Cadmium-ginger two way antagonistic relationship

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** ABSTRACT **

Forty two Wistar rats were equally divided into seven groups and investigated for induced cadmium toxicity, and the antagonistic effect of ginger on liver and kidney- accumulated cadmium. Group 1 (served as control) was fed with commercial pelleted food and water for the whole test interval (six weeks), Group 2 was fed with commercial food and cadmium water (50 ppm Cd in water). Group 3 was fed with commercial food and cadmium water (100 ppm Cd in water). Group 4 was fed with commercial food and cadmium water (200 ppm Cd in water). Group 5 was fed with commercial food- ginger (95:5, w/w) and cadmium water (50 ppm Cd in water). Group 6 was fed with commercial food- ginger (95:5, w/w) and cadmium water (100 ppm Cd in water). While Group 7 was fed with commercial food- ginger (95:5, w/w) and cadmium water (200 ppm Cd in water). Cadmium induced significant elevation for liver and kidney parameters, while ginger lowered these parameters. It was concluded that cadmium and Ginger act against each other producing two way antagonistic effect. It was finally observed that ginger expressed an antagonistic action on cadmium toxicity.

** Key words: ** Cadmium, antagonistic, ginger, wistar rats, GOT, GPT, creatinine, urea, uric acid.

** INTRODUCTION **

Cadmium (Cd) is a naturally occurring minor element; it was first discovered in Germany in 1817 as a by-product of the zinc refining process. Its name is derived from the Latin cadmia and the Greek kadmeia. It is one of the metallic components in the earth’s crust and oceans that released into the environment from both natural and anthropogenic sources including agricultural activities (Duruibe et al, 2007). Activities that cause the released of Cd into the soil, causing soil pollution, result in subsequent water pollution (Peplow, 1999). Presence of Cd in agricultural soils from phosphate fertilizers will also result in its increased uptake by plants, accumulating in plant tissues, more especially corns and vegetables (Andre et al, 2005). Cd is recognized to produce toxic effects on humans. Long-term occupational exposure can cause adverse health effects on the lungs and kidneys; there is a strong positive correlation between liver concentration of cadmium and death from heart disease (Voors and Shuman, 1977). More than 50000 residents of cadmium-polluted areas in Japan have taken health checks for preventing cadmium induced renal effects and Itai-Itai disease (Japanese Ministry of Health and Welfare (1968)). In the same trend, some investigators reported that many workers exposed to cadmium have been reported to...
suffer from cadmium health effects (Flanagan et al., 1978). Once residents of cadmium-polluted areas or workers occupationally exposed to cadmium show effects by accumulating cadmium in the renal cortex at a critical concentration (Friberg et al., 1974).

Also Cd is a highly toxic element for animals; produces severe lethal effects whenever animals are exposed to it. Moreover, lethality is directly affected by the route of administration or exposure. Oral administration for certain duration does not produce much mortality as intraperitoneal or intra muscular treatment (Buckley and David, 1987). Mortality in mice was reported after several low intraperitoneal doses of cadmium chloride. Mortality by cadmium is of sex related dose and age dependent effect (Anderson and Ole, 1988). On the other hand, other study (Klaassen and Liu, 1998) stated that mortality in animals due to cadmium toxicity does not occur due to cardio toxicity, but rather by liver injury, because the liver accumulates substantial amounts of cadmium after both acute and chronic exposures and Cd pretreatment does not alter its organ distribution. Cd is having no known beneficial function in animal life (Cocchioni et al., 1989). All the biological functions like excretion, digestion, respiration and reproduction are affected by cadmium intoxication causing death of the individual; once in the living system. Cd binds with enzymes having sulfhydryl groups (Grose et al., 1987), disturbs cell membrane permeability (Kazantzis, 1987), deposits in cell organelles (Nakano et al., 1987) and binds with the nucleic acids (Scicchiltano and Pegg, 1987). Chronic feeding of cadmium at low levels to rats, rabbits, lamb and pigs causes diminished growth and feed consumption (Rogenfelt et al., 1984). Another study revealed that the bio-effect of Cd on mice depends on dose administered, absorption and distribution in metallothionein-1 transgenic mice (Liu and Klaassen, 1996). Malgorzata, (1998) reported that Cd exposure to fishes resulted in 40% mortality 96 hr after the end of the exposure due to disturbances in physiological functions in the fishes. Previous surveys showed different treatment methods for Cd toxicity such as increased intake of Zn, Se, Cu, and Ge (Pizent et al., 2001, Paolo et al., 2005) which also act as metallic antioxidant (Yiin et al., 1998). And the use of dihydroxyethylthiocarbamate (DHDC), diethylthiocarbamate (DEDC), and dicarbox-ybethalthiocarbamate (DCDC) in mobilizing metallothionein-bound Cd from some organs and tissues of mice, and promoting the excretion (Gale et al., 1993a and b). However the use of ginger to suppress the Cd toxicity will be a good decision as it is used safely as a food additive. Ginger (Zingiber officinale) is a very famous plant in many countries, grows best in tropical and sub tropical areas, which have good rainfall with hot and humid conditions during the summer season. This member of the Zingiberaceae family originated in Southeast Asia and has been introduced to many parts of the globe where it proliferates in suitable environments. The main constituents of ginger include volatile oil, (bisabolene, cineol, phellandrene, citral, borned, citronellol, geranial linalool, limonene, zingeberol, zingeberene, and camphene), oleoresin (gingerol, shogoal), phenol (gingeol and zingerone), proteolytic enzymes (zingibain), vitamin B6, vitamin C, calcium, magnesium, phosphorus, potassium, linoleic acid (Kikuzaki and Nakatani, 1993). The pungency and aroma of ginger are because of the gingerol and volatile oil respectively (Kikuzaki et al., 1994). Ginger was introduced to Europe and other areas by Dutch, Portuguese, Arab and Spanish explorers or traders from around the 13th to 16th centuries. Belief in the medicinal properties of ginger existed in ancient Indian and oriental cultures where ginger was used alone or as a component
in herbal remedies. The beneficial effects of ginger have been intensively examined; this practice continues today in many areas of the world, including Africa, Asia, Brazil, China, Fiji, Mexico, Peru, and Thailand. It is useful in colds, flu and other infectious diseases and also in alleviation of nausea, vomiting of motion sickness (Jendrassik et al., 1938). Powdered ginger root was compared to standard drugs used in combating postoperative nausea and vomiting. Tests have shown that the requirement for postoperative anti-emetics was lower in those patients receiving ginger; and concluded that ginger is an effective and promising prophylactic anti-emetic, which may be especially useful for day case surgery (Philips et al., 1993). A Danish study has found that ginger ingestion is significant in relieving pain associated with rheumatoid arthritis, osteoarthritis and muscular disorder patients; where 56 patients (28 rheumatoid, 18 osteo, 10 muscular) were studied over periods ranging from 3 months to 2.5 years. Three quarters of the 46 arthritis patients experienced "relief in pain." Over the period of the testing, no patients reported any adverse effects from consistent ginger consumption (Srivastava and Mustafa, 1992). Other study have produced similar results, where patients reported that ginger "produced better relief of pain, swelling and stiffness than the administration of non-steroidal anti-inflammatory drugs (Srivastava and Mustafa, 1989). Gingerols found in ginger, have been identified as active compounds which are potent inhibitors of the biosynthesis of prostaglandins, which, in an oversupply situation will cause inflammation (Kiuchi et al., 1992).

Ginger plays an important role in bone formation, and curbing muscle spasm, depression hypertension, convulsion, nausea, gastrointestinal disorders, paralysis, kidney damage and a host of other bio-dysfunctions (Meyer et al., 1995). Ginger extracts exhibit numerous medicinal beneficial effects; antihypercholesterolemic (Tanabe et al., 1993), anticholigemic and antihistaminic (Qian and Liu 1992) and antihyperlipidawmic (Bhandari et al., 1998). Also other investigation revealed that ginger is very useful in treating of many diseases; migraine, motion sickness (Holtman et al., 1989) antitumor, anticarcinogenic and antitoxic agent (Vimala et al., 1999). The aim of the present research was to answer the question; is there a sort of antagonism between cadmium and ginger? This was done by studying the effect of cadmium induction on wistar rats and evaluation of the liver and kidney functions; followed by studying the ability of ginger to suppress different levels of Cd toxicity.

**MATERIALS AND METHODS**

Experimental protocol: Ginger was ground and sieved to a particle size of 250 µm. The commercial pelleted food- ginger concentrate (5% w/w of ginger in commercial food) was prepared by mixing the commercial food and ginger at 95:5 w/w ratios, Cd-water concentrate (Cd-H₂O) was prepared at 50, 100 and 200 ppm Cd concentrations in water. Healthy forty two Wistar adult albino rats, (180±20g body weight), were provided by the animal house in National Research Center, Cairo, Egypt. Experimental animals were randomly divided into 7 equal groups (1, 2, 3, 4, 5, 6 and 7) allowed ten days period for adapting with the new environment. Group 1 served as the control (fed with normal water and normal commercial food). Group 2 was fed with commercial food and 50 ppm Cd-H₂O, Group3 was fed with commercial food and 100 ppm Cd- H₂O; Group 4 was fed with commercial food and 200 ppm Cd- H₂O; Group 5 was fed with commercial food-ginger...
concentrate and 50 ppm Cd- H₂O; Group 6 was fed with commercial food-ginger concentrate and 100 ppm Cd- H₂O and Group 7 was fed with commercial food-ginger concentrate and 200 ppm Cd- H₂O. The grouping and the feeding pattern are summarized in Table 1. All administrations were through the oral feeding for the whole test period (six weeks). All tests for liver and kidney functions as well the Cd analyses were conducted at two-week interval; two specimens from each group were set for analyses where blood samples were collected; from which serum was extracted after coagulation for analysis of liver and kidney functions; GPT and GOT analyses were done according to Reitman-Frankel method (Reitman and Frankel, 1957). Blood urea analysis was done according to Rock et al., 1987; Creatinine analysis was done according to Henry (1974). Uric acid and Cd analyses were done according to Young (1999). This was done by feeding rats with Cd water (50ppm, 100ppm and 200ppm), followed by commercial pelleted food mixed with 5% (w/w) ginger. After the test period, the extent of accumulation of Cd in the liver and kidney along with the antidote effects of ginger on Cd poisoning was evaluated.

Results were expressed as means±SE. The intergroup variation was measured by one-way analysis of variance (ANOVA) followed by Tukey's LSD test. Statistical significance was considered at p<0.001 and 0.005. The statistical analysis was done using the statistical package for the social sciences (SPSS).

RESULTS AND DISCUSSION

It is well known that ginger is used worldwide as an antidote for heavy metals toxicity, however this ability differ greatly according to many factors such as the exposure time, animal condition, dose, sex, age etc. In the present study, cadmium caused significant elevation for all tested liver and kidney parameters comparing to the control group; except that for creatinine (Tables 2, 3 and 7). The same observations were also reported by many researchers (e.g. Samir Haouem et al., 2007). Results for the effect of cadmium and/or ginger on GOT and GPT are summarized in Tables 3 and 4, respectively. The results indicated that there was high significant increases in GOT activity by Cd administration at all doses tested and elevation is concentration dependent. GOT reduction occurred when rats of group 5 fed with 50 ppm cadmium followed by commercial food-ginger concentrate.

Table (1): Summary of rat grouping with six weeks feeding.

<table>
<thead>
<tr>
<th>Week</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>C+W</td>
</tr>
<tr>
<td>2</td>
<td>C+W</td>
</tr>
<tr>
<td>3</td>
<td>C+W</td>
</tr>
<tr>
<td>4</td>
<td>C+W</td>
</tr>
<tr>
<td>5</td>
<td>C+W</td>
</tr>
<tr>
<td>6</td>
<td>C+W</td>
</tr>
</tbody>
</table>

*+= Control; C= Commercial pelleted food; ᵗ Cd= Cadmium (Cd)
Wₐ₂₅₀= Cd. H₂O (50ppm); Wₐ₁₀₀₀= Cd. H₂O (100ppm); Wₐ₂₀₀₀= Cd. H₂O (200ppm); Cg= Commercial pelleted food-ginger concentrate.
Significant decreases in the elevated enzyme activity by Cd (100 and 200 ppm) were noticed by ginger constrate administration (groups 6 and 7) (Table 3). The effect of ginger as protective agent was more pronounced after 6 weeks of administration. The effect of cadmium with and without ginger concentrate on GPT activity is presented in Table (4). The data obtained are similar to that obtained in GOT activity which revealed that there was a highly significant (p<0.001) GOT reduction occurred when rats of group 5 fed with 50 ppm cadmium in water followed by commercial food- ginger concentrate and significant (p<0.005) for groups 6 and 7 that fed with 100 and 200 ppm cadmium in water, respectively followed by commercial food- ginger concentrate. Results for the same effect on GPT revealed that there was a highly significant (p<0.001) reduction occurred for all the given ginger groups. The above findings are in full agreement with these proposed by Bhandari et al. (2003); who reported that ginger is useful and lowers the serum glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) levels. Also other study (Ezeuko Vitalis et al., 2007) stated that ginger has a protective effect on the hepatotoxicity.

### Table (2): Cadmium concentration in rat liver of the tested groups.

<table>
<thead>
<tr>
<th>Week</th>
<th>Liver Cd concentration ( ppm or mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1•</td>
</tr>
<tr>
<td>2</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>ND</td>
</tr>
</tbody>
</table>

*= Control  ND= not detected

### Table (3): Effect of Cd with and without ginger on serum GOT.

<table>
<thead>
<tr>
<th>Week</th>
<th>Serum GOT concentration (units/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1•</td>
</tr>
<tr>
<td>2</td>
<td>14.15</td>
</tr>
<tr>
<td>4</td>
<td>14.02</td>
</tr>
<tr>
<td>6</td>
<td>13.86</td>
</tr>
</tbody>
</table>

*= Control  *= significant P<0.005  **= significant P<0.001  # = significant p<0.005 (from control)

### Table (4): Effect of Cd with and without ginger on serum GPT.

<table>
<thead>
<tr>
<th>Week</th>
<th>Serum GPT concentration (units/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1•</td>
</tr>
<tr>
<td>2</td>
<td>5.00</td>
</tr>
<tr>
<td>4</td>
<td>4.96</td>
</tr>
<tr>
<td>6</td>
<td>4.70</td>
</tr>
</tbody>
</table>

*= Control  *= significant P<0.005  **= significant P<0.001  ## = significant p<0.001 (from control)

Tables (5 and 6) show the changes in blood urea and creatinine, as affected by Cd with and without ginger. Ginger show very high effect (p<0.001) on decreasing blood urea in all administrations used. In contrast to this observation, cadmium caused elevation to blood creatinine but there was no significant effect of ginger on blood creatinine in all
administrations. Therefore, we could conclude that ginger may have a beneficial effect for urea removal from plasma and it may be considered as a therapeutic herb to manage renal function in patient with uremia but with a little reducing effect on creatinine levels. This finding is in full agreement with that proposed by Mehrdad et al. (2007). Also Ajith et al. (2006) reported that, ethanol extract of ginger alone and in combination with vitamin E partially ameliorated cisplatin-induced nephrotoxicity.

Table (5): Effect of Cd with and without ginger on serum blood urea.

<table>
<thead>
<tr>
<th>Week</th>
<th>Group1*</th>
<th>Group2 ##</th>
<th>Group3 ##</th>
<th>Group4 ##</th>
<th>Group5**</th>
<th>Group6**</th>
<th>Group7***</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>23.0</td>
<td>29.0</td>
<td>31.50</td>
<td>32.25</td>
<td>38.85</td>
<td>39.50</td>
<td>40.75</td>
</tr>
<tr>
<td>4</td>
<td>26.0</td>
<td>31.0</td>
<td>31.85</td>
<td>32.75</td>
<td>38.00</td>
<td>39.10</td>
<td>40.50</td>
</tr>
<tr>
<td>6</td>
<td>28.5</td>
<td>31.5</td>
<td>32.10</td>
<td>33.10</td>
<td>37.50</td>
<td>38.50</td>
<td>40.10</td>
</tr>
</tbody>
</table>

*= Control  *= significant P<0.005  **= significant P<0.001  ## = significant P<0.001 (from control)

Concerning effect of ginger as a reducing agent for uric acid; data presented in Table (7) show that there was a high significant reduction (p<0.001) for all commercial food-ginger administrations. Obtained data confirmed the use of ginger as a therapeutic herb to remove the uric acid from the body, Atef and Talal (2007) reported that ginger and ginger oil reduce uric acid from cadmium exposed rats.

Table (7): Effect of Cd and/or ginger on serum uric acid.

<table>
<thead>
<tr>
<th>Week</th>
<th>Group1*</th>
<th>Group2 ##</th>
<th>Group3 ##</th>
<th>Group4 ##</th>
<th>Group5**</th>
<th>Group6**</th>
<th>Group7**</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.55</td>
<td>2.75</td>
<td>3.00</td>
<td>3.30</td>
<td>4.50</td>
<td>4.75</td>
<td>5.10</td>
</tr>
<tr>
<td>4</td>
<td>2.45</td>
<td>2.90</td>
<td>3.15</td>
<td>3.4</td>
<td>4.65</td>
<td>4.85</td>
<td>5.25</td>
</tr>
<tr>
<td>6</td>
<td>2.30</td>
<td>3.10</td>
<td>3.25</td>
<td>3.45</td>
<td>4.70</td>
<td>4.90</td>
<td>5.30</td>
</tr>
</tbody>
</table>

*= Control  *= significant P<0.005  **= significant P<0.001  ## = significant P<0.001 (from control)

Overall, the present study confirmed that cadmium and ginger act against each other; while cadmium elevates the liver and kidney functions; ginger lowers the same parameters, this reduction could be attributed to the fact that ginger contains high content of antioxidants that makes it a free radical scavenger (Krishnakanta and Lockesh, 1993). Moreover, another study by Yuki Masuda et al. (2008), reported that the antioxidant activity of ginger might be due to not only radical scavenging activity of antioxidants but also their affinity to the substrates. While Egwurugwu et al. (2007) reported that ginger...
therapy was more effective as more Cd intake was avoided. We assumed that ginger through the said antioxidant activities, first improved the blood balance with the confirmed results improving the liver functions followed by improving the kidney functions. This is the first hypothesis explaining the role of ginger in improving liver and kidney functions; so it is very early to confirm it, much more studies are needed before any firm conclusions can be drawn.

ACKNOWLEDGEMENT

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Cadmium-ginger antagonistic relationship

123


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الكادميوم والزنجبيل علاقة ثنائية متبادلة الأثر

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تم تقسيم الفنير المستخدمة في البحث (اثنان وأربعون) إلى سبعة مجموعات متساوية وأختبار مدى تأثير الكادميوم عليهم. وأيضا دراسة تأثير الزنجبيل على وظائف الكبد والكلي. المجموعة الأولى كانت عبقرة الكودنرول (تم تغذيتها على الغذاء التجاري لفنير التجارب والماء) المجموعة الثانية (تم تغذيتها على الغذاء التجاري ومام تحتوي على تركيز 50 كادميوم) المجموعه الثالثة (تم تغذيتها على الغذاء التجاري ومام تحتوي على تركيز 100 كادميوم) المجموعة الرابعة (تم تغذيتها على الغذاء التجاري ومام تحتوي على تركيز 200 كادميوم) المجموعة الخامسة (تم تغذيتها على خليط من الغذاء التجاري والزنجبيل بنسبة 95:5 w/w ومام تحتوي على تركيز 50 كادميوم) المجموعة السادسة (تم تغذيتها على خليط من الغذاء التجاري والزنجبيل بنسبة 95:5 w/w ومام تحتوي على تركيز 100 كادميوم) المجموعة السابعة (تم تغذيتها على خليط من الغذاء التجاري والزنجبيل بنسبة 95:5 w/w ومام تحتوي على نسب 200 كادميوم). أثبتت النتائج المحصل عليها أن الكادميوم قد أدى إلى حدوث ارتفاع معنوي في وظائف الكبد والكلي بينما أدى تناول الزنجبيل إلى انخفاض تلك الوظائف بدرجة معنوية. وقد تم استنتاج أن كل من الكادميوم والزنجبيل يعملان ضد بعضهما مما يؤكدا وجود فعال مضاد للزنجبيل ضد التسمم بالكادميوم.