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Biochemical and histopathological toxicity of an aqueous extract of ginger in female rats

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ABSTRACT

In the present study, the effects of oral (PO) and intraperitoneal (IP) administration of an aqueous extract of ginger were investigated in rats at two dose levels for hematological, serum enzymes and systemic toxicity. It was observed that hematocrit was not affected by ginger administration, whereas hemoglobin levels decreased in rats receiving an IP dose of 500 mg kg^{-1} of ginger. Total lactate dehydrogenase (LDH) levels in serum were significantly higher in rats treated with 500 mg kg^{-1} ginger compared to control rats. This increase was apparently due to increased levels of cardiac LDH isozyme in serum. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were variably affected only in the group of rats receiving PO ginger and not in the IP group. Lactate dehydrogenase levels in liver were also increased in rats receiving 500 mg kg^{-1} ginger IP. The liver acid phosphatase levels were unaffected by ginger. Serum proteins were also unaffected by ginger treatment, while liver protein content was decreased in both PO and IP groups receiving 500 mg kg^{-1} ginger. Histopathological examination of the lungs and livers indicated that only the 500 mg kg^{-1} ginger treated (IP) rats had apparent histopathological changes in the organs studied. Overall, administration of the low dose of ginger (50 mg kg^{-1}) showed no toxicity or histological changes in liver and lungs of rats. Therefore, we can conclude that toxicity of ginger is low and ingestion of this spice at reasonable levels would be considered quite safe.

Keywords: Ginger *(Zingiber officinale)*, Hb, histopathology, LDH, liver, lung, toxicity.

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* The authors would like to dedicate this paper to our dear colleague and friend, Prof. Tariq Mustafa, who recently passed away. Prof. Mustafa will be remembered for his pioneering work and contributions in the area of natural products and their medical applications. His contribution to the present work is greatly appreciated.

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INTRODUCTION

Medicinal plants or materials derived from plants and used for the treatment and prevention of disease have been important in all cultures throughout history. The significance of their ameliorative and preventive effects in various diseases is seen today in their continued use. Ginger (*Zingiber officinale* Roscoe) is one of the most widely used herbs in various cultures since antiquity (Mustafa *et al.* 1993). In the last two decades, ginger has become popular in Western cultures and several studies have documented its efficacy in the amelioration of rheumatism (Srivastava & Mustafa 1989, 1992, Bliddal *et al.* 2000, Altman & Marcussen 2001), hypermesis gravidarum (morning sickness in early pregnancy) (Fisher-Rasmussen *et al.* 1990), vomiting (anti-vomiting) (Grotnved *et al.* 1988), and migraine (Mustafa & Srivastava 1990). Further details on the pharmacology of ginger and its uses in health and diseases can be found in the review of Mustafa *et al.* (1993).

Recently, as the use of oriental herbs and spices has considerably increased in Western diets, questions relating to their adverse effects and toxicity have become more relevant. The cellular toxicity (mutagenicity and carcinogenicity) of various herbs is relatively better understood than the systemic adverse effects of these herbs. Our group has recently studied the adverse histopathological effects of garlic *(Allium sativum)* and onion *(Allium cepa)* on liver and lung tissues of rats. High doses of aqueous extracts of garlic and onion in rats resulted in apparent histopathological changes in liver and lung tissues (Alnaqeeb *et al.* 1996,Thomson *et al.* 1998). In contrast, the toxicity of ginger is not known. The U. S. Food and Drug Administration lists ginger as "generally regarded as safe" (Substances Generally Regarded as Safe 1998). In view of the established low toxicity, presence in the diet, relative low price, and its use in the above mentioned diseases and occurrence in various herbal remedies, it is prudent to evaluate the systemic toxicity of ginger *(Zingiber officinale)*. To investigate the hypothesis that ginger may have toxic properties, the effects of an aqueous extract of ginger on the hematology, serum and liver enzymes, and the histopathology of the liver and lung of rats have been investigated in this study.

MATERIALS AND METHODS

Preparation of ginger extract

Aqueous ginger extract was prepared from commercially available ginger *(Zingiber officinale)* roots. The ginger roots were peeled on crushed ice, and 50 g of ginger was cut into small pieces and homogenized in 75 ml of cold, sterile 0.9% NaCl in the presence of some crushed ice. The homogenization was carried out in a blender at high speed using 2 min. bursts for a total of 12 min.

The homogenized mixture was filtered 3 times through cheesecloth and the filtrate was centrifuged at 5000 RCF for 10 min. at 4°C and the clear supernatant was made up to 100 ml with normal saline. The concentration of this ginger preparation was considered to be 500 mg ml^{-1} on the basis of the weight of the starting material (50g/100ml). The aqueous extract of ginger root was stored in small aliquots at -20°C until use. Lower concentrations of ginger were prepared by dilution of this solution with cold, sterile 0.9% NaCl.

Animal treatment

For comparison purposes, we used the same animal treatment protocol previously used to study the adverse effects of garlic and onion in rats (Alnaqeeb *et al.* 1996, Thomson *et al.* 1998). Female Sprague-Dawley rats, 12 weeks old and with starting weight of 160-165g, were used in the study. Rats were fed a normal diet and were divided into six groups, each group containing seven rats. All rats received daily 0.5 ml of normal saline or ginger extract (50 mg or 500 mg kg^{-1} adjusted according to the weight of the rat) orally via stomach gavage (PO) or intraperitoneally (IP) as indicated below. Group 1 was a control group that received normal saline orally (control PO). Group 2 also served as a control group and received normal saline intraperitoneally (control IP). Group 3 rats received a low oral dose (PO) of ginger extract (50 mg kg^{-1}). Group 4 rats received a high oral dose (PO) of ginger (500 mg kg^{-1}). Group 5 rats received a low IP dose of ginger (50 mg kg^{-1}). Group 6 rats received a high IP dose of ginger (500 mg kg^{-1}). This group was reduced to six rats as one animal died early in the protocol. All rats received the treatment for a period of four weeks. Animals were observed for clinical symptoms daily. The weight of each animal was recorded at the start of the study and after two and four weeks. The rats were sacrificed after four weeks under sodium pentobarbitone (May & Baker, England) anesthesia. The blood and the required organs were removed, and processed further as indicated below. A portion of the liver from each animal was frozen at -80°C and reserved for enzyme and protein analyses.

Blood collection and preparation of plasma

The blood was collected by cardiac puncture and allowed to clot for 30 min. at room temperature. The clotted blood was then centrifuged at 3500 RCF for 30 min. The serum was separated and stored at -20°C until protein and enzyme analyses were performed.

Hematocrit and hemoglobin determinations

Hematocrit was measured by centrifuging a small amount of whole blood in a heparinized capillary tube until the red cells were reduced to a constant packed

volume as described in Gibson (1990). The hematocrit (%) was calculated by comparing the height of the column of packed red cells with the height of the entire column of the blood. Hemoglobin was determined in whole blood by the cyanomethemoglobin method of Van Kampen and Zijlstra (1961).

Enzyme assays

Serum lactate dehydrogenase (LDH) isozyme activities were assayed by the method of Bergmeyer and Bernt (1974). Under the conditions defined in this method DEAE-Sepharose A-50 (Amersham Pharmacia Biotech, Sweden) adsorbs the heart muscle-type LDH, while the liver-type LDH remains in solution. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were assayed by the method of Karmen (1955), and Wroblewski & LaDue (1956) respectively. A 1-gram portion (wet wt.) of each liver was homogenized in 9 ml of 0.05 M Tris-HCl, pH 7.6 (BDH Chemicals, UK) for 3 minutes in an IKA-T25 tissue homogenizer (IKA Laboratory Technology, Germany). The homogenate was centrifuged at 10,000 RCF for 15 min. at 4°C and the clear supernatant was analyzed as the source of liver LDH activity by the method of Bergmeyer and Bernt (1974) and acid phosphatase activity by the hydrolysis of p-nitrophenylphosphate (Sigma, USA) (Waymack & Van Etten 1991).

Protein determination

Plasma and liver protein concentrations were determined by the Bradford method (1976). Liver homogenates were prepared as above and the protein was determined in the supernatant.

Histological preparation

Liver and lung samples were removed for histological examination. The lung was slowly infused *in situ* via the trachea with formalsaline (10%, pH 7.0). The left lobe of the lung was then ligated, excised and immersed in formalsaline for 7 days. Segments of liver sample were removed and also immersed in formalsaline for 7 days. After completion of fixation, the samples were dehydrated in a series of alcohols, cleared in toluene and then embedded in Paraplast (Sherweed Medical Co., USA). Blocks were cut at 5-7 μm. Sections were de-waxed, re-hydrated in a series of alcohols, stained in Harris hematoxylin (Cole Parmer, USA) and counterstained in 1% aqueous eosin (Sigma, USA). Sections were then mounted in DePeX (GURR, BDH, UK) and examined under a light microscope. Representative slides were photographed under an Olympus Vanox photomicroscope (Olympus, USA).

Statistical analysis

The data is expressed as mean ± SEM. Readings within a group were compared using the one-way ANOVA analysis and readings between groups were compared using the independent sample test. Multiple comparisons for least squares differences were carried out for all groups independently. Statistical analysis was performed with the SPSS program (Version 7.1). A level for $p < 0.05$ was considered to be significant. Figures were drawn using Graphpad Software, San Diego, CA, USA.

RESULTS

Ginger administered either orally (PO) or intraperitoneally (IP) did not cause mortality of rats. One of the rats in Group 6 died early due to causes other than ginger administration. The other rats showed no ill effects. No difference in food and water intake among the groups was observed. All animals had normal droppings and no sign of diarrhea was observed. As can be seen from the data in Table 1, rats in the first two weeks of treatment in all experimental groups gained weight at similar rates. In the last two weeks the rate of weight gain was relatively slower in all groups. There were no significant differences in weight gains between the saline or the low and high doses of ginger-treated rats or between the saline or ginger administration (i.e. PO vs. IP mode).

Table 1: The effect of normal saline and ginger (50 and 500 mg/kg) administered orally (PO) and intraperitoneally (IP) on body weight.

	Body weight (g)		
Experimental group	**Start**	**2 weeks**	**4 weeks**
Control oral saline	165 ± 3.2	216 ± 4.8[a]	237 ± 5.2[a,b]
Control IP saline	160 ± 3.7	207 ± 3.3[a]	231 ± 4.6[a,b]
Oral 50 mg/kg ginger	162 ± 3.9	206 ± 3.5[a]	231 ± 4.1[a,b]
IP 50 mg/kg ginger	163 ± 2.1	211 ± 1.8[a]	238 ± 3.2[a,b]
Oral 500 mg/kg ginger	160 ± 2.6	204 ± 2.9[a]	227 ± 4.6[a,b]
IP 500 mg/kg ginger	162 ± 2.9	217 ± 2.6[a]	248 ± 5.1[a,b]

Animal weight significantly different when compared to start weight[a] or weight at 2 weeks[b] ($P < 0.05$).

Figure 1 shows the hematocrit and hemoglobin levels in all PO and IP ginger-treated rats. Hematocrit levels were maintained at about 42 - 44 percent in all treatment groups. Hemoglobin levels did not change significantly in rats given oral ginger. However, rats administered the high dose of ginger (500 mg kg^{-1}) intraperitoneally (IP) had a significantly lower level of hemoglobin than rats receiving either saline or 50 mg kg^{-1} ginger IP.

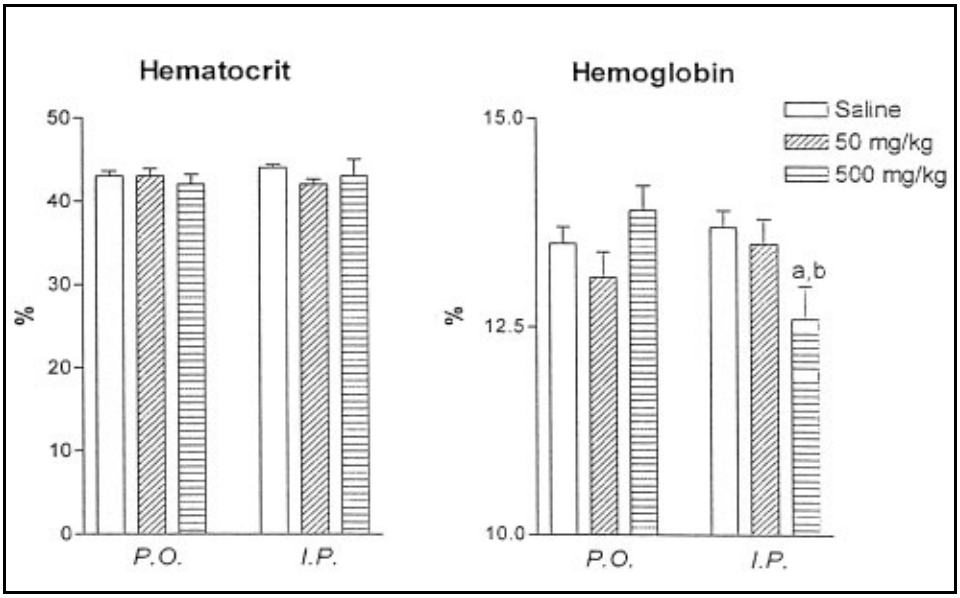

Fig.1. Effects of normal saline and different doses of ginger administered orally (PO) and intraperitoneally (IP) on the hematocrit and hemoglobin levels. N = 7 in all groups, except N = 6 in 500 mg kg^{-1} IP group. Significantly different when compared to normal saline[a] and 50 mg/kg[b] ginger ($P < 0.05$).

The effects of ginger administration on serum total LDH levels and hepatic and cardiac LDH isozyme levels in serum of the rats are shown in Figure 2. It is apparent that total serum LDH levels in rats treated with the high dose of ginger by both administrative routes were significantly higher than the control levels (Fig. 2, left panel). In the animals treated with 500 mg kg^{-1} ginger IP, the total serum LDH levels were also significantly higher when compared to the levels in rats treated with 50 mg kg^{-1} ginger IP (Fig. 2, left panel). Hepatic LDH isozyme levels in the serum were not significantly affected either by low or high dosages of ginger administration either by PO or IP administration mode (Fig. 2, middle panel). Cardiac LDH isozyme levels increased significantly in 500 mg kg^{-1} IP treated rats (Fig. 2, right panel).

The effect of aqueous extract of ginger on the levels of serum aspartate amino transferase (AST) and alanine amino transferase (ALT) is shown in Figure 3. In the case of these two liver enzymes, the effects are confined to the oral treatment group (PO) and are variable with increased levels of AST and decreased levels of ALT in serum of rats treated with 50 mg ginger kg^{-1}. In serum of rats treated with 500 mg ginger kg^{-1} PO , AST levels were significantly decreased and ALT levels were significantly increased when compared to the 50 mg ginger kg^{-1} PO treatment group. The animals treated with ginger IP showed no significant change in these enzyme levels.

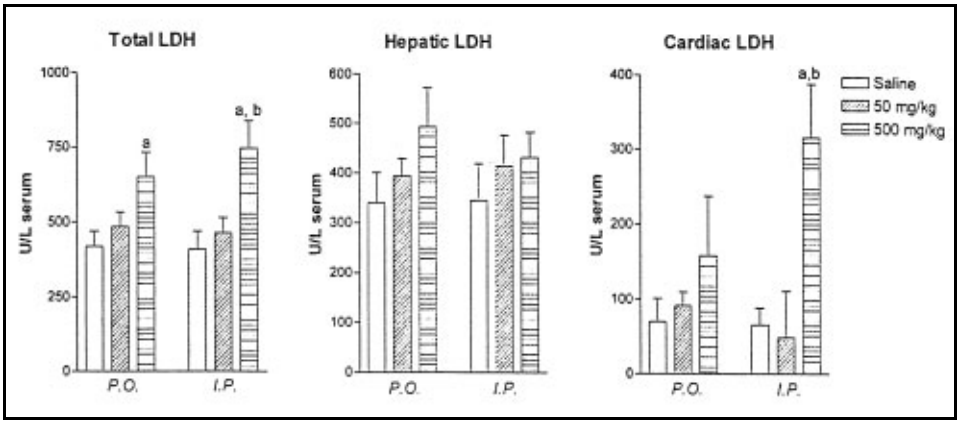

Fig.2. Effects of normal saline and different doses of ginger administered orally (PO) and intraperitoneally (IP) on the total serum, hepatic LDH and cardiac LDH isozyme levels. N = 7 in all groups, except N = 6 in 500 mg kg^{-1} IP group. Significantly different when compared to normal saline[a] and 50 mg/kg[b] ginger ($P < 0.05$).

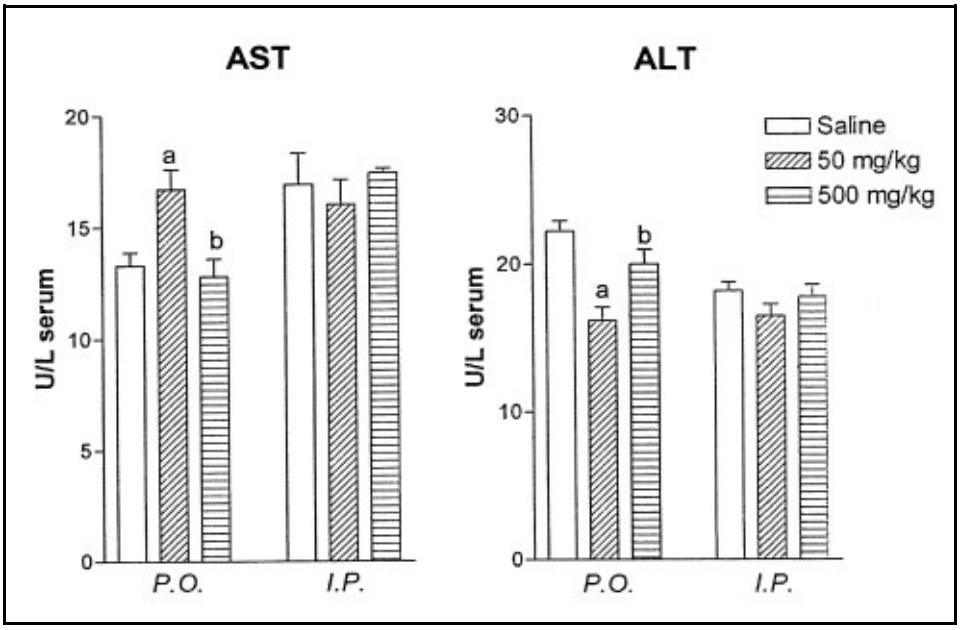

Fig.3. Effect of normal saline and ginger (50 and 500 mg/kg) administered orally or intraperitoneally on AST and ALT. N = 7 in all groups, except N = 6 in 500 mg kg^{-1} IP group. Significantly different when compared to normal saline[a] and 50 mg/kg[b] ginger ($P < 0.05$).

Figure 4 represents the hepatic tissue LDH and acid phosphatase enzyme levels in 500 mg kg^{-1} PO and IP treated groups. The liver LDH increased significantly in the animals receiving the ginger extract IP. No significant differences in acid phosphatase levels were observed in PO and IP ginger-treated groups. Figure 5 shows the serum and liver protein contents in four of the

treatment groups. As is clear from the data, serum protein levels were unaffected by ginger treatment, while liver protein content decreased in the 500 mg kg-1 PO and IP treated groups.

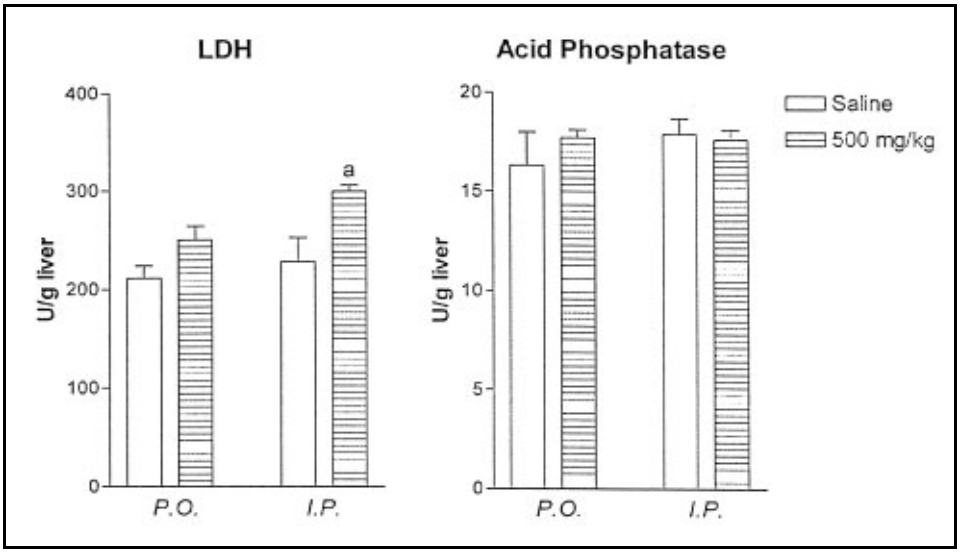

Fig.4. The effect of normal saline and 500 mg/kg ginger administered orally (PO) and intraperitoneally (IP) on liver tissue supernatant LDH and acid phosphatase. N = 7 in PO and N = 6 in IP group respectively. Significantly different when compared to normal saline[a] ($P < 0.05$).

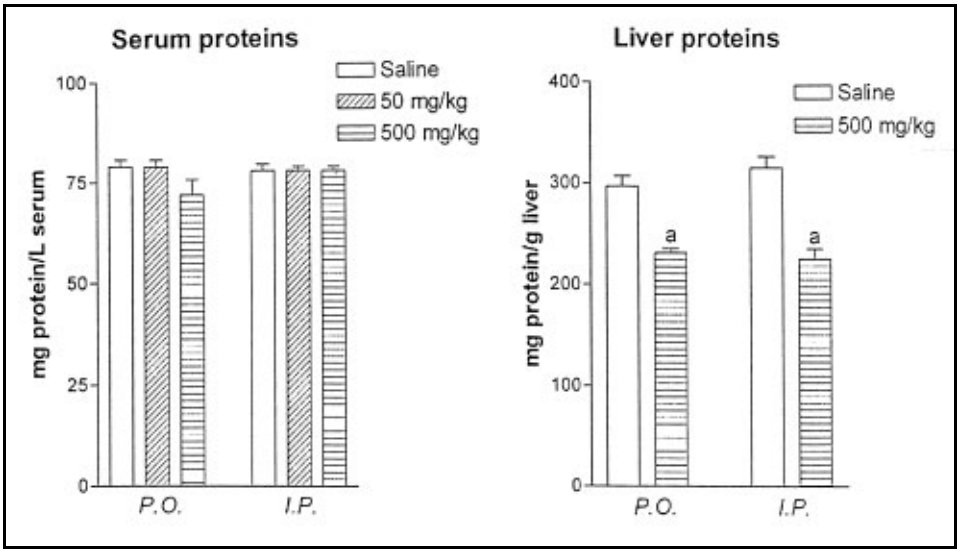

Fig.5. The effect of normal saline and ginger administered orally (PO) and intraperitoneally (IP) on serum and liver proteins. N = 7 in all groups, except N = 6 in 500 mg kg^{-1} I.P group. Significantly different when compared to normal saline[a] ($P < 0.05$).

Histopathological examination of the lungs and livers of rats treated with ginger revealed that ginger is not very toxic to either the livers or the lungs. Both the lungs and livers of rats fed ginger orally had nearly the same appearance as control livers and lungs. In the rats fed the higher dose of ginger (500 mg kg^{-1}), the lungs exhibited very little and infrequent differences compared to control. The livers of these animals were mostly similar to control with a few congested capillaries and intercellular spaces that were less tight than control in some areas (data not shown).

IP administration of ginger did result in some toxic effects in the lungs and livers of rats. These effects are illustrated in Figure 6. As in the case of oral ginger, IP administration of 50 mg ginger kg^{-1} had no deleterious effects on the lungs and livers of the rats. However, lungs of rats given a high IP dose of 500 mg kg^{-1} ginger appeared abnormal with thickened alveolar walls and RBCs aggregating in some alveoli (Fig. 6b) when compared to control lung tissue (Fig. 6a). In control rats, given IP doses of saline, the livers showed the classical hepatic pyramidal arrangement with tight intercellular spaces and smooth cytoplasm (Fig. 6c), while livers of rats given a high IP dose of 500 mg kg^{-1} ginger had granular cytoplasm, larger intercellular spaces that were occupied on many occasions by RBCs filling even the hepatic acini (Fig. 6d).

DISCUSSION

No studies of the effect of aqueous extract of ginger on hematology, serum enzymes and histopathological changes in liver and lungs of an animal have been previously reported. However, scattered reports indicate that aqueous extracts of ginger produce cytotoxicity and mutagenicity *in vitro* in plant and bacterial cells. The ethanolic extract of ginger has been reported to have cytotoxic activity in Dalton's lymphoma ascites cells where 200 μg ml^{-1} of the extract produced 50% cell death (cf review Mustafa *et al*. 1993). A few reports are present in the literature relating to the allergic, asthmatic and immunological responses to inhalation of ginger (Van Toorenenbergen & Dieges 1986, Zuskin *et al*. 1988, Stäger *et al*. 1991). However, no studies have investigated the potential toxic effects of ingestion of ginger in raw, powdered or in the form of an aqueous extract. In the present study, we investigated the effects of administration of an aqueous ginger extract to rats at two dose levels (50 mg kg^{-1} and 500 mg kg^{-1}).

Body weight

Animals in all groups irrespective of saline and ginger administration PO or IP gained significant body weight throughout the treatment period. Administration of ginger extract did not cause any apparent adverse gastrointestinal effects

among the rats. Thus, we suggest that weight gain is attributed to the normal growth of the rats and supports the conclusion that the ginger treatment did not adversely affect the health of the animals.

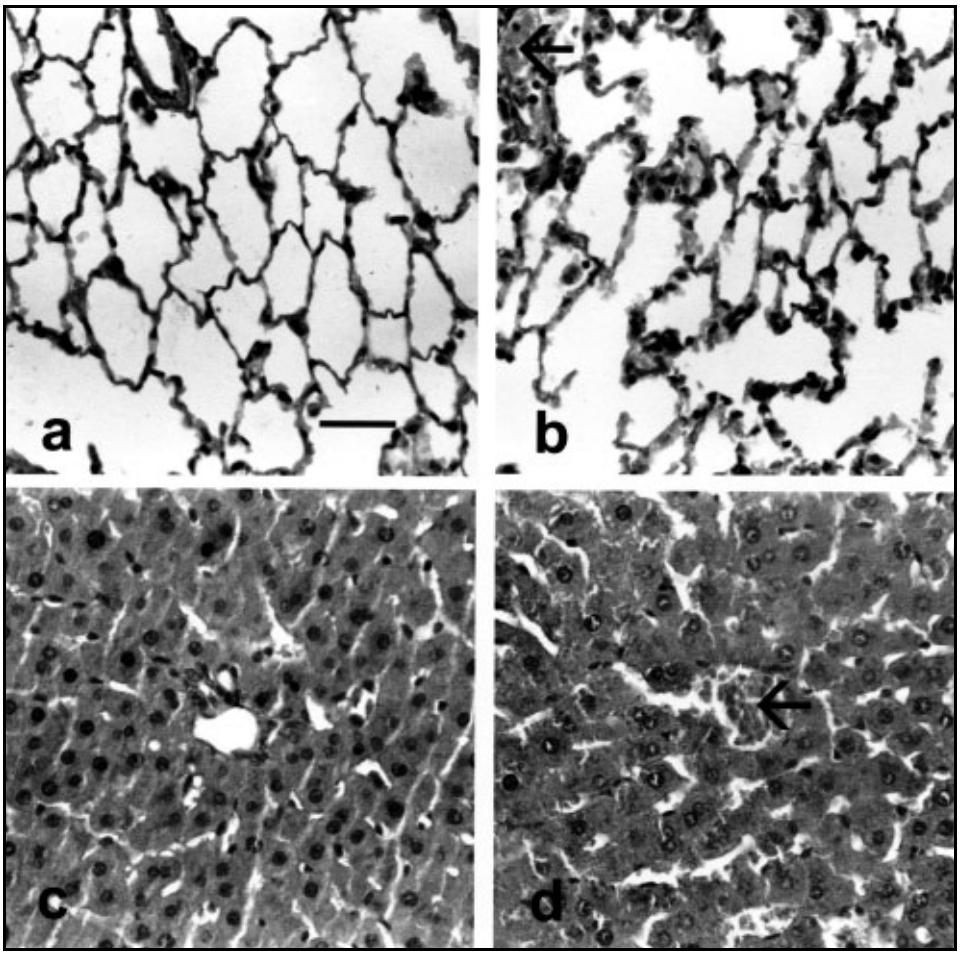

Fig.6. Effect of intraperitoneal (IP) administration of ginger on the lung and liver tissues of rat. (a) Control rat lung given IP doses of saline appeared normal; (b) Lungs of rats given a high IP dose of 500 mg kg^{-1} appeared abnormal with thickened alveolar walls and RBCs aggregating in some alveoli (←); (c) Control rat liver given IP dose of saline showed the classical hepatic pyramidal arrangement with tight intercellular spaces and smooth cytoplasm; (d) Livers of rats given a high IP dose of 500 mg kg^{-1} had granular cytoplasm, larger intercellular spaces that were occupied on many occasions by RBCs filling even the hepatic acini (←). Size of bar = 50 μm.

Hematological changes

Hematocrit levels in all of the groups throughout the length of the protocol remained unchanged, i.e. in the range of 42- 44%. Therefore, ginger did not

cause RBC hemolysis. In addition, this suggests that administration of ginger did not cause polycythemia, which would cause a higher hematocrit value due to erythrocytosis (Martini 1993). Hemoglobin values in the rats receiving saline or ginger in PO mode were unchanged. In contrast, hemoglobin values from rats receiving 500 mg kg^{-1} ginger in IP mode decreased significantly (about 9%) as compared to the rats in both 50 mg kg^{-1} and the saline treatment groups. The cause of lowered hemoglobin due to the higher ginger dose cannot be explained at the moment, but as no other deleterious hematological effects were noticed, we suggest that high doses of ginger may affect erythropoeisis, hemoglobin synthesis or packaging of hemoglobin in red blood cells in some way. It must be noted here that a reduction of 9% hemoglobin does not affect any of the body's functions.

Serum enzymes and serum proteins

This is the first report that presents the effects of ginger on serum LDH. It is evident from the data that the increase in total serum LDH (Fig.2, left panel) is due to an increase in cardiac (Fig.2, right panel) rather than hepatic (Fig. 2, middle panel) LDH suggesting that the higher dose (500 mg kg^{-1}) of ginger is causing some damaging effects on the heart and not the liver.

Liver enzymes and proteins

The liver is the primary organ regulating the composition of the circulating blood. AST, ALT, LDH, acid phosphatase and proteins are routinely assayed to assess the liver function mediated by the above-mentioned enzymes and proteins. In the present study, two major amino acid metabolizing enzymes, i.e. AST and ALT, were slightly and variably affected by the PO administration of ginger, while IP administration of ginger caused no changes in AST and ALT enzyme levels (Fig. 3). Liver LDH activity also slightly increased in the rats receiving 500 mg kg^{-1} of ginger in IP mode (Fig. 4). The acid phosphatase activities remained unchanged even in rats receiving 500 mg kg^{-1} ginger by either PO and IP mode (Fig. 4), which indicates that the lysosomal membrane stability is maintained in the liver even at the high dosage of ginger. Serum protein levels (Fig. 5) are also unaffected by ginger extract administration. As most of the serum proteins are synthesized by hepatocytes (Martini 1993), this suggests that ginger components (i.e. probably gingerol and shogaol) do not affect serum protein synthesis. In contrast, these or other components of ginger may have an inhibitory effect on the synthesis of other liver proteins, since the total liver protein levels are slightly but significantly decreased with 500 mg kg^{-1} of ginger extract administration (Fig. 5).

Route of administration

In this study we have compared the effects of administration of an aqueous extract of ginger to female rats by IP and PO routes. In our previous studies with garlic and onion, we had observed that the IP route of administration resulted in a more significant toxic effect of these spices (Alnaqeeb *et al.* 1996, Thomson *et al.* 1998). We attributed this difference to better absorption via the IP route, plus lack of possible destruction of active compounds in the GI tract. In the present study, the results are less consistent. In the case of decrease in hemoglobin levels and increase in total and cardiac LDH, the IP route of administration was more effective. In addition, histopathological effects were only observed in the rats receiving ginger IP. However, the results with AST and ALT only showed changes in rats given the aqueous extract of ginger PO. It is unclear why this discrepancy exists.

Conclusion

This study demonstrated that aqueous extract of ginger at 500 mg kg^{-1} in IP mode appears to be slightly toxic to the rats. This toxicity was evidenced by consistently lower hemoglobin, increased cardiac LDH isozymes in serum, and a slight decrease in liver proteins. Histopathological evaluation of lungs and liver also revealed that ginger only at 500 mg kg^{-1} in IP mode caused abnormality indicating a toxic effect. It could also be concluded that the low dose of ginger either in IP or PO mode did not have any significant toxic effects on the parameters tested in this study. Thus, in comparison with our previous observations with garlic and onion (Alnaqeeb *et al.* 1996, Thomson *et al.* 1998), toxicity of ginger is low and ingestion of this spice at reasonable levels would be considered to be quite safe. In humans the 500 mg/kg dose administered in this experiment would represent 35 grams of raw ginger in a 70 kg man. This is equivalent to a relatively small piece of ginger root that could be easily consumed on a daily basis.

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السُمية الكيمياء حيوية والنسيجية المرضية على إناث الجرذان للمستخلص المائي للزنجبيل

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خلاصة

تم في البحث دراسة تأثير إعطاء جرعات عن طريق الفم وعن طريق التجويف الصفاقي لمستويين من جرعات المستخلص المائي للزنجبيل على الدم ومكوناته ومستويات الأنزيمات يه وعلى سُميته لأجهزة الجسم. وقد لوحظ أن الجرعات لم تؤثر على نسبة الكريات الحمراء في الدم بينما انخفضت كمية هيموجلوبين الدم في الجرذان التي أخذت جرعات صفاقية من الزنجبيل بمعدل 500 ملغم/كغم. وارتفعت معدلات إجمالي أنزيم LDH في مصلالدم بدرجة مؤثرة في الحيوانات التي تلقت جرعات 500 ملغم/كغم من الزنجبيل مقارنة بمستواها في الجرذان الضابطة. واتضح أن سبب الزيادة يعود إلى زيادة معدلات أنزيم LDH القلبي. أما معدلات أنزيم AST وLDH فكانت متفاوتة في درجاتها مُظهرة تأثره بالجرعات عن طريق الفم دون تأثرها بالجرعات الصفاقية. وأما مستوى أنزيم LDH في الكبد فقد ارتفع في الجرذان التي أخذت جرعات 500 ملغم/كغم صفاقية. ولم يتأثر أنزيم فوسفاتيز الحمضي بجرعات الزنجبيل. لم تتأثر بروتينات مصل الدم بجرعات الزنجبيل بأي شكل بينما انخفضت بروتينات الكبد نتيجة تعرض الحيوان لجرعات 500 ملغم/كغم من الزنجبيل عن طريق الفم وكذلك عن الطريق الصفاقي.

أوضح فحص أنسجة الرئة والكبد لأي أعراض مرضية انعدام التغييرات إلا في الجرذان التي تعرضت إلى جرعات صفاقية بمعدل 500 ملغم/كغم حيث ظهر بعض الشذوذ. أما الجرعات المنخفضة (50 ملغم/كغم) فلم تظهر سُمية في الدم وأنزيماته ولا في أنسجة الرئة والكبد في الجرذان.

الواضح من الدراسة أن سمية الزنجبيل منخفضة. وأن استعماله بكميات معقولة في الأكل كنوع من التوابل يمكن اعتباره آمن ودون ضرر.