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Research Article

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Evaluation of the Protective Effects of Ginger Extract on Cisplatin Induced Cardiotoxicity in Male Albino Rats

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ABSTRACT

Purpose: This study was aimed to evaluate the protective effect of ginger extract against cisplatin-induced cardiotoxicity in male albino rats. Methods: The animals were divided into seven groups of 10 animals in each group and treated as follow: a control group, DMSO, Ginger only, cisplatin (cisplatin, 10 mg/kg, i.p), and a groups that received both cisplatin and ginger extract (200, 400 and 600 mg/kg body/day) euthanized in 19th days. Cisplatin induced a significant increase in triglyceride, cholesterol, LDH, Troponin-T, CK-MB, MDA, nitric oxide and caspase-3 levels. However, catalase levels were significantly diminished. Conversely, ginger extract significantly modulated cardiotoxicity and oxidative markers. Thus, ginger extract may be combined with cisplatin to alleviate cardiotoxicity in cancer chemotherapy.

Keywords: Cisplatin; Ginger extract; Apoptosis; Caspase-3

INTRODUCTION

Cisplatin (CP) is an inorganic, divalent, water soluble, platinum containing compound. CP is used as a highly efficient anti-neoplastic drug commonly used as a first-line therapy for treatment of various solid tumors such as: stomach cancer, ovarian cancer, lung cancer, bladder cancer and germ cell tumors [1]. The antitumor effect of CP is mediated by apoptosis and DNA-crosslinks with subsequent cytotoxic lesions in malignant cells [2]. However, its clinical use is associated with dose and duration-dependent nephrotoxic side effect [3].

However, despite of its beneficial antitumor activity, cisplatin showed numerous adverse effects and toxicities affecting gastrointestinal, renal, neurological and hematological system, even when administered at standard doses [4]. Cardiotoxicity is the most feared adverse effect of anticancer therapy, due to the fact that life expectancy obtained as a result of the anticancer treatment, may be reduced by the death rate determined by cardiac problems arising as a consequence of the treatment [5]. Nephrotoxicity of cisplatin was the main complication of cisplatin. Earlier studies reported cardiotoxicity with cisplatin treatment [6].

It has been reported that cisplatin is able to generate reactive oxygen species (ROS), such as hydroxyl radical and superoxide anion radical [7]. This very reactive oxygen species can cause tissue damage through reaction with biological macromolecules (lipids, proteins and nucleic acids) leading to the formation of oxidized substances. Cisplatin therapy is usually associated with oxidative stress that has important role in cardiovascular toxicity after cisplatin treatment [8]. Ginger belongs to a tropical and sub-tropical family-Zingiberaceae, it has been cultivated for thousands of years as a spice and for medicinal purposes [9]. Extracts of the ginger are rich in shagaols and gingerols which exhibit anti-inflammatory, anti-oxidant and anti-carcinogenic proprieties under ‘‘in vitro’’ and ‘‘in vivo’’systems [10].

MATERIALS AND METHODS

Preparation of ginger extract

Fresh rhizome of the plant was purchased from a local market. The rhizome was dried and ground into fine powder using an electrical blender. Fine powder (100 g) was homogenized in ethanol (95%; 500 mL) and left in a conical flask at room temperature for 3 days. Then, the mixture was filtered through a fine muslin cloth and a

filter paper. Using rotary evaporator, the extract became concentrated. The extract was then lyophilized. DMSO was used to dissolve the extract [11].

Animal management

Seventy adult male albino rats weighing 18 -200 g were obtained from the animal house, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt and were housed in metabolic cages under controlled environmental conditions (25°C and a 12 h light/dark cycle) one week before starting the experiment as acclimatization period. The animals were fed with a standard diet and provided with drinking water and libitum.

Dose selection and treatment

Treated doses of ginger extract selected based on previously reported by who found that there was no clinical and behavioral abnormality. Also, histopathological assessment also confirmed that the extract is safe in doses less than 5 g/kg [11]. LD50 of CP in rats is 12 mg/kg body weight [13]. The dose of CP was selected on the basis of its effectiveness in inducing nephrotoxicity [14].

Experimental protocol

The animals were divided into seven groups of 10 animals in each group and treated as follow:

Group 1(Negative control):

Animals injected intraperitoneal (i.p.) with 1 ml single saline dose and animals were sacrificed after 19 days**.**

Group 2 (DMSO):

Treated orally with 1 ml of 6.5 % DMSO daily for 19 days then scarified.

Group 3 (ginger only):

Pretreated orally with ginger extract alone (600 mg/kg/day) for 19 day

Group 4 (cisplatin):

Animals injected intraperitoneal (i.p.) with cisplatin (10 mg/kg) (was purchased from Sigma Chemical Co) as single dose on the 15^{th} day of the experiment and animals were sacrificed after 5 days.

Group 5, 6 and 7:

Animals pretreated with oral dose of ginger extract (200 mg, 400 mg and 600 mg /kg/day respectively) for 19 day before and 5 successive days after single IP cisplatin (10mg/kg). Animals were sacrificed after 19 days.

Collection and sampling of blood

At the end of experimental period (19 day), the animals were fasted for 12 hours, animals were killed by cervical decapitation and blood was collected according to a described procedure. Serum was prepared by collection of blood in anticoagulant –free tube, then left for 10 minutes in water bath at 37 ºC until clot, then centrifuged at 2000 rpm for 10 minutes for separation of serum which was transferred into another tube and kept frozen at -20 ºC.

Tissue processing for histopathological examination

After blood collection heart tissues were quickly excised from the animals, rinsed with ice-cold phosphate-buffered saline (pH 7.4) to flush out any blood, blotted dry on a paper towel.

For determination of lipid peroxidation, nitric oxide levels, catalase activity and Caspase-3 concentration, Portions from each rat's heart were minced and homogenized in ice-cold phosphate buffer saline (pH 7.4) for tissue homogenate preparation.

For histopathological examination, heart tissue was cut into 3 millimeter pieces , fixed in 10% formaldehyde solution , processed and embedded in paraffin , blocks were cut by microtome into 5micrometer ,thick sections , washed in water bath and left in the oven for dewaxing ,then stained with haematoxyline and eosin stain and then examined under light microscope [12].

Estimation of biochemical parameters

Serum LDH activity was determined by Bergmeyer [15]. Also, serum triglyceride by Carlson [16]. Serum total cholesterol was estimated by Roeschlau [17]. Also, serum Troponin T determined by Immunoassay Kit (Cloud – Clone Crop) [18]. Serum CK-MB activity determined by Wu and Bowers [19]. Level of MDA in tissue homogenate was determined according to Ohkawa [20] using colorimetric kit. Also, level of NO was analyzed using colorimetric kit according to Montgomery and Dymock [21]. The activity of catalase was measured using colorimetric kit according to Aebi [22]. Kits of MDA, NO, GSH and GST were purchased from Biodiagnostic Company (Biodiagnostic, Egypt). Caspase-3 was determined by Rat/Mouse Rat (Caspase-3/CPP32)

Immunoassay Kit, Catalog Number 201-11-0281 provided by (Technical MSN service online, eMail:sunredbio@msn.cn).

Statistical analysis

All results were analyzed by SPSS software (version 14). Data were expressed as mean ± SD. Comparison of mean values of studied variables among different groups was done using ANOVA test. P<0.05 was considered to be significant [23]**.**

RESULTS

Effect of treatment with ginger extract on heart function tests

Table (1) indicated that serum levels of Cholesterol, Triglyceride, Troponin T also, LDH and CK MB activities showed statistically non-significant difference in DMSO and ginger treated groups compared to control group (p>0.05). While the administration of cisplatin (group 4) showed highly significant increase in serum Cholesterol, Triglyceride and troponin T concentration of treated rats that amounted to 90.9, 73.9 and 95.3 % respectively. Also, LDH and CK MB activity (p<0.001) which amounted to 145.3 and 200 % respectively, While in group 5, 6 and 7 serum levels of Cholesterol, Triglyceride, LDH, Troponin T and CK MB were reduced compared to group 4. Group 5 (ginger 200 + cisplatin) showed significant increase in serum Cholesterol, Triglyceride and troponin T concentration of treated rats that amounted to 58.3, 41.3 and 51.2 % respectively. Also LDH and CK MB activity which amounted to 110.8and 174.5 % respectively compared to control group. Group 6 (ginger 400 + cisplatin) showed moderate increase which was statistically non-significant in serum Triglyceride concentration and LDH activity (p>0.05) and statistically significant in cholesterol, troponin T concentration and CK MB activity which amounted (p<0.05) compared to control group. Group 7 (ginger 600 + cisplatin) showed slight elevation in Cholesterol, Triglyceride, Troponin T concentration also, LDH and CK MB activities which was statistically non-significant (p>0.05) compared to control group (Figures 1-5).

Table 1: Effect of ginger extract on heart function tests of the experimental groups

Group	Parameter					
		Cholesterol (mg/dl)	Triglyceride (mg/dl)	LDH (U/L)	TroponinT (pg/ml)	CK-MB (ng/ml)
Control	Mean ± SE	55.2 ± 3.5	97.7 ± 4.4	308.8 ± 28.9	60.2 ± 7.0	4.6 ± 0.6
DMSO	Mean ± SE	60.7 ± 4.7	96.3 ± 7.8	323.0 ± 30.5	64.8 ± 6.5	4.9 ± 0.6
	P *	0.371	0.884	0.743	0.638	0.748
	% *	10	-1.4	4.6	7.8	6.1
Cisplatin (Positive)	Mean ± SE	105.3 ± 9.0	169.8 ± 15.8	757.7 ± 34.3	117.5 ± 12.8	13.9 ± 1.9
	P *	0.001	0.002	< 0.0001	0.004	0.001
	% *	90.9	73.9	145.3	95.3	200
Ginger only	Mean ± SE	55.8 ± 4.4	99.5 ± 8.7	306.7 ± 33.6	67.3 ± 8.3	5.3 ± 0.4
	P *	0.908	0.854	0.962	0.524	0.403
	% *	1.2	1.9	-0.7	11.9	14
Ginger 600+cisplatin	Mean ± SE	72.5 ± 8.2	107.5 ± 5.3	389.0 ± 79.8	72.0 ± 7.2	9.9 ± 2.0
	P *	0.081	0.186	0.367	0.268	0.029
	% *	31.4	10.1	26	19.7	113.3
	P **	0.023	0.006	0.001	0.016	0.172
	% **	-31.2	-36.7	-48.7	-38.7	-28.9
Ginger 400+cisplatin	Mean ± SE	81.3 ± 6.7	127.3 ± 16.4	522.5 ± 95.9	87.5 ± 8.2	11.2 ± 2.4
	P *	0.006	0.111	0.059	0.03	0.023
	% *	47.4	30.4	69.2	45.4	142.4
	P **	0.068	0.091	0.024	0.094	0.391
	% **	-22.8	-25	-31	-25.5	-19.2
Ginger 200+cisplatin	Mean ± SE	87.3 ± 5.7	138.0 ± 9.9	651.2 ± 40.8	91.0 ± 8.0	12.7 ± 2.6
	P *	0.001	0.004	< 0.0001	0.016	0.012
	% *	58.3	41.3	110.8	51.2	174.5
	P **	0.145	0.142	0.068	0.133	0.71
	% **	-17.1	-18.7	-14.1	-22.6	-8.5

P * = P Value compared to control group; P** =P Value compared to cisplatin (positive) group. The mean difference is significant at P< 0.05.; % * = Percent of change compared to control group; % ** = Percent of change compared to cisplatin (positive) group

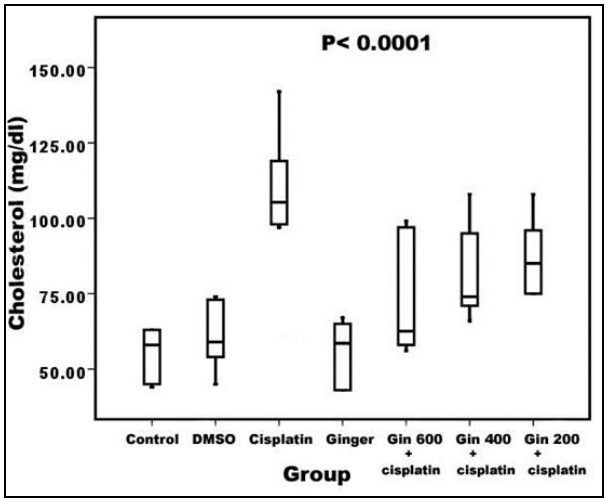

Figure 1: Box plots of cholesterol for comparison between laboratory data of all groups in heart disease. The box represents the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value. Overall significance of differences between laboratory data of all groups was determined by ANOVA test (p < 0.0001)

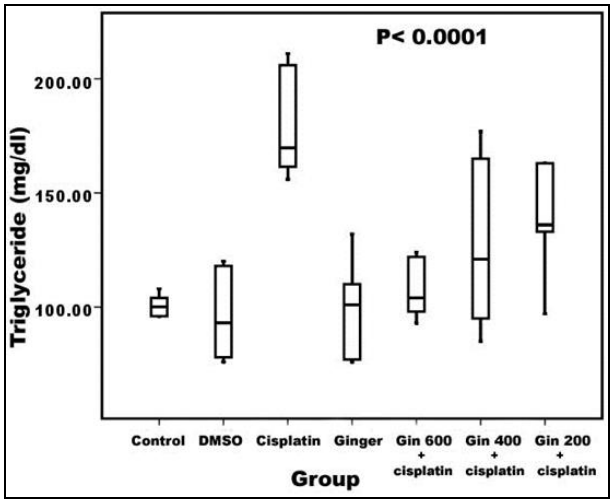

Figure 2: Box plots of triglyceride for comparison between laboratory data of all groups in heart disease. The box represents the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value. Overall significance of differences between laboratory data of all groups was determined by ANOVA test (p < 0.0001)

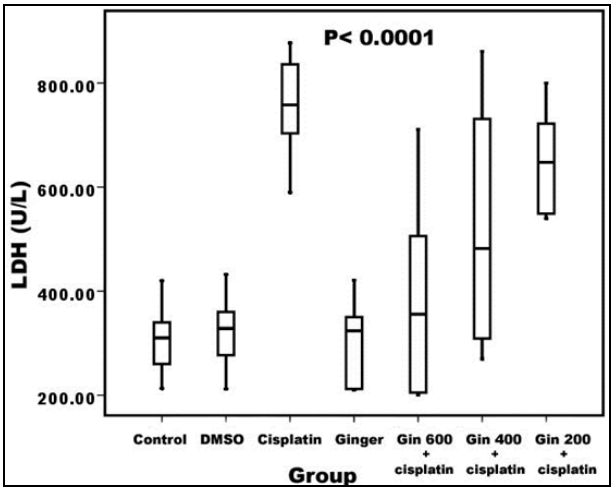

Figure 3: Box plots of LDH for comparison between laboratory data of all groups in heart disease. The box represents the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value. Overall significance of differences between laboratory data of all groups was determined by ANOVA test (p < 0.0001)

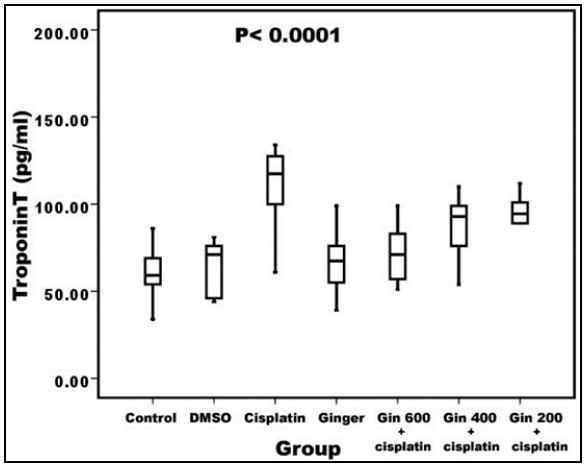

Figure 4: Box plots of troponinT for comparison between laboratory data of all groups in heart disease. The box represents the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value. Overall significance of differences between laboratory data of all groups was determined by ANOVA test (p < 0.0001)

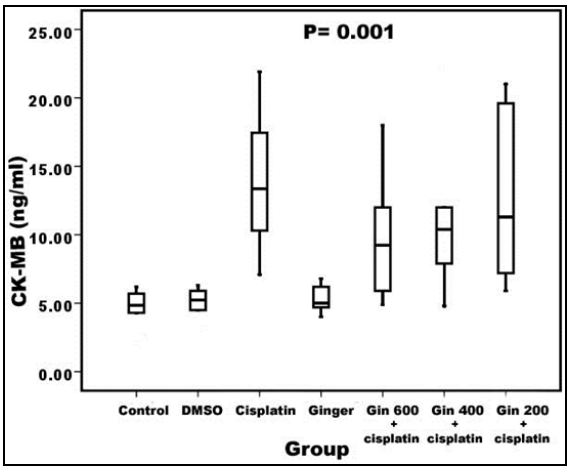

Figure 5: Box plots of CK-MB for comparison between laboratory data of all groups in heart disease. The box represents the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value. Overall significance of differences between laboratory data of all groups was determined by ANOVA test (p = 0.001)

Changes of oxidative stress parameters

The levels of MDA and NO were significantly higher in cisplatin group comparing to control group. Administration of ginger extract before and along with cisplatin significantly reduced their levels comparing to cisplatin group (Table 2), (Figures 6-8).

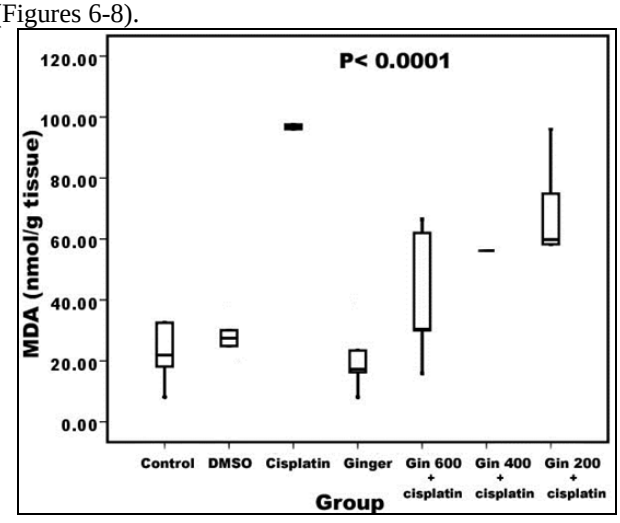

Figure 6: Box plots of MDA for comparison between laboratory data of all groups in heart disease. The box represents the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value. Overall significance of differences between laboratory data of all groups was determined by ANOVA test (p < 0.0001)

Table 2: Effect of ginger extract on levels of malondialdehyde, nitric oxide and catalase in cardiac tissue of the experimental groups

Group		MDA (nmol / g tissue)	No (µmol/L)	Catalase (U/g)
Control	Mean ± SE	22.5 ± 3.8	24.19 ± 4.9	8.68 ± 1.0
DMSO	Mean ± SE	27.39 ± 3.0	27.37 ± 3.9	7.54 ± 1.2
	P *	0.335	0.603	0.5
	% *	21.7	13.2	-13.1
Cisplatin (Positive)	Mean ± SE	94.86 ± 4.1	124.68 ± 21.98	2.55 ± 0.5
	P *	< 0.0001	0.001	< 0.0001
	% *	321.3	415.5	-70.6
Ginger only	Mean ± SE	20.18 ± 4.2	22.62 ± 4.3	8.95 ± 0.89
	P *	0.69	0.807	0.847
	% *	-10.4	-6.5	3.1
Ginger 600+cisplatin	Mean ± SE	39.16 ± 8.3	31.36 ± 2.0	7.35 ± 1.1
	P *	0.097	0.176	0.399
	% *	74	29.7	-15.3
	P **	< 0.0001	0.002	0.003
	% **	-58.7	-74.9	188.6
Ginger 400+cisplatin	Mean ± SE	50.6 ± 6.5	43.43 ± 8.5	6.56 ± 1.8
	P *	0.004	0.059	0.34
	% *	124.9	79.6	-24.4
	P **	< 0.0001	0.021	0.063
	% **	-46.6	-65.2	157.4
Ginger 200+cisplatin	Mean ± SE	67.87 ± 6.2	76.53 ± 13.0	6.06 ± 1.5
	P *	< 0.0001	0.003	0.179
	% *	201.5	216.4	-30.2
	P **	0.005	0.089	0.05
	% **	-28.5	-38.6	137.8

P * = P Value compared to control group; P** =P Value compared to cisplatin (positive) group. The mean difference is significant at P< 0.05; % * = Percent of change compared to control group; % ** = Percent of change compared to cisplatin (positive) group.

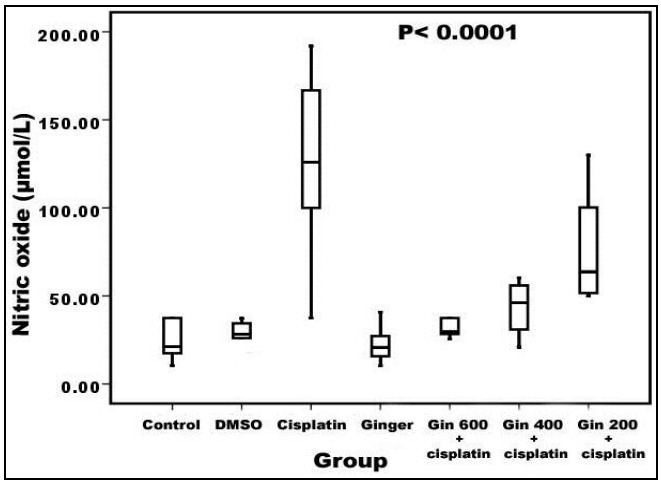

Figure 7: Box plots of nitric oxide for comparison between laboratory data of all groups in heart disease. The box represents the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value. Overall significance of differences between laboratory data of all groups was determined by ANOVA test (p < 0.0001)

Effect of treatment with ginger extract on heart tissue caspase-3 level

The mean level of Caspase-3 showed statistically non-significant increase in DMSO and ginger only treated groups which amounted to 0.8 and 8.5 % respectively compared to control group (p>0.05).

In group 4 administration of cisplatin induced apoptosis by causing significant elevation in caspase-3 level in heart tissue which amounted to 70.3 % compared to control group (p<0.001).

Treatment with ginger extract reduced the elevation in caspase-3 level in group 5, 6 &7 which amounted to 29.6, 20.2 and 7.9 % with p value (P < ,001), (P > 0.05) and respectively compared to control group (Table 3), (Figure 9).

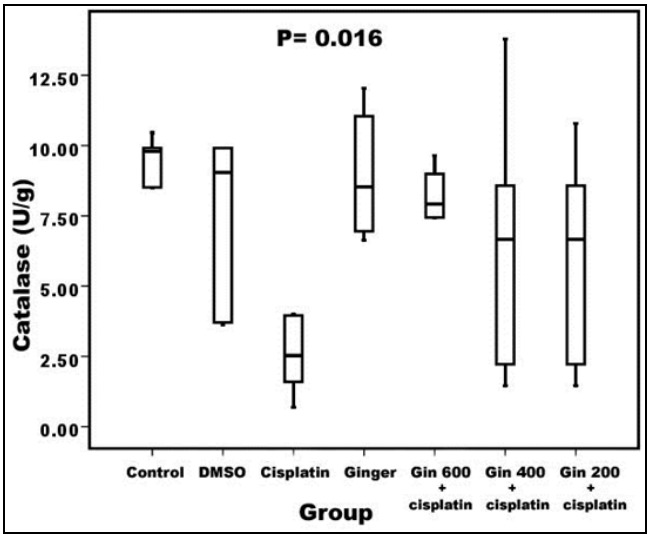

Figure 8: Box plots of catalase for comparison between laboratory data of all groups in heart disease. The box represents the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value. Overall significance of differences between laboratory data of all groups was determined by ANOVA test (p = 0.016)

Table 3: Effect of ginger extract on levels of caspase-3 in the experimental groups

Group		Caspase-3 (ng/ml)
Control	Mean ± SE	13.22 ± 0.4
DMSO	Mean ± SE	13.198 ± 0.4
	P *	0.978
	% *	-0.1
Cisplatin (Positive)	Mean ± SE	15.19 ± 0.5
	P *	0.012
	% *	15
Ginger only	Mean ± SE	13.45 ± 0.47
	P *	0.718
	% *	1.8
Ginger 600+cisplatin	Mean ± SE	14.44 ± 0.3
	P *	0.045
	% *	9.3
	P **	0.238
	% **	-4.9
Ginger 400+cisplatin	Mean ± SE	13.87 ± 0.3
	P *	0.251
	% *	5
	P **	0.052
	% **	-8.7
Ginger 200+cisplatin	Mean ± SE	13.43 ± 0.4
	P *	0.723
	% *	1.6
	P **	0.02
	% **	-11.6

P * = P Value compared to control group; P** =P Value compared to cisplatin (positive) group. The mean difference is significant at P< 0.05. % * = Percent of change compared to control group; % ** = Percent of change compared to cisplatin (positive) group.

Histological examination of heart tissue sections

Histological examination of tissue sections from the heart muscle showed degeneration and necrosis of cardiac muscle fiber cells with dilated blood vessel, and mononuclear cells infiltration were observed in the group 3 (cisplatin). While in group 7 (ginger 600 + cisplatin) the cardiac tissues were protected against cisplatin-induced damage and show heart showing apparently normal myocardial muscles when compared with the control heart tissue slide (Figures 10-15).

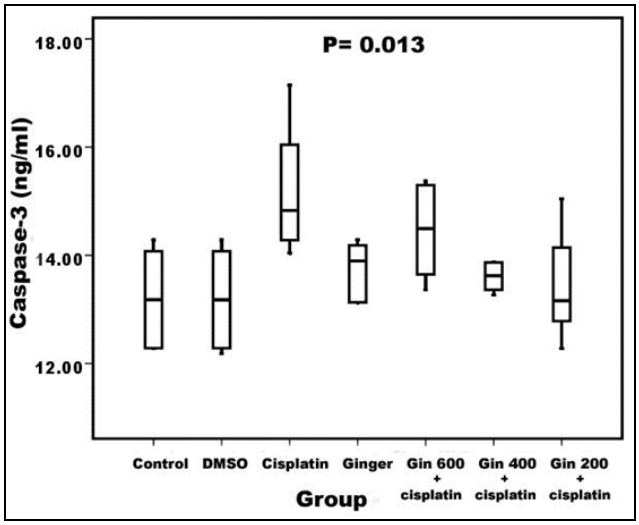

Figure 9: Box plots of caspase-3 for comparison between laboratory data of all groups in heart disease. The box represents the interquartile range. The whiskers indicate the highest and lowest values, and the line across the box indicates the median value. Overall significance of differences between laboratory data of all groups was determined by ANOVA test (p = 0.013)

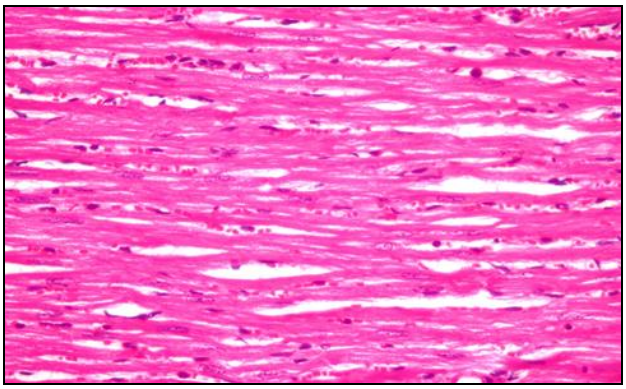

Figure 10: Control negative group: heart showing normal myocardial muscles (H&E X 400)

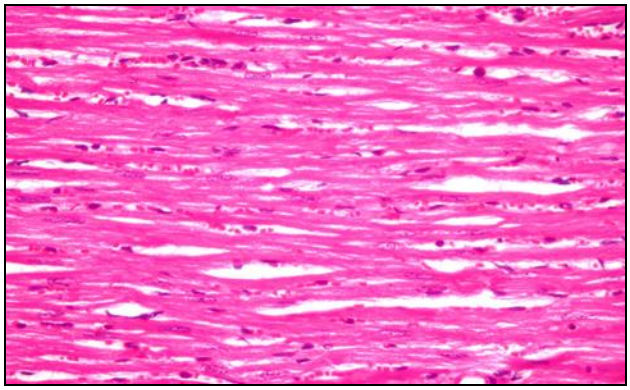

Figure 11: DMSO group: heart showing normal myocardial muscles (H&E X 400)

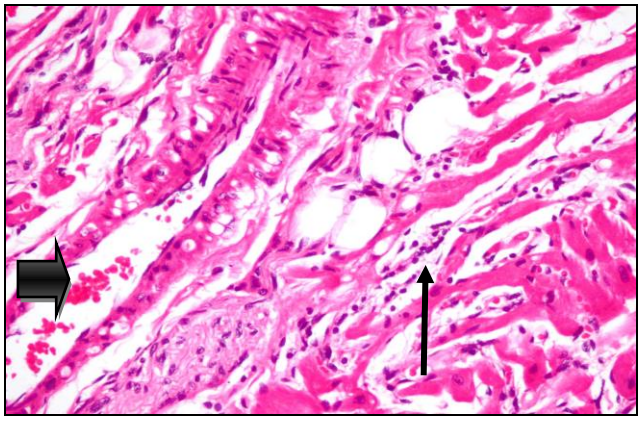

Figure 12: Cisplatin (positive) group: heart showing dilated blood vessel (arrow head), and mononuclear cells infiltration (arrow) (H&E X 400)

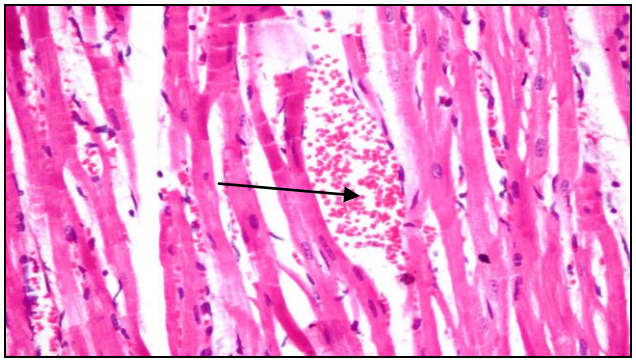

Figure 13: Ginger 200 + Cisplatin group: Heart showing focal inter muscular congested blood capillaries (arrow) (H&E X 400)

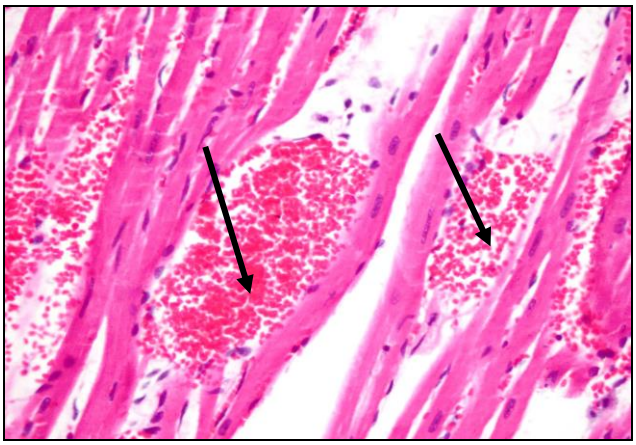

Figure 14: Ginger 400 + Cisplatin group: Heart showing diffuse inter muscular congested blood capillaries (arrows) (H&E X 400)

DISCUSSION

Cisplatin is an inorganic complex formed by an atom of platinum surrounded by chlorine and ammonia. One of the possible mechanisms by which cisplatin accumulates in the cells is by a carrier-mediated processes [24]. Cisplatin becomes activated once it enters the cell. In the cytoplasm the chloride atoms on cisplatin are displaced by water molecules. This hydrolyzed product is a potent electrophile that can react with any nucleophile, including the sulfhydryl groups on proteins and nitrogen donor atoms on nucleic acids. Cisplatin binds to the N7 reactive center on purine residues and as such can cause deoxyribonucleic acid (DNA) damage in cancer cells, blocking cell division and resulting in apoptotic cell death [25].

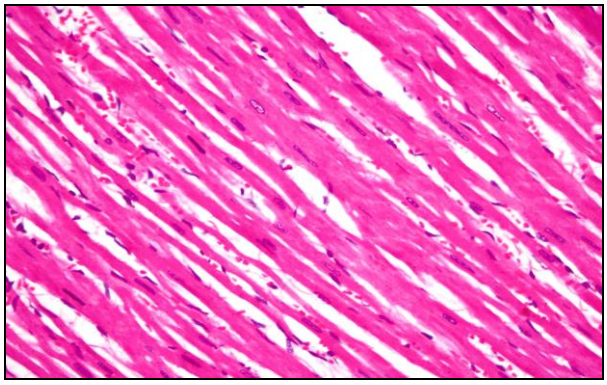

Figure 15: Ginger 600 + Cisplatin group: heart showing apparently normal myocardial muscles (H&E X 400)

Numbers of cardiotoxic effects are reported to be accompanied with chronic cisplatin therapy, such as various types of arrhythmia, ischemic heart disease and heart failure [26]. Many of cardiac (and other) adverse effects of cisplatin alone, and in combination with some other chemotherapeutic agents, are connected with cisplatin-induced oxidative damage [27].

This study revealed that administered a single IP dose of cisplatin (10mg/kg) caused significant elevation of serum total cholesterol, triglyceride, LDH, troponin-T and CK levels compared to the control rats (Table 1), those are in line with other studies [28] which reported that cisplatin-induced cardiotoxicity as a secondary event following cisplatin-induced lipid peroxidation of cardiac membranes with the consequent increase in the leakage of LDH and CK from cardiac myocytes. Workers also, assessed that the oxidative stress plays an important role in the mediation of cardiotoxicity and this in return would influence the levels of serum cardiac markers [29]. Our results are opposite to who found that serum troponin, CKMB are not significantly change in cisplatin treated groups (single dose) compared with control group [40].

Al-Majed reported that kidney damage induced by cisplatin may lead to inhibition of carnitine synthesis and also inhibition of carnitine reabsorption by the proximal tubule of the nephron consequently leading to carnitine deficiency. This marked decrease (78%) of carnitine level in cardiac tissue after treatment of cisplatin was parallel to the marked increase in LDH and CK and the degenerative changes in cardiac tissues, which may point to the possible consideration of carnitine deficiency as a risk factor in cisplatin-induced cardiomyopathy [30].

The cardiac protection of ginger extract is very well established in this study, where increasing the dose consequently reflected in better protection; the reduction of serum enzymes levels. The extent of cardioprotection offered by ginger is associated with a possible explanation is that, ginger , via its effect against lipid peroxidation, causes stabilization of cardiac membranes and prevents the leakage of cardiac enzymes, also may be due to amelioration of renal functions and inhibition of suppression of carnitine levels and antioxidant enzymes such as catalase and superoxide dismutase [31].

Our results showed that cisplatin treatment caused significant increase in cardiac MDA, NO levels and significant decrease in catalase activity (Table 2). Our results are in agreement with who reported that cisplatin increased levels of H2O2, O2− and TBARS and decreased superoxide dismutase and reduced glutathione in serum [38]. Also, studies demonstrated that cisplatin application interrupts redox homeostasis by stimulation of ROS overproduction and reduction of antioxidative enzymes activity [8]. Results reported by Ma et al., [41] showed that cisplatin induces an increase in oxidative stress and alters intracellular Ca^{2+} concentration, including cytosolic and mitochondrial Ca2+ in cisplatin-sensitive SKOV3 cells. Cisplatin induces mitochondrial damage and triggers the mitochondrial apoptotic pathway in cisplatin-sensitive SKOV3 cells.

Amal et al., [42] declared that Cisplatin induced a significant increase in malondialdehyde, and nitric oxide levels. However, glutathione, superoxide dismutase, and catalase levels were significantly diminished

The proposed mechanism of induced cardiotoxicity of cisplatin could be explained as in the following: During the physiological process, the mitochondrial respiratory chain continuously generates ROS. Approximately 2% of the electrons which flow along the respiratory chain escape from the chain and partially reduces molecular oxygen, originating superoxide anion (O2−•). Superoxide anion, the precursor of most of the reactive oxygen species generated in mitochondria as for example hydroxyl radicals HO. An efficient mitochondrial antioxidant defense system maintains the balance between ROS generation and detoxification [32]. Cisplatin unbalances the oxidant–antioxidant ratio by (i) Augmenting ROS generation, mainly hydroxyl radical and (ii) Inhibition of the antioxidant defense system which are SOD, CAT and GSH. These radicals can evoke extensive tissue damage, reacting with membrane lipids, proteins and nucleic acids [33].

Antioxidants have proven to be effective in ameliorating cisplatin-induced toxicity. Ginger extract is a potent antioxidant which is reported to have antitumor effect and to enhance the effect of many known anticancer agents in addition to reducing their toxicities as well.

This study declared that administration of ginger decreased the elevation in MDA and NO levels and increase catalase activity and these changes were nearly normalized, when ginger extract in dose of 600 mg/kg/day-was co-administered with cisplatin. Studies using ginger had reported the significant antioxidant activities. Antioxidant activity through protection of cells and tissues from oxidative damage by scavenging oxygen-free radicals and inhibiting lipid peroxidation, leading to regeneration of damaged tissues and cells [34].

In this study administration of cisplatin induced apoptosis by causing significant elevation in caspase-3 level in heart tissue which amounted to 70.3 % compared to control group (Table 3). This in accordance with who reported that cisplatin generates reactive oxygen species, it triggers the opening of the mitochondrial permeability transition pore that permits the release of cytochrome c from mitochondria to cytosol and hence it will activate the mitochondrial dependent pathway leading to apoptosis [35]. Previous studies shown that cisplatin induces liver cells apoptosis by cytochrome-c release and caspase 3 release activation and causes hepatotoxicity by increasing messenger ribonucleic acid (mRNA) expression of nuclear factor-kappa B (NF-κb) dependent cyclo-oxygenase (COX-II) and inducible nitric oxide synthase (iNOS) [36].

Ginger shows anti-inflammatory action by direct inhibition of COX activity, also exhibits greater inhibitory activity toward the evolution of pro-inflammatory signaling compound prostaglandin-E2 (PG-E2) from COX-II in lipopolysaccharide-activated macrophages [37].

Our results demonstrated that treatment with ginger extract reduced the elevation in caspase-3 level. This is in line with Dugasani who indicated that the ginger extract had protective effects against mitochondrial damage and was able to prevent caspase cascade activation [38].

In the current study histological examination of tissue sections from the heart muscle showed degeneration and necrosis of cardiac muscle fiber cells with dilated blood vessel, and mononuclear cells infiltration were observed in the group 4 (cisplatin). While in group 7 (ginger 600 + cisplatin) the cardiac tissues were protected against cisplatin-induced damage and show heart showing apparently normal myocardial muscles when compared with the control heart tissue slide (Figure 10:15). This is in agreement with who reported that there is no histological difference between control and ginger extract groups, ginger is safe and well tolerated and coadministration of ginger extract in dose of 250 mg/kg with diclofenac sodium partially ameliorated the histotological changes produced in the liver by diclofenac toxicity [43].

Also, other study showed that the cardiac damage produced by cisplatin revealed degeneration and necrosis of cardiac muscle fiber cells with fibrous tissue reaction. Ginger extract also improves the histological changes produced by cisplatin in the liver cells and cardiac muscle fiber cells in comparison with the control [44].

CONCLUSION

Overall, ginger extract is a potent antioxidant and enhance the effect of anticancer agents in addition to reducing their toxicities .Ginger extract before and during co-administration with cisplatin provided near complete protection in terms of plasma biochemical changes and organs histological changes.

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