Studies on the Protective Effects of Ginger Extract and in Combination with Ascorbic Acid against Aluminum Toxicity Induced Hematological Disorders, Oxidative Stress and Hepatorenal Damage in Rats

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ABSTRACT

The present study was conducted to evaluate the protective effect of ginger extract and in combination vitamin C (AA) against the toxicity of aluminum chloride (AlCl3). Sixty rats were divided into 6 equal groups. Group 1 (GP 1): served as control, GP 2: treated with AlCl3 (150 mg/kg BW), GP 3: treated with ginger (100 mg/kg BW), GP 4: treated with vitamin C (50 mg/kg BW), GP 5: treated with AlCl3 & ginger, GP 6: treated with AlCl3 & vitamin C with those a previous mentioned doses. Rats were orally treated daily for 4 weeks. Whole blood, serum samples and liver specimens were collected to evaluate hematological, biochemical alterations and hepatic antioxidant parameters. Our result revealed that AlCl3 treatment induced a decrease in erythrocytes (RBCs) count, hemoglobin (Hb) concentration and hematocrit (Hct), meanwhile total leukocyte (TL) and neutrophil counts as well as liver enzymes (ALT, AST, ALP and LDH) activities, glucose, cholesterol, triglyceride (TG) levels and hepatic malondialdehyde (MDA) were elevated. In contrast hepatic reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) and serum total antioxidant capacity (TAC) were decreased. The ginger treatment improved the adverse effects induced by AlCl3, moreover co-administration with vitamin C upgrade action of ginger and ameliorate the toxic effect of AlCl3 on hematological, hepatorenal damage and antioxidant parameters. In conclusion, ginger showed an apparent protective effect against AlCl3 induced toxicity especially if in combination with vitamin C.

Keywords: Aluminum chloride; ginger extract; vitamin C; hematological parameters; hepatorenal and antioxidant parameters.

INTRODUCTION

Aluminum (Al) is the third most abundant element in the earth’s crust and used extensively in modern daily life. It is present in our food product, medicines and is also added to drinking water for purification purposes (Ochmanski and Barabasz, 2000). It has been estimated that about 20% of daily intake of aluminum comes from cooking utensils made of aluminum (Greger et al., 1985). Humans are exposed to aluminum from mouth, nose and epidermal route inducing toxic effects to a variety of organ systems including brain, kidney, liver, lungs as well as bone and blood (Oteiza et al., 1993).

The chronic consumption of aluminum produces neurotoxic effects on human and animals, also it causes alteration in skeletal, hematopoietic and respiratory systems (Nayak, 2002 and Chaitanya et al., 2012). Aluminum ions alter the properties and structure of cellular membranes, inhibit many enzymes like alkaline phosphatase, acetylcholinesterase, and adeny cyclase. Antagonistic interactions between aluminum ions and other elements such as: calcium, magnesium, iron, silicon, phosphorus, copper, and zinc were observed in biological systems (Kowaleczyj et al., 2004). Also aluminum generates reactive oxygen species, resulting in oxidative deterioration of lipids, proteins and DNA (EL-Dermendorf, 2004).

Today many botanicals natural products are used in therapy of different diseases. Ginger is an example of botanicals which is gaining popularity amongst modern physicians (El-Sharalky et al., 2009). The main constituents of ginger include volatile oil (b-bisabolene, cineol, phellandrene, citral, borned, citronellol, geranial, linalool, limonene, zingerberol, zingerberene, camphene, oleoresin, gingerol and shogoal), phenol (gingerol and zingerone), proteolytic enzymes (zingibain), vitamin B6, vitamin C, calcium, magnesium, phosphorus,
potassium, and linoleic acid (Onwuka et al., 2011). Its constituents are stated to have antiemetic, antithrombotic, anthepatotoxic, anti-inflammatory, and androgenic and antioxidant (Khaki and Khaki, 2010). The antioxidant value of ginger is due to its ability to scavenge a number of free radicals and protect cell membrane lipids from oxidation in a dose dependent manner (Farag et al., 2010).

Ascorbic acid (AA) is an essential micronutrient required for normal metabolic functioning of the body. It is an important water-soluble antioxidant in biological fluids. Many biochemical, clinical, and epidemiologic studies indicated that AA may be of benefit in chronic diseases such as cardiovascular disease, cancer, and cataract, probably through antioxidant mechanisms (Carr and Frei, 1999). Vitamin C (Vit C) is effective scavenge reactive oxygen radicals (ROS), thus preventing tissue damage. It can act to overcome oxidative stress, forming part of the antioxidant system (Mor and Ozmen, 2010). Oral supplementation with vitamin free radical scavengers as ascorbic acid may protect the animals from the harmful effect of aluminum, it acts against the toxic, mutagenic and carcinogenic effects of environmental pollutants by stimulating liver detoxifying enzymes (Sallam et al., 2005).

This work evaluated the protective effect of ginger extract and in combination with vitamin C against the AlCl₃ toxicity in rats through some hematological and hepatorenal markers as well as hepatic oxidative stress and antioxidant parameters.

**MATERIALS AND METHODS**

**Experimental animal**
Sixty male albino rats of 1-2 month old (average body weight 100-120 gm) were obtained from Helwan farm of laboratory Animals (Ministry of Public Health). The animals were acclimatized under standard laboratory conditions for 2 weeks prior to dosing. They had free access to standard diet and water ad-libitum.

**Chemicals**

**Experimental design**
Sixty male albino rats were randomly divided into six equal groups. The groups treated as follows. Group 1 (GP 1) served as control take a normal saline. GP 2 treated orally with 150 mg/kg BW of AlCl₃. GP 3: treated orally with ginger extract at a dose 100 mg/kg BW, GP 4: treated orally with vitamin C (AA) at a dose 50 mg/kg BW, GP 5 : treated orally with AlCl₃ at a dose 150 mg/kg BW and ginger extract at a dose 150 mg/kg BW. Rats were treated with their doses daily for 4 weeks.

**Blood samples**
At the end of the 4th week post treatment two blood samples were withdrawn from the medial canthus of the eye, the first sample in eppendorf tubes with EDTA for hematological examination and the second blood samples were collected in clean test tubes and allowed to clot, then centrifuged for ten minutes at 3000 r.p.m. Serum was separated and stored into in eppendorf tubes at – 20°C to be used for biochemical analysis.

**Hematological parameters**
Whole blood used for the determination of erythrocyte count, hemoglobin content and Hct, mean corpuscular volume (MCV),
mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) values according to Feldman et al. (2000).

**Total and differential leukocytic count**
Total leukocyte count was performed by using improved neubauer hemocytometer and diluting fluids of leukocyte count. The blood film made as soon as possible after collection of blood sample. By manual method, two blood films were made for each blood sample, stain the blood film by giemsa stain and differential leukocyte count were done (Feldman et al., 2000).

**Selective biochemical parameters**
Serum ALT and AST were determined using diagnostic kits obtained from (Colorimetric Randox, UK) according to Reitman and Frankel (1957). ALP and LDH were estimated with commercial diagnostic kits (Teco diagnostics, USA) according to Roy (1970) and Buhl and Jakson (1978) respectively. Glucose, cholesterol, and triglycerides were measured spectrophotometrically by using read made kits provided by Spinract according to Young (2001), while total protein and albumin were estimated according to Burtis and Ashwood (1999) and Dumas and Biggs (1972) respectively. Serum urea and creatinine were assayed spectrophotometrically using diagnostic kits (Human, Germany. Co) according to Fawcett and Soctt (1960) and Szasz et al. (1979) respectively.

**Measurement of antioxidant and oxidative stress markers**
**Preparation of liver homogenate**
At the end the 4th week post treatment one gram of liver tissues was collected from each rat. Liver tissue was washed by ice-cold 0.9% NaCl solution and homogenized in 9ml ice-cold PBS (PH 7.5) using homogenizer instrument. The homogenate was cold centrifuged for 15 minutes at 3000 r.p.m and the supernatant was collected used directly, or stored into eppendorf tubes and kept at −80°C for further use (Ferdandez-Botran et al., 2002).

**Hepatic Malondialdehyde (MDA) and antioxidant markers**
Hepatic MDA, GSH, SOD, CAT and serum TAC levels, were determined spectrophotometrically using commercial kits provided by (Bio-diagnostic, Egypt) according to the methods of Satoh (1978), Beutler et al. (1963), Nishikimi et al. (1972), Cohen et al. (1970) and Koracevic et al. (2001) respectively.

**Statistical analysis**
Data were analyzed using statistical software program (SPSS for Windows, version 20, USA). Means and standard error for each variable were estimated. Differences between means of different groups were carried out using one way ANOVA with Duncan multiple comparison tests. Dissimilar superscript letters in the same column show a significance (P<0.05).

**RESULTS**

**Hematological results**

**Erythrogram**
AlCl$_3$ administration in rats (GP.2) significantly reduced RBCs count, Hb and Hct value (p < 0.05) when compared with the control group. Meanwhile the treatment of AlCl$_3$ treated group either with ginger extract alone or with vitamin C significantly increased Hb and Hct value when compared with (GP.2). While MCV and MCHC levels were insignificantly changed in between all groups (table, 1).

**Leukogram**
As presented in table (1), oral administration of AlCl$_3$ (GP.2) significantly increased TL and neutrophil counts comparing by control one. Also the treatment with ginger extract alone (GP.3) significantly increased TLC when compared with control group. Only co- administration of ginger and Vitamin C
were able to improve the increase of TLC induced by AlCl$_3$ treatment.

**Biochemical results**

**Liver function markers**

The activities of liver aminotransferases (ALT & AST), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) were significantly increased upon AlCl$_3$ administration in GP.2 when compared with control one. Both aminotransferases and LDH were corrected by the treatment with ginger alone or with ginger and vitamin C (GP. 5 & GP.6) respectively. Meanwhile ALP enzyme significantly decrease only in (GP.6) comparing with AlCl$_3$ treated group (GP.2) as displayed in table (2).

**Cholesterol, triglyceride and glucose levels**

Total cholesterol and triglyceride levels were significantly increased in AlCl$_3$ treated GP.2 comparing by control one. But GP. 5 and GP. 6 total cholesterol and triglyceride levels were significantly reduced compared with AlCl$_3$ treated group (GP.2). The same trend was adopted by glucose level in the serum (table.2).

**Total protein and albumin levels**

The total protein (TP) and albumin levels fell much lower in AlCl$_3$ treated group (GP.2) than control one. Only a TP return to its normal level in AlCl$_3$ group treated with ginger extract and vitamin C (GP.6) but albumin levels insignificantly changed when compared either with AlCl$_3$ treated group (GP.2) or with control one (table.3).

**Kidney function markers**

As shown in table (3), AlCl$_3$ treated rats (GP.2) showed a significant elevation in both serum urea and creatinine levels when compared with control one. Moreover, no

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Table 1: Some Hematological Parameters (Mean ± S.E) at the 4th week post treatment with ginger and vitamin C in AlCl$_3$ intoxicated rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>RBC 10$^6$/μL</th>
<th>Hb g/dl</th>
<th>PCV %</th>
<th>MCV fl</th>
<th>MCH Pg</th>
<th>MCHC %</th>
<th>TLC 10$^9$/μL</th>
<th>Neutro 10$^3$/μL</th>
<th>Lymphocytes 10$^3$/μL</th>
<th>Eosino 10$^3$/μL</th>
<th>Mono 10$^3$/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP1(Cont)</td>
<td>6.75 ± 0.49a</td>
<td>18.29 ±</td>
<td>52.20 ±</td>
<td>78.99 ±</td>
<td>27.77 ±</td>
<td>35.09 ±</td>
<td>14.59 ±</td>
<td>1.39 ±</td>
<td>12.60 ±</td>
<td>0.24 ±</td>
<td>0.35 ±</td>
</tr>
<tr>
<td>GP2(Al)</td>
<td>5.24 ± 0.36d</td>
<td>11.47 ±</td>
<td>35.70 ±</td>
<td>70.66 ±</td>
<td>22.42 ±</td>
<td>32.18 ±</td>
<td>17.01 ±</td>
<td>3.87 ±</td>
<td>12.38 ±</td>
<td>0.47 ±</td>
<td>0.28 ±</td>
</tr>
<tr>
<td>GP3(G)</td>
<td>6.57 ± 0.32b</td>
<td>17.07 ±</td>
<td>50.01 ±</td>
<td>77.20 ±</td>
<td>26.16 ±</td>
<td>34.21 ±</td>
<td>17.22 ±</td>
<td>2.16 ±</td>
<td>14.78 ±</td>
<td>0.06 ±</td>
<td>0.20 ±</td>
</tr>
<tr>
<td>GP4(VitC)</td>
<td>6.91 ± 0.34c</td>
<td>17.15 ±</td>
<td>49.10 ±</td>
<td>71.87 ±</td>
<td>24.93 ±</td>
<td>35.01 ±</td>
<td>15.13 ±</td>
<td>1.38 ±</td>
<td>10.47 ±</td>
<td>0.00 ±</td>
<td>0.36 ±</td>
</tr>
<tr>
<td>GP5(Al+G)</td>
<td>6.13 ± 0.46b</td>
<td>15.06 ±</td>
<td>46.00 ±</td>
<td>76.81 ±</td>
<td>25.84 ±</td>
<td>32.73 ±</td>
<td>15.56 ±</td>
<td>2.36 ±</td>
<td>12.76 ±</td>
<td>0.06 ±</td>
<td>0.36 ±</td>
</tr>
<tr>
<td>GP6(Al+G+VitC)</td>
<td>6.12 ± 0.25c</td>
<td>15.20 ±</td>
<td>48.20 ±</td>
<td>79.21 ±</td>
<td>24.95 ±</td>
<td>31.66 ±</td>
<td>14.66 ±</td>
<td>2.35 ±</td>
<td>12.17 ±</td>
<td>0.11 ±</td>
<td>0.00 ±</td>
</tr>
</tbody>
</table>

Cont.( control), Al (Aluminum chloride ), G (Ginger extract ), Vit C (Vitamin C), Al+G (Aluminum chloride & Ginger), Al+G+Vit C (Aluminum chloride , Ginger & Vitamin C). The same column not followed by the same letter differ significantly (P<0.05).
significant changes were observed in serum urea and creatinine levels, in the ginger and vitamin C alone treated groups (GP.3 &.4). On the other hand, the treatment of AlCl₃ group either with ginger extract (GP.5) or with ginger extract and vitamin C (GP.6) resulted in significant improvement in serum urea and creatinine levels compared with AlCl₃ treated rats (GP. 2).

Table (2): Some selective Serum Biochemical parameters (Mean ± S.E) at the 4th week post treatment with ginger and vitamin C in AlCl₃ intoxicated rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>ALT U/L</th>
<th>AST U/L</th>
<th>ALP U/L</th>
<th>LDH U/L</th>
<th>Cholesterol mg/dl</th>
<th>TG mg/dl</th>
<th>Glucose mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP 1(Cont)</td>
<td>23.39±</td>
<td>42.60±</td>
<td>287±</td>
<td>1706.6±</td>
<td>105.46±</td>
<td>118.80±</td>
<td>115.60±</td>
</tr>
<tr>
<td>GP 2(AI)</td>
<td>±1.08±</td>
<td>±1.50±</td>
<td>±11.04±</td>
<td>±91.64±</td>
<td>±8.29±</td>
<td>±1.15±</td>
<td>±2.50±</td>
</tr>
<tr>
<td>GP 3(G)</td>
<td>33.60±</td>
<td>51.96±</td>
<td>384±</td>
<td>2234.8±</td>
<td>±78.12±</td>
<td>±8.99±</td>
<td>±7.67±</td>
</tr>
<tr>
<td>GP 4 (Vit C)</td>
<td>±1.50±</td>
<td>±1.73±</td>
<td>±5.33±</td>
<td>±33.16±</td>
<td>±4.68±</td>
<td>±2.58±</td>
<td>±2.13±</td>
</tr>
<tr>
<td>GP 5(Al+G)</td>
<td>19.42±</td>
<td>40.82±</td>
<td>286±</td>
<td>1650.2±</td>
<td>115.40±</td>
<td>115.79±</td>
<td>115.37±</td>
</tr>
<tr>
<td>GP 6 (Al+G+VitC)</td>
<td>±1.23±</td>
<td>±0.69±</td>
<td>±6.96±</td>
<td>±44.66±</td>
<td>±6.20±</td>
<td>±1.13±</td>
<td>±4.53±</td>
</tr>
</tbody>
</table>

Table (3): Some selective Serum Biochemical parameters (Mean ± S.E) at the 4th week post treatment with ginger and vitamin C in AlCl₃ intoxicated rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>TP g/dl</th>
<th>Albumin g/dl</th>
<th>Globulin g/dl</th>
<th>A\G ratio</th>
<th>Urea mg/dl</th>
<th>Creatinine mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP1(Cont.)</td>
<td>8.90±</td>
<td>4.15±</td>
<td>4.74±</td>
<td>0.90±</td>
<td>52.64±</td>
<td>0.59±</td>
</tr>
<tr>
<td>GP2(AI)</td>
<td>±0.46±</td>
<td>±0.14±</td>
<td>±0.44±</td>
<td>±0.09±</td>
<td>±3.91±</td>
<td>±0.02±</td>
</tr>
<tr>
<td>GP3(G)</td>
<td>6.95±</td>
<td>3.54±</td>
<td>3.22±</td>
<td>1.14±</td>
<td>68.10±</td>
<td>0.85±</td>
</tr>
<tr>
<td>GP4 (Vit C)</td>
<td>±0.42±</td>
<td>±0.15±</td>
<td>±0.33±</td>
<td>±0.10±</td>
<td>±2.14±</td>
<td>±0.05±</td>
</tr>
<tr>
<td>GP5(Al+G)</td>
<td>7.99±</td>
<td>3.77±</td>
<td>4.21±</td>
<td>0.95±</td>
<td>49.89±</td>
<td>0.55±</td>
</tr>
<tr>
<td>GP6 (Al+G+VitC)</td>
<td>±0.31±</td>
<td>±0.27±</td>
<td>±0.40±</td>
<td>±0.16±</td>
<td>±1.50±</td>
<td>±0.01±</td>
</tr>
</tbody>
</table>

Cont (control), Al (Aluminum chloride ), G (Ginger extract), Vit C (Vitamin C), Al+G (Aluminum chloride & Ginger), Al+G+Vit C (Aluminum chloride , Ginger & Vitamin C). The same column not followed by the same letter differ significantly (P<0.05).
**Oxidative stress and antioxidant markers in serum and hepatic homogenates**

As in figures (1-5) oral administration of AlCl₃ in rats (GP.2) resulted in a significant increase in the hepatic MDA level (p < 0.05) when compared with control one (GP.1). In contrast hepatic SOD, CAT, GSH and serum TAC levels were significantly down-regulated in AlCl₃ treated group (GP.2) comparing with control one. These alterations were ameliorated upon treatment either with ginger (GP.5) or ginger and vitamin C (GP.6) comparing with AlCl₃ treated group (GP.2) except hepatic MDA and serum TAC levels were not improved with ginger treatment (GP5).

**DISCUSSION**

Aluminum is a nonessential metal to which humans are frequently exposed. Aluminum in the food supply comes from natural sources, water used in food preparation, food ingredients, and utensils (WHO, 1996). This study evaluates the protective effect of supplementation of ginger extract alone or with vitamin C against aluminum chloride induced toxicity in rats. The erythrogram in our work revealed that AlCl₃ treatment resulted in normocytic normochromic anemia. Where several mechanisms have been proposed for the aluminum-induced anemia, but the exact mechanism of aluminum-induced anemia is unknown (Osman et al., 2012). Our result agree with Al-Hashem (2009) who recorded normocytic normochromic anemia in rats treated orally with AlCl₃ (0.5 mg/kg BW for 30 day) that may be attributed to a shortened life span of circulating erythrocytes and reduced RBCS production in bone marrow as a result of the oxidative stress induced by AlCl₃ as well as increase RBCs membrane fragility. Also the reduced level of hemoglobin content can be associated with RBCs hemolysis which confirmed by reduced RBCs count in the present study. Other proposed mechanism appears to involve in anemia is inhibition of heme synthesis, either by inhibition of enzyme activity or interference with iron incorporation or utilization (Ganchev et al., 1998; Han and Dunn, 2000). Also the induced anemia may be related to an increase in heme oxygenase activity (Fulton and Jeffery, 1994; Chmielnicka et al., 1996). Leukogram in our study showed leukocytosis and neuterophilia in aluminum-treated rats that may indicate activation of the immune system (El-Demerdash, 2004). This in the same line with Joshi et al. (2013) who found that orally administration of AlCl₃ to male rats for 90 resulted in leukocytosis. The corrective effect of ginger extract on alterations of erythrogram and leukogram induced by aluminum toxicity may be attributed either due to its antioxidant activity as oil of ginger contain antioxidants such as polyphenol (6-gingerol and its derivatives), flavonoids and total tannin which reduce or scavenge free radicals, or may be due to rebuilding activities of nutrient and phytochemicals found in the extract (Mindell, 1992). Also ginger has an immunostimulant effect (Bairwa et al., 2012), as observed in our result with increase the TLC. Moreover co-administration of vitamin C with ginger can potentiate its action as the antioxidant effect of Vitamin C had a role in modulating the effect of toxins on blood parameters (Hamed, 2006). Al exposure resulted in Al accumulation in the liver and the metal can be toxic to hepatic tissue at high concentrations (Wilhelm et al., 1996). This is correlated with our study as oral administration of aluminum chloride produce a significant increase in both aminotransferase activities (ALT & AST). The elevation of serum AST and ALT activities may be referred to escapes from the injured hepatic cells in the plasma as a result of the cellular degeneration or destruction occurs in this organ (Hassoun and Stohs, 1995). As aluminum toxicity lead to the accumulation
of calcium in the mitochondria and resulted in irreversible damage to its membrane (Anane and Creppy, 2001) leading to discharge of its enzymes content to the circulation (Farber et al., 1981). Our result in accordance with Türkez et al. (2010) and Yeh et al. (2009) who observed increase in both aminotransferase activities upon oral administration of aluminum in rats. In our study aluminum chloride treatment induced elevation of serum ALP that may be referred to either increase osteoblastic activity, provoked by the disturbance of bone formation caused by aluminum (Szilagyi et al., 1994) or it may be contributing to the increased permeability of the plasma membrane or cellular necrosis of hepatic cell (Rahman et al., 2000) and (Gaskill et al., 2005). Our result agree with El-Demerdash (2004) and Türkez et al. (2010) who found that treatment of AlCl3 in rats at dose (34 mg \kg bw, Orally , for 30 days) resulted in a significant increase in the plasma activities of ALT, AST, ALP and LDH.
The activity of lactate dehydrogenase (LDH) in serum consider as a biological marker for liver damage (Suzuki et al., 1995). The present study demonstrated that AlCl₃ significantly increase serum LDH, that may be due to escape of LDH into the serum provides an index of cell death, also the elevation in its activity occurred as a result of cell membrane disintegration and enzyme leakage (Lindell et al., 1996). In the same line Al-Hashem et al. (2009) recorded elevation of LDH activity following the oral treatment of rats with AlCl₃.

Ginger can ameliorate aluminum hepatotoxicity as it lower the activity of liver enzymes AST, ALT, ALP and LDH. As mentioned by Al Rikabi and Jawad (2013) and Gehan and Amin (2009) who cleared that treating of rats orally with ginger resulted in lowering the elevation of liver enzymes induced by cadmium toxicity. This may attributed to the fact that ginger contains high content of antioxidant that makes it a free radical scavenger (Bhandari et al., 2003). Also may be due to that ginger component stabilize hepatocytes plasma membrane and prevent delivery of AST, ALT, ALP and LDH to the extracellular fluid (Darbar et al., 2010 and Ajith et al., 2007a).

Currently, it is very important, to search for protective substances that could minimize the toxic effects of different chemicals. Vitamin C is an efficient in preventing oxidative stress induced cytotoxicity by aluminum (Fahmy and Aly, 2000) and (Anane and Creppy, 2001). Our study showed an improvement for all liver function tests in AlCl₃ group treated with both ginger and vitamin C. This agree with Mahmoud and Elsoadaa (2013) who reported that orally administration of vitamin C for 8 weeks in rats treated with AlCl₃ at dose (34 mg/ kg bw/ daily , orally) down regulate the ALT, AST, ALP activities . As vitamin C stimulate the protein synthesis mechanism through breaking down the binding of aluminum with DNA and RNA( Ochmanski and Barabasz , 2000), also vitamin C is a highly effective antioxidant ,even in small amounts can protect indispensable molecules in the body from damage by free radicals and reactive oxygen species (ROS) that can be generated during normal metabolism as well as through exposure to toxins and pollutants (Carr and Frei ,1999).

Our result revealed that the oral administration of AlCl₃ caused a significant increase in serum cholesterol and triglyceride levels, this documented by Wen et al. (2012) and Joish et al. (2013) who recorded a significant elevation of serum cholesterol and triglycerides in rats after orally administration of Al (NO₃)₃ and AlCl₃ respectively, which may indicate a loss of membrane integrity and disturbance of lipid metabolism (Sarin et al., 1997). Also the increase in serum TG is possibly due to hypoactivity of lipoprotein lipase in blood vessels which breaks up TG and higher serum cholesterol level may be due to hepatic dysfunction (Kojima et al., 2004 and Al-Hashem, 2009).

In present study treatment with ginger improved the level of cholesterol, this agree with Al-Rikabi and Jawad (2013), as ginger administration increases the activity of hepatic cholesterol 7-alpha-hydroxylase that has an important role in the biosynthesis of the bile acids and excretion of cholesterol from the body (Kronhausen et al., 1989 and Srinivasan and Sambaiah, 1991). Meanwhile the TG level improved in ginger extract treated groups by insulin stimulation and enhanced lipoprotein lipase activity (Lopes-Virella , 1977). Also our work showed that AA up grade the effect of ginger on the lipid profile. This agree with Yousef (2004) who approved that administration of vitamin C in rabbits for 16 weeks with AlCl₃ intoxication resulted in reduce the level of cholesterol , as vitamin C involved in the metabolism of cholesterol to bile acids.

Hyperglycemia upon aluminum toxicity may be induced by the increase glucose production, glycogenolysis and decrease glucose utilization (El-Demerdash, 2004).
In addition, oxidative stress has been proposed as a major pathogenic link to both insulin resistance and the dysfunction of the pancreatic beta cell by the formation of amyloid proteins, which not only prevents the release of insulin into the circulation, but also destroys the insulin secreting beta cells (Hayden, 2002). Our result in the same line with Shati and Alamri (2010) and Wen et al. (2012) who recorded hyperglycemia in mice and rats treated with AlCl₃ and Al(NO₃)₃ respectively. Our study showed that, there is hypoglycemic effect of ginger in aluminum treated group, this is in accordance with Al-Rikabi and Jawad (2013). The presence of ascorbic acid with ginger in aluminum intoxication alleviated its harmful effect on blood glucose. These results are in agreement with the previous studies of Yousef et al. (2003) and Yousef (2004).

With regards to renal damage, our findings were in agreement with other studies demonstrating that the oral administration of AlCl₃ resulted in a decrease of total protein and albumin levels and a significant increase in serum urea and creatinine. These may referred to degeneration of renal tubular cells by aluminum accumulation leading to nephrotoxicity (Katyal et al., 1997). Also hypoproteinemia and hypoalbuminemia may be due changes in protein synthesis and/or metabolism in the liver due to hepatotoxicity (Chinoy and Memon, 2001). Hepatoprotective effect of ginger and vitamin C mainly based on their antioxidant activities which protect cells against oxidative stress. Our data confirmed the medical importance and the curative effects of vitamin C in amelioration of serum protein fraction concentrations, total protein content, liver function enzyme activities, that may result from vitamin C stimulation of the protein synthesis mechanism through breaking down the binding of aluminum with DNA and RNA (Annae and Creppy, 2001).

In our study the level of urea and creatinine were elevated in AlCl₃ treated rats. This may be related to metabolic disturbances secondary to renal dysfunction (Szilagyi et al., 1994), also the increase in urea serum concentration may be due to aluminum-mediated changes in liver function (Katyal et al., 1997). In the present experiment the levels of urea and creatinine decreased by ginger administration alone or with vitamin C, as treatment with ginger extract could significantly prevent the depletion of antioxidant enzymes activities in the kidneys. In addition presence of polyphenols and flavonoids in the ginger extract might be responsible for the antioxidant nephroprotective activities and the reduction of serum urea and creatinine levels (Ajith et al., 2007b and Gehan and Amin, 2009).

Lipid peroxidation is a chemical mechanism capable of disrupting the structure and the function of the biological membranes that occurs as a result of free radicals attack on lipids, which was usually reflected by levels of MDA (Schinella et al., 2002). In this study hepatic MDA level in aluminum treated groups was significantly elevated, indicated the increase of lipid peroxidation and oxidative stress in the liver, this agree with Wen et al. (2012) who recorded an increase in hepatic, renal and neural lipid peroxidase after administration of Al(NO₃)₃ in rats. This may attributed to increase in free radical production that induced membrane damage as evidenced by the elevated lipid peroxidation in terms of MDA reactive substances (Cheng et al., 2012).

Several classical antioxidants (SOD, CAT, GSH and TAC) have been shown to protect hepatocytes against lipid peroxidation or inflammation, therefore preventing the occurrence of hepatic necrosis (Waters et al., 2001). These enzymes represent the first line of defense against the oxygen free radical and the reduction in them associated with accumulation of free radicals, leading to injury of cell function (Okamoto and Colepicolo, 1998). In the present study, there was a significant reduction in the activities of hepatic SOD, catalase, GSH
and serum TAC in rats exposed to aluminum compared to control group. This may be due to the mechanism of Al-mediated suppression of antioxidant enzymes by direct interaction of aluminum with free radical scavenging enzymes. According to our data the levels of MDA, SOD, CAT, GSH were improved with ginger and vitamin C supplementation. This agree with Farag et al. (2010) and Abdel-Azeem et al. (2013) who reported reduction in MDA and elevated antioxidant enzymes in rats intoxicated with fenitrothion and acetaminophen respectively and treated with ginger. This may be attributed to ginger products exert their antioxidant effect by quenching free radicals due to the effect of polyphenol compounds (6-gingeriols and its derivatives) (Wilkinson, 2000). While vitamin C is naturally occurring free radical scavenger, as such its presence assists various other mechanisms in decreasing numerous disruptive free radical processes from taking place, including lipid peroxidation (Knight et al., 1993).

CONCLUSION

Based on our data, It was concluded that ginger extract showed promising protective effect against AlCl3 induced toxicity in rats especially if in combination with vitamin C without the risk of toxicity.

Conflict of interest
The authors have no conflict to declare.

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