Protective Effect of Ginger Extract Against Cisplatin-Induced Hepatotoxicity and Cardiotoxicity in Rats.

Ahmed M. Attyah* and Sajida H. Ismail*,[1]

*Department of Pharmacology and Toxicology,College of Pharmacy,University of Baghdad, Baghdad,Iraq.

Abstract

The protective effect of ginger extract against cisplatin-induced hepatotoxicity and cardiotoxicity was evaluated in 30 albino white rats(weighing 200-300 gm) classified into 5groups (6 rats per each group). The rats were treated with 0.5g/kg/day or 1g/kg/day ginger extract orally 5 successive days before and 5 successive days after induction of toxicity with intraperitoneal (IP) injection of (10mg/kg) cisplatin, resulted in a significant reduction in the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) , total serum billirubin(TSB) , lactate dehydrogenase (LDH) and creatine kinase(CK) enzymes in comparison with the cisplatin treated animals; ginger extract also improves the histological changes produced by cisplatin in the liver cells and cardiac muscle fiber cells in comparison with the control . It is concluded that , ginger extract when used concomitantly with cisplatin protects the liver and heart against the toxicity induced by this cytotoxic drug.

Key wards :Ginger, Cisplatin,Oxidative Stress.

تأثيرات الحماية لمستخلص الزنجبيل ضد التسمم الكبدي والقلبي المستحدث بعقار السزبلاتين في الجرذان

احمد محمد عطية* و ساجدة حسين اسماعيل*،[١]

* فرع الأدوية والسموم ، كلية الصيدلة ، جامعة بغداد ، بغداد ، العراق

الخلاصة

إن الهدف من هذه الدراسة هو تقييم التأثير الوقائي المحتمل لمادة مستخلص الزنجبيل ضد التلف الذي تسببه مادة السزبلاتين في خلايا الكبد وخلايا عضلة القلب في الجرذان (٣٠جرذ من النوع الامهق وقسمت الى خمسة مجاميع ولكل مجموعة ٦جرذان) أظهرت النتائج ان اعطاء مادة مستخلص الزنجبيل وبجرعة (٠,٥غم/كغم او١غم/كغم يوميا من خلال الفم) للجرذان لمدة خمسة ايام قبل وخمسة ايام بعد اعطاء جرعة واحدة من السزبلاتين (١٠ملغم/كغم عن طريق البريتون) أدى ذلك الى انخفاض معنوي بمستويات الانزيمات (, CK,TSB,AST ,ALT LDH) مقارنة بمستوياتها عند مجموعة الجرذان التي تم علاجها بجرعة السزبلاتين فقط . كذلك اسهم مستخلص الزنجبيل في تحسين التلف الحاصل في نسيج خلايا الكبد وخلايا عضلة القلب لدى مجموعة الجرذان التي تم علاجها بجرعة مستخلص الزنجبيل قبل وبعد جرعة السزبلاتين مقارنة بتلك التي تم علاجها بجرعة السزبلاتين فقط .وقد استنتج من الدراسة ان استعمال مادة مستخلص الزنجبيل مع عقار السزبلاتين قد يوفر الحماية الكافية لنسيج خلايا الكبد وخلايا عضلة القلب من التلف الذي يسببه عقار السزبلاتين.

الكلمات المفتاحية :الزنجبيل، السزبلاتين ، جهد التأكسد.

Introduction

Cisplatin is a platinum-based drug [(1)], which is one of the most effective anti-neoplastic agents used for treatment of testicular, ovarian, bladder, cervical, lung, and neck cancers [(2)]. The cytotoxic effect of cisplatin is believed to result mainly from its interaction with DNA, via the formation of covalent adducts between certain DNA bases and the platinum compound[(3)], despite its clinical usefulness,cisplatin treatment has been associated with several toxic side effects including nephrotoxicity[(4)], hepatotoxicity and cardiotoxicity [(5)]. Cardiac events have been reported in many case reports as well including electro- cardiographic changes , arrhythmias , myocarditis, cardiomyopathy and congestive heart failure[(3)] . It has been reported that oxidative stress through the generation of reactive oxygen species , decreases antioxidant defense system including antioxidant enzymes and non enzymatic molecules , reduced glutathione, are major alterations in the cisplatin toxicity[(6)]. 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 [(7)] . For centuries, it has been an important ingredient in Chinese, Ayurvedic and Tibb-Unani herbal medicines for the treatment of rheumatism, gingivitis, toothache, asthma , stroke, nausea, vomiting and diabetes [(8)]. 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 [(9)]. This work was designed to assess the protective effect of orally administered ginger extract against cisplatin-induced hepatotoxicity and cardiotoxicity in rats .

[1] Corresponding author E- mail : ph.sajida@yahoo.com

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Materials and Methods

Preparation of Ethanolic Ginger Extract

The ethanolic extract of ginger was made according to the method of Ajith *et al*.[10], by washing of fresh rhizomes of *Zingiber officinale* several times with water. The 500 g of rhizome was cut into small pieces and juice was prepared in 70% ethanol. The extract was prepared by heating the juice at 50–60 ^{0}C for 24 hr with intermitted shaking , filtration made, then centrifuge the extract at 2500g ,supernatant layer were pooled.The solvent was evaporated completely at 50–60 ^{0}C with the help of rotary vacuum evaporator. The residue thus obtained (6.5 g w/w) was used for this study.

Animals and Experimental protocol

Thirty white Albino rats of both sexes, weighing 200- 300 gm were used in this study; they were obtained from and maintained in the Animal House of the Pharmacy College, University of Baghdad under conditions of controlled temperature. The animals were fed commercial pellets and tap water/*ad libitum*. The animals were divided into five groups of six animals and treated as follow: **Group I**- received single IP dose of normal saline . The animals were sacrificed after 5 days , this group served as a negative control . **Group II** - received single IP dose of cisplatin (10mg/kg) and animals were sacrificed after 5 days, this group served as positive control. **Group III**- pretreated with oral dose of ginger extract alone (1g/kg/day) and animals were sacrificed after 10 days . **Group IV** and **V**- animals pretreated with oral dose of ginger extract (0.5g and 1g /kg/day respectively) for 5 successive days before and 5 successive days after single IP cisplatin (10mg/kg) . Animals were sacrificed after 10 days . Animals have been anesthetized by ether, blood was collected directly from the heart by (intracardiac puncture) and poured into plain tubes , the clot was dispersed with glass rod and then centrifuged at 3000 rpm for 15 minute ; the serum was used within 2 days for the estimation of AST[11], ALT[11] ,TSB[12], LDH[13] and CK[14]. Histological sections of the hepatic and myocardial tissues were prepared according to the method of Junqueira LC. *et al* in 1995[15] for evaluating the histopathological changes with ordinary microscope, using paraffin sections technique , tissues 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 . The data presented as Mean±SD . The significance of differences between the mean values were calculated using unpaired student's *t*-test. *p* -values less than 0.05 were considered to be significantly different.

Results

Table (1) indicated that serum levels of AST, ALT and TSB were significantly elevated in the gp.II in comparison with the gp.I ($p<0.05$). While in gp. IV and gp.V the serum levels of AST, ALT and TSB were significantly reduced , (fig.1,2&3). Histological examination of tissue sections from the liver showed certain degeneration and necrosis of hepatocytes with inflammatory cells infilteration around portal area with sinusoidal dilatation were observed in the gp.II (fig.5). While in gp.V the hepatic tissues was protected against the cisplatin-induced damage and shows normal liver tissues with no significant degenerative changes when compared with the gp.I liver tissue slide (fig. 4&6).

Table 1 : The effect of ginger extract on the serum levels of AST, ALT and TSB of the treated animals.

Groups N=6/each group	Control (Grp.I)	Cisplatin (10mg/kg) (Grp.II)	Ginger (1g/kg) alone (Grp.. III)	Ginger (0.5g /kg) + cisplatin (Grp.IV)	Ginger (1g/kg) + cisplatin (Grp.V)
Serum AST level (U/L) and percent of change	6.5± 1.05	18± 2.28* 177 %	5.33±1.37 18%	9.17 ± 1.94^S 49 %	8.5 ± 1.64 ^{S} 52.78 %
Serum ALT level (U/L) and percent of change	4.5± 0.55	10.17 ± 2.99* 126 %	3.67±1.37 18.4%	5.17 ±1.17 ^{S} 49.1 %	5 ±1.41 ^{S} 50.84 %
TSB level (U/L) and percent of change	1.36±0.29	6.15 ± 0.83* 352 %	1.38 ± 0.15 1.47%	2.55 ± 0.15 ^{S} 58.5 %	2.25 ± 0.21 ^{S} 63.4%

- Each value represents mean ± SD.
- * $p < 0.05$ in respect to the gp I .
- s = significant difference in respect to the gp II.
- N = number of animals

Table(2) indicated that serum levels of LDH and CK were significantly elevated in the gp.II in comparison with the gp.I ($p<0.05$), While in gp.IV and gp.V the serum levels of LDH and CK were significantly reduced in comparison to the gp.II (fig.7& 8).Histological examination of tissue sections from the heart muscle clearly showed degeneration and necrosis of cardiac muscle fiber cells with fibrous tissue reaction were observed in the gp.II (fig.10). While in gp.V the cardiac tissues was protected against cisplatin-induced damage and shows normal tissue with no significant degenerative changes when compared with the gp.I heart tissue slide (fig. 9&11).

Table (2):The effect of ginger extract on the serum levels of LDH and CK of the treated animals.

Groups N=6/each group	Control (Grp.I)	Cisplatin (10mg/kg) (Grp.II)	Ginger (1g/kg) alone (Grp. III)	Ginger (0.5g /kg) + cisplatin (Grp.IV)	Ginger (1g/kg) +cisplatin (Grp.V)
Serum LDH level (U/L) and percent of change	98.6± 18.04	275.6 ± 29.26* 179.58 %	96.7 ± 14.5 1.86%	176.7 ± 32.8 ^{S} 36 %	156 ± 30.2 ^{S} 43.37 %
Serum CK level (U/L) and percent of change	78.73± 5.73	148.87± 10.4* 89 %	75.73± 6.21 3.81%	128.71±7.93 ^{S} 13.54 %	96.57 ± 3.59 ^{S} 35.13 %

- Each value represents mean ± SD.
- * $p < 0.05$ in respect to the gp I.
- s= significant difference in respect to the gp II.
- N = number of animals

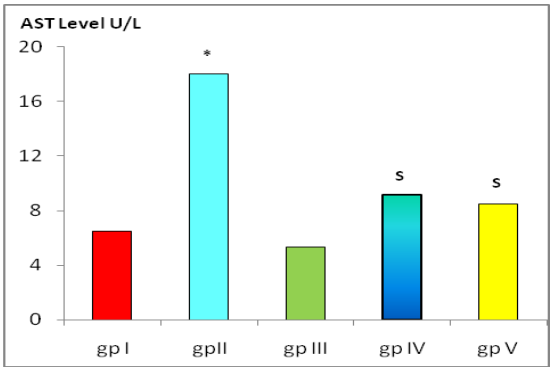

Figure 1 : Effect of ginger extract on the serum levels of aspartate aminotransferase (AST) in rats with hepatotoxicity induced by cisplatin .
*P<0.05 in comparison with the gp I.
- s = significant difference in respect to the gp II.

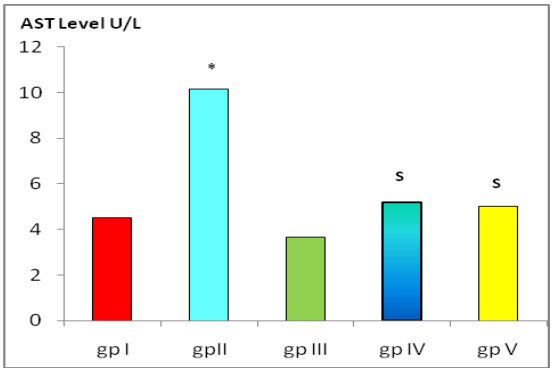

Figure 2 : Effect of ginger extract on the serum levels of alanine aminotransferase (ALT) in rats with hepatotoxicity induced bycisplatin.
*P<0.05 compared with the gp l.
- s=significant difference in respect to the gp II.

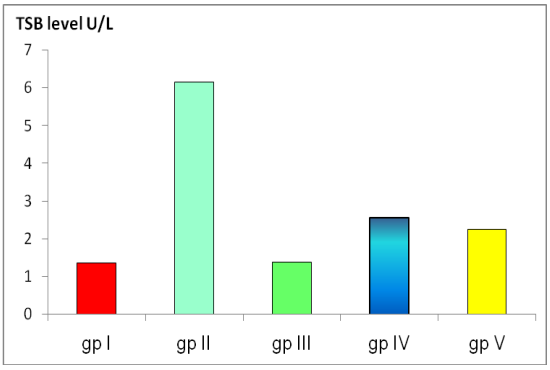

Figure 3: Effect of ginger extract on the serum levels of total serum billirubin (TSB) in rats with hepatotoxicity induced by cisplatin
*P<0.05 compared with the gp I.
- s= significant difference in respect to the gp II.

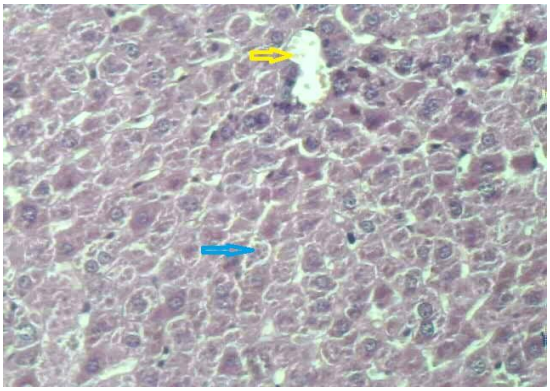

Figure 4 : Section showing the normal liver tissue of rats as control group. magnification :100X , staining : haematoxylline &eosin.

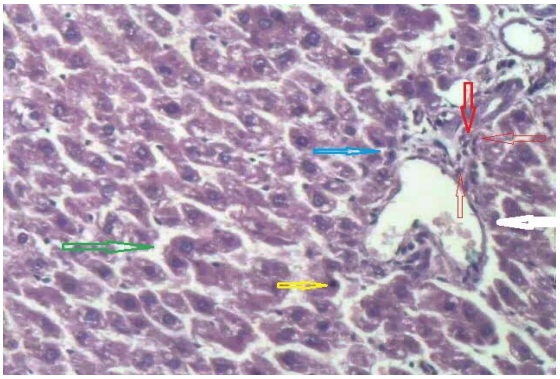

Figure 5 : Section showing morphological alteration of liver tissue for cisplatin –treated rats. Blue arraw represents hepatocyte degeneration. Yellow arraw represents hepatocyte necrosis. Red arraw represents inflammatory cells infilteration around portal area (white arraw) . Green arraw represents sinusoidal dilatation . magnification :200X, staining :haematoxylline &eosin.

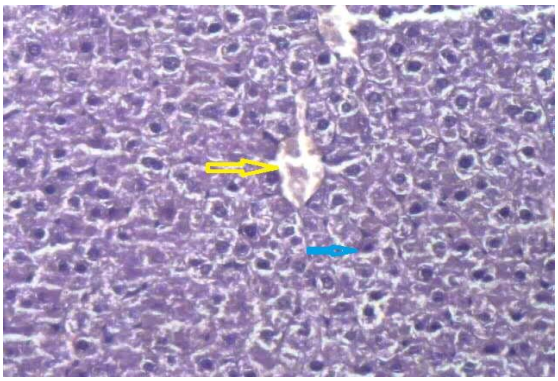

Figure 6: Section showing near normal structural appearance of hepatocytes in gp Vby administration 1g/kg/day ginger extract against cisplatin-induced liver damage. Blue arraw represents normal hepatocyte.Yellow arraw represents normal central vein. Magnification : 200X, staining :haematoxylline & eosin.

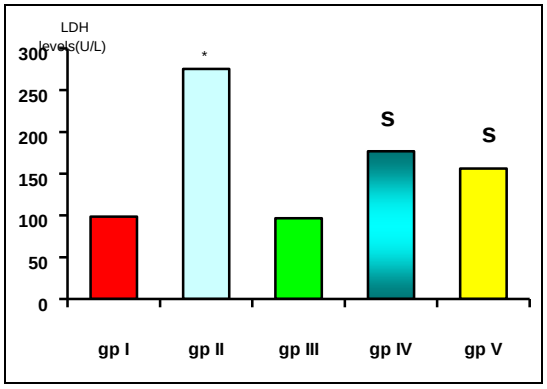

Figure 7: Effect of ginger extract on the serum levels of lactate dehydrogenase (LDH) in rats with cardiotoxicity induced by cisplatin .
*P< 0.05 compared with the gp I.
- s= significant difference in respect to the gp II.

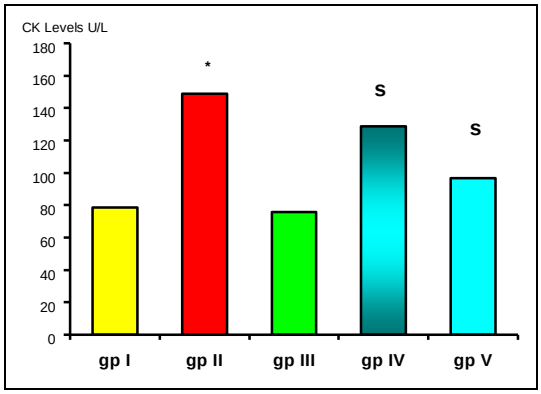

Figure 8 : Effect of ginger extract on the serum levels of creatine kinase (CK) in rats with cardiotoxicity induced by cisplatin .
*P<0.05 compared with the gp I.
- s= significant difference in respect to the gp II.

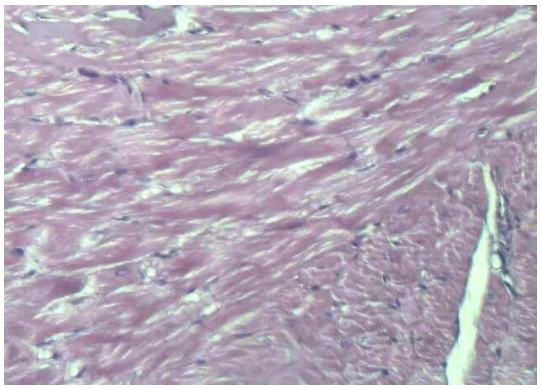

Figure 9: Section showing the normal cardiac muscle fiber cells of rats as control group . magnification :200X, staining :haematoxylline &eosin.

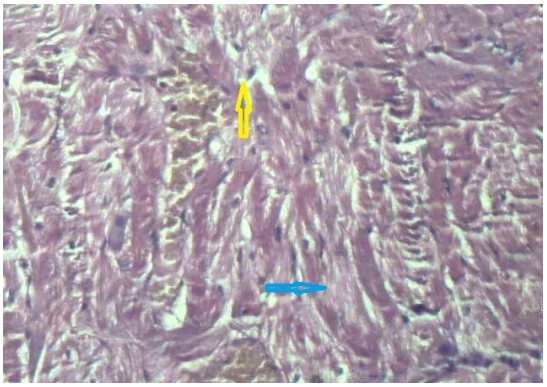

Figure 10: Section showing morphological alteration of cardiac muscle fiber cells from cisplatin-treated rats(gp II). Yellow arraw represents degeneration and necrosis of myocardial fibers cells. Blue arraw represents fibrous tissue reaction. magnification :200X, staining : haematoxylline &eosin.

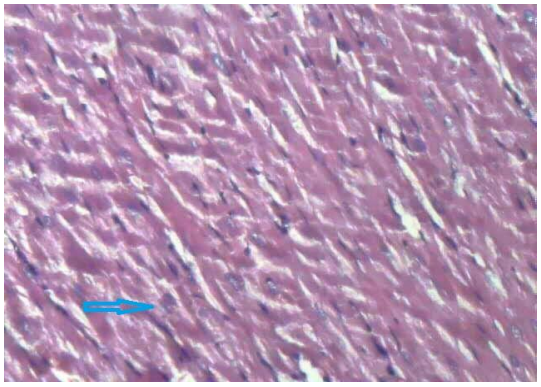

Figure 11 :Section of heart from rats treated by ginger extract 1g/kg/day(gp V). showing near normal like structure appearance of cardiac muscle fiber cells (Blue arraw). magnification : 200X, staining :haematoxylline &eosin.

Discussion

The cytotoxic effect of Cisplatin is enhanced by the elevation of the dose, however,at higher doses, the less common toxic effects, such as hepatotoxicity, may arise [16].It has been suggested that oxidative stress is an important mechanism of cisplatin-induced toxicity possibly due to depletion of reduced glutathione GSH[17], also many studies reported that there were a significant elevation in the hepatic malonaldehyde(MDA) and reduction in the level of antioxidant enzymes in rats treated with cisplatin[18,19]. Transaminases are the most sensitive biomarkers directly implicated in the extent of cellular damage and toxicity because they are cytoplasmic in location and are released into the circulation after cellular damage [20], elevation of the serum levels of the hepatic enzymes and bilirubin are the indicators for impaired liver functions [21]. In this study,the hepatotoxicity of cisplatin was clearly observed through an a significant elevation of serum AST,ALTand TSB levels in cisplatin-treated rats compared with the control (fig.1,2&3) as it had been previously reported that cisplatin administration causes deteriorations of liver function tests such as serum ALT, AST, LDH and TSB revealed hepatic dysfunction, which could be a secondary event following cisplatin-induced liver damage with the consequent leakage from hepatocytes [19,21&22]. Several reports[23,10] which showed the protective effects of ginger extract or its constituents, through their antioxidant properties and improve the hepatic dysfunctions and hepatic damage that induced by hepatotoxicants, CCl4 and acetaminophen. Results of this study demonstrated that ginger extract improve the elevated levels of the serum AST , ALT and TSB when compared to the cisplatin treated group ($p<0.05$), and these may be attributed to ginger components which may stabilize hepatocytes plasma membrane and prevent delivery of AST and ALT to the extracellular fluid[10]. Histopathological changes observed in the present study including necrosis and degeneration of hepatocytes with inflammatory cells infilteration around portal area with sinusoidal dilatation (fig.5) are consistent in general with the other reports [6, 24& 25] , and these changes were nearly normalized, when ginger extract in dose of 1g/kg/day was co-administered with cisplatin (fig. 6). In addition to antioxidant effects , ginger may also exert its hepatoprotective effect by means of different ways. For example , in the mechanism of cisplatin toxicity it was 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)[26]. However, ginger shows anti-inflammatory action by direct inhibition of COX activity [27], also exhibits greater inhibitory activity toward the evolution of pro-inflammatory signaling compound prostaglandin-E2(PG-E_2) from COX-II in lipopolysaccharide-activated macrophages[28], also Cisplatin hepatotoxicity was shown to be exacerbated by elevated expression of cytochrome P450-$2E_1$ enzyme[29], on the other hand Foster *et al*. (2003) demonstrated that ginger components showed significant inhibition of cytochrome P450 mediated metabolism of marker substrates[30] and also ginger prevents bromobenzene-induced hepatotoxicity by blocking the enzyme cytochrome P450-$2E_1$[31].In this study ,the group administered a single IP dose of cisplatin(10mg/kg) revealed significant elevation of serum LDH and CK levels compared to the control rats (fig.7&8), are consistent with those observed in other studies[3,32] which were reported that cisplatin-induced cardiotoxicity could be 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 . Concerning the histological changes ,the cardiac damage produced by cisplatin revealed degeneration and necrosis of cardiac muscle fiber cells with fibrous tissue reaction,(Fig.10), are consistent in general with findings observed by Al-Majed *et al*. in 2006 which showed degenerative changes, vacuolated cytoplasm of many muscle cells and blood vessels are engorged with blood [32].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 [(32)]. cisplatin elevates serum cardiotoxicity enzymatic indices (LDH and CK) and causes severe histopathological lesions in cardiac tissues,the effect could be 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 [(32)]. There are many evidences deal with the administration of antioxidants may be effective in ameliorating cisplatin-induced cardiotoxicity, acetyl-L-carnitine, DL-α-lipoic acid and silymarin, which have been proven to possess antioxidant potentials, appear to be potential candidates to ameliorate cardiotoxicity associated with cisplatin use in rats[(33)]. The cardiac protection of ginger is very well evident in this study, where increasing the dose consequently reflected in better protection; the reduction of serum enzymes levels and reversing the histological changes revealed by low incidence of degeneration and necrosis in addition diminishing fibrous tissue reaction as shown in figures 7,8&11.Mansour *et al*. in 2008 showed that 6-gingerol act as apotentially selective cardioprotective agent , against cardiotoxicity induced by doxorubicin by augmentation of endogenous myocardial antioxidants activities [(33)] . The extent of cardioprotection offered by ginger is associated with a significant attenuation of serum LDH ,CK ,AST and ALT levels , 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 [(34)].In conclusion Oxidative stress plays a major role in cisplatin-induced toxicities during the normal clinical regimens of treatment. Antioxidants have proven to be effective in ameliorating cisplatin-induced toxicity in many preclinical and few clinical interventions. 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.Ginger extract prior and co-administration with cisplatin provided near complete protection in terms of plasma biochemical changes and organs histological changes .

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