integrity of kidney. This suggestion was supported by Rahmat et al. [33] report. Who attributed the renoprotective action of *Cnestis ferruginea* to the accumulation of its bioactive compounds in kidney since it is an excretory organ and subsequently these compounds may concentrate in renal tubules and ameliorate the renal disorders through their antioxidant capacities.

Trace elements are integral portions of enzyme molecules and contribute in acceleration or inhibition of some enzymatic reactions. Importance of essential metals backed to its role, as they considered as major component of metalloenzymes and metallohormones which altered by the radiation [34]. Thereby, assessment of essential metals concentrations is considered a sensitive indicator for alterations provoked by γ-irradiation [5]. γ-irradiation elicits significant decline in the serum metalloelements levels (Ca, Ph, Mg, Fe and Cu) in comparison with control. The present investigation relates the decreased level of Ph to the hyperproduction of ALP activity that evidenced in this study. Since ALP hydrolyses phosphate monoesters and hence the overproduction of ALP considered a risk to the cell viability as it is Ph dependent and the decline of the latter adversely affect the cellular vital process [22]. Noaman and Gharib [35] reported that radiation reduce red blood cell counts, hemoglobin concentration and hematocrit and this interpret the reduction of most of the essential metals in blood in rats exposed to γ-irradiation in the present study. Unfortunately, the reduction in essential metalloelement-dependent enzyme activity (Cu, Fe, and Zn) resulted in severe tissue damage and the present finding revealed a marked decrease in the Zn concentration in γ-irradiated group. Hawas [5] added that Zn deficiency induced many diseases in human's body. Nada et al. [2] reported that the change in the trace element levels induced by γ-irradiation provoke disturbances of enzymatic functions and hence hinder the cellular activities. On the contrary, administration of CAE to γ-irradiated rats returned the altered serum Ca, Ph, Mg, Zn, Fe and Cu levels near to control values. The present work observed a significant rise in Ph concentration of CAE rats, as compared with control group. This may be due to the phosphorus content existing in *Cicer aritienum* as O'Neil et al. [36] recorded. Further, the ongoing study links the decreased Ph level of the γ-irradiated rats treated with CAE to its ability to minimize the hyperproduction of ALP activity in γ-irradiated rats. Concerning the elevation of Zn in the γ-irradiated rats treated with CAE than the untreated ones, the current work consider this elevation as a resistance mechanism against radiation hazard as it is the only metal that is present in coenzyme of all enzyme classes [37]. This may occur due to the increased Zn concentration in CAE group.

CONCLUSION

CAE has the capability to ameliorate the mild hepatorenal dysfunction as well as the disturbance of trace elements induced by γ-irradiation in this pilot study. Thus, CAE may consider as a dietary hepatoreno-protective agent which needs additional and complementary investigation in the future to study its mechanism of action against γ-irradiation.

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