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A 35-day gavage safety assessment of ginger in rats

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Abstract

Ginger (*Zingiber officinale* Roscoe, Zingiberacae) is one of the most commonly used spices around the world and a traditional medicinal plant that has been widely used in Chinese, Ayurvedic and Unani-Tibb medicines for several thousand years. However, there was still lack of systemic safety evaluation. We conducted a 35-day toxicity study on ginger in rats. Both male and female rats were daily treated with ginger powder at the dosages of 500, 1000 and 2000 mg/kg body weight by a gavage method for 35 days. The results demonstrated that this chronic administration of ginger was not associated with any mortalities and abnormalities in general conditions, behavior, growth, and food and water consumption. Except for dose-related decrease in serum lactate dehydrogenase activity in males, ginger treatment induced similar hematological and blood biochemical parameters to those of controlled animals. In general, ginger treatment caused no overt organ abnormality. Only at a very high dose (2000 mg/kg), ginger led to slightly reduced absolute and relative weights of testes (by 14.4% and 11.5%, respectively). This study provides a new understanding of the toxicological properties of ginger.

Keywords

Ginger; Safety; Toxicity; Rat

1. Introduction

Ginger (*Zingiber officinale* Roscoe, Zingiberacae) is one of the most commonly used spices around the world, especially in the South-Eastern Asian countries. Ginger is also a medicinal plant that has been widely used in Chinese, Ayurvedic and Unani-Tibb medicines, since antiquity, for a wide array of ailments that include arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, constipation, indigestion, vomiting, hypertension, dementia, fever, infectious diseases and helminthiasis (Dedov et al., 2002; Jiang et al., 2006; Ali et al., 2008). Ginger has been demonstrated to have various pharmacological activities such as antiemetic, antiulcer, anti-inflammatory, antioxidant, anti-platelet, glucose- and lipid-

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Conflict of interest
None.

lowering, cardiovascular and anti-cancer activities (Bhandari et al., 1998; Nicoll and Henein, 2009; Shukla and Singh, 2007).

Ginger is generally considered as a safe herbal medicine. An acute (≤4 days) experimental study suggested that a patented ginger extract (25–100 mg/kg) with a high content of gingerols and shogaols did not induce significant changes in blood glucose, blood coagulation, blood pressure and heart rate in normal male rats (Weidner and Sigwart, 2000). An oral ethanol extract at 2.5 g/kg was not associated with mortality in mice, and the acute oral LD_{50} of ginger oil in rats and the acute dermal LD_{50} in rabbits exceeded 5 g/kg (Anonymous, 2003). A ginger extract at the dosages of 100, 333 and 1000 mg/kg administered to pregnant rats for 10 days during the period of organogenesis caused neither maternal nor developmental toxicity at daily doses of up to 1000 mg/kg (Weidner and Sigwart, 2001). However, ginger is suggested to contain mutagenic and antimutagenic constituents (Anonymous, 2003; Soudamini et al., 1995). Alcoholic extract of ginger is more cytotoxic than aqueous extracts in cultured Dalton's lymphoma ascites tumor cells, human lymphocytes and Chinese Hamster Ovary cells and Vero cells (Unnikrishnan and Kuttan, 1988). The observed marginal genotoxicity of ginger is possibly due to a combination of pro- and anticlastogenic constituents (Anonymous, 2003). Teratogenicity studies show that ginger tea up to 50 g/l had no impact on maternal toxicity in rats but doubled the embryonic losses relative to those of the controls (Wilkinson, 2000; Weidner and Sigwart 2001). Fetuses exposed to ginger tea were heavier than controls and had more advanced skeletal development (Wilkinson, 2000). In human, ginger may cause gastric reflux (Anonymous, 2003). High dose (>6 g) ginger may act as a gastric irritant (Desai et al., 1990). Inhalation of ginger dust may produce IgE-mediated allergy (Van Toorenenbergen and Dieges, 1985). Thus, the potential toxicity of ginger cannot be ruled out, especially when ginger is consumed in a longer term and at higher dosages. Further, ginger has been used not only in the type of extract, but also in whole root type (e.g., a dried root powder, a fresh root).

In the present study, we evaluated the safety of a ginger powder by conducting a 35-day toxicity study in both male and female rats.

2. Materials and methods

2.1. Chemicals and reagents

The kits for determination of triglyceride (TG) (TG IE), non-esterified fatty acid (NEFA), total cholesterol (TC) (T-Cho IE), 6-gingerol and 6-shogarol (the authentic standard samples) were purchased commercially from Wako, Osaka, Japan. Galanolactone was isolated and purified from Japanese ginger as described previously (Huang et al., 1991).

2.2. Identification of ginger

Japanese ginger (*Z. officinale* Roscoe, Zingiberaceae) was immigrated and cultured in the suburban of Hanoi, Vietnam. The roots were harvested in 2005. The plant was authenticated carefully and a voucher specimen has been deposited in Pharmafood Institute, Kyoto, Japan. The roots were sliced, dried in air, and ground into fine powder.

While a variety of gingers mainly contain 6-gingerol and 6-sho-gaol (Yoshikawa et al., 1993; Ali et al., 2008), Japanese ginger contains mainly 6-gingerol and galanolactone (Yoshikawa et al., 1993); the later is not detectable in the gingers produced in other countries (Yoshikawa et al., 1993). Therefore, the above three components were used as markers for identification of ginger used in the present study. Ginger powder (0.05 g) was ultrasonicated in ethanol for 30 min and extracted. The extract was filtrated with 0.45 μm membrane filters. The filtrate was characterized by HPLC. HPLC with Photodiode array (PDA) detection (SHIMADZU Class VP system) analysis was carried out on an Inertsil ODS-3 (GL-Science,

5 μm, 4.6 × 250 mm) column with oven temperature held at 40 °C. The extract was eluted at a flow rate of 1 ml/min with a mobile phase gradient consisting of a mixture of solvent A (water:methanol:1,4-dioxane, 50:15:35) and solvent B (acetonitrile:methanol:1,4-dioxane, 50:15:35) (0 min, 80:20; 20 min, 60:40; 25 min, 15:85; 25–30 min, 0:100; >30 min, 80:20). The peaks of 6-gingerol, 6-shogaol and galanolactone were identified by comparing their retention times and coincidence of UV–visible spectra with corresponding standard solutions, respectively. Spectral data for the authentic standard: 6-gingerol, retention time 8.6 min λ_{max} at 210, 280 nm; 6-shogaol, retention time 17.2 min, λ_{max} at 212, 278 nm; galanolactone, retention time 22.6 min, λ_{max} at 215 nm. The contents of 6-gingerol, 6-shogaol and galanolactone in the extract were quantified to be 9065.87, 1596.87 and 95.38 ppm, respectively.

2.3. Animals and treatment

All experimental procedures were carried out in accordance with the Guiding Principles for the Care and Use of Laboratory Animals approved by The Japanese Pharmacological Society. Sprague–Dawley rats (Kiwa Laboratory Animals, Wakayama, Japan) were housed (2–3 rats each cage) in an air-conditioned room at 23 ± 1 °C and 30–70% relative humidity with a 12-hour light/dark cycle. Rats were provided *ad libitum* with water and standard pel-leted diet containing water 8.2%, crude protein 20.4%, crude fat 6.9%, ash 5.6%, fiber 1.7% and soluble non-nitrate 57.2% (Oriental Yeast, Chiba, Japan). Animals were allowed free access to the food and water for 1 week before the experiments were started.

After acclimation, 20 male and 20 female Sprague–Dawley rats (the initial body weight shown in Table 2) were divided into eight groups (5 rats each group in a cage): (1) Group A: male control; (2) Group B: male ginger 500 mg/kg; (3) Group C: male ginger 1000 mg/kg; (4) Group D: male ginger 2000 mg/kg; (5) Group E: female control; (6) Group F: female ginger 500 mg/kg; (7) Group G: female ginger 1000 mg/kg; (8) Group H: female ginger 2000 mg/kg. The fine ginger powder was suspended in 5% Gum Arabic and given orally at a constant volume of 5 ml/kg to animals by a gavage method once daily for 35 days. The same volume of vehicle (5% Gum Arabic) was given to animals of the control group. During the study, each animal was weighed once every 3–4 days. Food and water consumptions were measured weekly per cage and mean food and water consumptions by individual rats were calculated. Animals were fasted overnight, but allowed free access to water prior to blood collection (Day 36, under anesthesia with ether). After blood sampling, food was returned to animals, which were sacrificed the next day (Day 37).

2.4. Clinical observation

All animals were observed twice daily for mortality. Cage-side observations were made daily during the study and any abnormal findings, if any, recorded. Detailed observations were recorded on Day 1 (prior to administration of test article) and weekly thereafter on all animals. These observations were conducted both while handling the animal and placing the animal in an open field. Observations included, but were not limited to, changes in skin, fur, eyes, and mucous membranes, occurrence of secretions and excretions and autonomic activity (e.g., lacrimation, piloerection, pupil size, unusual respiratory pattern). Changes in gait, posture and response to handling as well as the presence of clonic or tonic movements, stereotypies (e.g., excessive grooming, repetitive circling), or aberrant behavior (e.g., self-mutilation, walking backwards) were also recorded.

2.5. Body weight (BW) and BW gain

Individual BWs were recorded before study initiation (Day 0), and weekly thereafter. Mean BW gains were calculated for each group at each interval and for the overall (Days 1–35) testing

interval. Animals were also weighed immediately prior to sacrifice (fasted body weight) for calculation of organ to BW ratios.

2.6. Clinical pathology examinations

All animals were fasted overnight prior to each blood collection. Blood samples for hematology and clinical biochemistry from the control and test groups were collected via orbital sinus bleeding under ether anesthesia on study Day 36. All blood samples were evaluated for quality by visual examination prior to analysis. Examination of hematology and clinical chemistry parameters (Table 1) was made by Japan Medical Laboratory, Osaka, Japan.

2.7. Necropsy and histopathology

At scheduled sacrifice, all rats were euthanized by exsanguinations under halothane anesthesia. All male and female rats from each group were sacrificed. Gross necropsy of all males and females included an initial examination of external surfaces and orifices, as well as the cranial, thoracic and abdominal cavities and their contents. Rats were examined for gross lesions. Tissues of interest and any gross lesions were retained in 10% formalin. The lungs, heart, liver, kidneys, adrenals, spleen, uterus, ovaries, and testes of all animals were weighed as soon as possible after dissection to avoid drying. The lungs, trachea, heart, adrenals, liver, spleen, kidneys, ovaries, testes, uterus (with attached urinary bladder, cervix and vagina), esophagus, ileum, cecum, accessory genital organs (epididymides, prostate, and seminal vesicles), stomach, duodenum, jejunum, colon, rectum, pancreas and salivary glands were examined for gross lesion. The heart and liver from all animals were preserved in neutral 10% formalin for histopathological examination. They were trimmed, processed, embedded in paraffin, sectioned, placed on glass microscope slides, and stained with hematoxylin and eosin (H.E.). Histopathological assessments were performed.

2.8. Data analysis

All quantitative data are expressed as means ± SD. Treated and control groups were compared using a one-way analysis of variance (ANOVA). If a statistically significant effect was found, then the Student–Newman–Keuls test was performed to isolate the difference among the groups. A 95% confidence level was used to determine statistically significant differences between treated and control groups. P values less than 0.05 ($P < 0.05$) were considered as indicative of significance.

3. Results

3.1. General information from 35-day rat toxicity study

Rats received vehicle and ginger powder (500, 1000, or 2000 mg/kg/day) by oral gavage for 35 days. All animals survived until they were sacrificed at the endpoint of the experiment, and no clinical sign was observed over the duration of the experiment. The mean BW and mean BW gain for control and treated rats of both genders were not different (Table 2) and food and water intake by all animals were unaffected by exposure to ginger powder (Table 3).

3.2. Clinical pathology

3.2.1. Hematology—Compared to the controls, there was no significant difference in hematological parameters among the male or female groups (Table 4A and B).

3.2.2. Blood biochemistry—Treatment with ginger powder showed dose-dependent decrease in serum lactate dehydrogenase (LDH) activity, with significance at the dosages of 1000 and 2000 mg/kg (Table 5A and B). There was no significant difference in other

biochemical parameters measured in the present study among the male or female groups (Table 5A and B).

3.2.3. Necropsy—There were no gross lesions observed in any of the rats from any of the groups. Mean absolute and relative (ratio of organ weights to BWs) organ weights for all organs evaluated were comparable to respective control values (Table 6) with one exception.

A slight but significant decrease compared to the control was observed in the testes weight and the ratio of testes weight to BW of the male rats treated with ginger powder at 2000 mg/kg (by 14.4% and 11.4%, respectively) (Table 6).

3.2.4. Histology—No evidence of pathological abnormality was found in both male and female rat hearts and livers (data not shown) after ginger powder treatment.

4. Discussion

Although ginger has been used in clinic for several thousand years, there was still lack of systemic safety evaluation. In contrast to the previous acute experimental studies, the present study evaluated the safety of ginger by conducting a 35-day toxicity study in rats. Our results demonstrated that oral administration of ginger powder up to 2000 mg/kg to male and female rats was not associated with any mortalities and abnormalities in general conditions, behavior, growth, and food and water consumption of animals. Various parameters of hematology and blood biochemistry except for LDH decrease in male rats were similar in both control and treated animals. The results of necropsy suggest that all of the examined organs except for the testes of rats treated by 2000 mg/kg of ginger are normal.

Ginger has been reported to interfere with the activities of some digestive enzymes. In animals which are diabetic, deficient in the apolipoprotein E gene or have been fed a high lipid diet, ginger significantly lowered serum total cholesterol, LDL, VLDL, and triglycerides, and raised HDL (Thomson et al., 2002; Fuhrman et al., 2000; Verma et al., 2004). It was found that ginger acted on the liver to reduce cholesterol biosynthesis and may stimulate cholesterol's conversion to bile acids and increase its faecal excretion (Verma et al., 2004). On the other hand, Ramakrishna Rao et al. (2003) demonstrated that ginger enhanced the activity of pancreatic lipase and amylase when they were directly in contact with the enzyme. However, Han et al. (2005) recently demonstrated that an aqueous extract of ginger inhibited the hydrolysis of triolein emulsified with phosphatidylcholine by pancreatic lipase *in vitro* and reduced the elevation of rat plasma triacylglycerol levels after oral administration of a lipid emulsion containing corn oil. Additionally, ginger brought about significant dose-dependent inhibition of arachidonic acid-induced platelet aggregation, cyclooxygenase-derived thromboxanes and prostaglandins and prostacyclin synthesis, with an increase in fibrinolytic activity, in *in vitro* and animal studies (Bordia et al., 1997; Thomson et al., 2002; Verma et al., 2004; Koo et al., 2001;Nurtjahja-Tjendraputra et al., 2003). These results suggest anti-platelet effect of ginger. Therefore, we were concerned with whether ginger also affects glucose and lipid metabolism, and platelets under normal condition. In the present study, treatments of rats with ginger powder up to 2000 mg/kg for 35 days did not affect serum glucose, total cholesterol and triglyceride levels, and platelet number in male and female rats. These results suggest that ginger does not interfere with glucose and lipid metabolism, and platelet under physiological status.

An increase in serum LDH activity is one of important biomarkers to evaluate myocardial injuries due to various pathological causes, such as drug toxicity, myocardial ischemia-induced acute or chronic cardiac inflammation. Recent studies demonstrated that ginger shows considerable anti-inflammatory, antioxidant, antiplatelet, hypotensive and hypolipidemic effect *in vitro* and *in vivo* (Nicoll and Henein, 2009; Ali et al., 2008). Ansari et al. (2006)

reported that treatment with an ethanolic extract of ginger in isoproterenol-treated rats increased the levels of endogenous myocardial antioxidants (catalase, superoxide dismutases and tissue glutathione), decreased the levels of serum marker enzymes [LDH, creatinine kinase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] and increased myocardial lipid peroxides. The cardioprotective property was further confirmed by histological examination, which demonstrated that the ginger treatment largely protected the rats from isoproterenol-induced myocardial injury. In the present study, ginger powder at 1000 and 2000 mg/kg reduced serum LDH activity in male rats. This change was not accompanied by other abnormalities in hematology, blood biochemistry, cardiac size and cardiac histology. However, a single 35-day study here cannot on its own, completely exclude toxic effect of ginger on LDH activity. The exact underlying mechanism of the decreased LDH activity needs to be further clarified.

It has been reported that oral administration of an aqueous extract of ginger at dose of 600 mg/kg for 6 days significantly increased the relative weight of the testis, the serum testosterone level and testicular cholesterol level in Wistar rats, suggesting androgenic activity of ginger (Kamtchouing et al., 2002). An oral pretreatment of an ethanol extracts of ginger (1 g/kg) for 26 days restored cisplatin-induced decrease in relative weights of testes and epididymid, and reduced the extent of cisplatin-induced sperm abnormality and enhanced sperm motility in rats (Amin and Hamza, 2006). Furthermore, this treatment reduced cisplatin-induced rat reproductive toxicity, as evidenced by restoring the testis normal morphology accompanied by improvement of cisplatin-induced alterations of testicular lipid peroxidation (Amin et al., 2008). In contrast, our present results demonstrated that oral administration of ginger powder at 2000 mg/kg for 35 days slightly but significantly decreased the weight of testes and the ratio of the testis weight to body weight in rats. It would be interesting to further investigate whether long-term administration of ginger powder at higher dosage reduces testicular mass due to a feedback reaction of its androgenic activity.

Taken together, the present results from a 35-day toxicity study demonstrated minimal toxic effects of a ginger aqueous extract in rats. This study provides a new understanding of toxicological properties of ginger, the unique traditional medicine and spice.

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References

Anonymous. *Zingiberis rhizoma*, ESCOP Monographs. Stuttgart, New York: Thieme Press; 2003. p. 547-553.

Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): a review of recent research. Food Chem. Toxicol 2008;46:409–420. [PubMed: 17950516]

Amin A, Hamza AA. Effects of Roselle and Ginger on cisplatin-induced reproductive toxicity in rats. Asian J. Androl 2006;8:607–612. [PubMed: 16751998]

Amin A, Hamza AA, Kambal A, Daoud S. Herbal extracts counteract cisplatin-mediated cell death in rat testis. Asian J. Androl 2008;10:291–297. [PubMed: 18097501]

Ansari MN, Bhandari U, Pillai KK. Ethanolic *Zingiber officinale R.* extract pretreatment alleviates isoproterenol-induced oxidative myocardial necrosis in rats. Indian J. Exp. Biol 2006;44:892–897. [PubMed: 17205709]

Bhandari U, Sharma JN, Zafar R. The protective action of ethanolic ginger (*Zingiber officinale*) extract in cholesterol fed rabbits. J. Ethnopharmacol 1998;61:167–171. [PubMed: 9683348]

Bordia A, Verma SK, Srivastava KC. Effect of ginger (*Zingiber officinale* Rosc.) and fenugreek (*Trigonella foenumgraecum* L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. Prostaglandins Leukot. Essent. Fatty Acids 1997;56:379–384. [PubMed: 9175175]

Dedov VN, Tran VH, Duke CC, Connor M, Christie MJ, Mandadi S, Roufogalis BD. Gingerols: a novel class of vanilloid receptor (VR1) agonists. Br. J. Pharmacol 2002;137:793–798. [PubMed: 12411409]

Desai HG, Kalro RH, Choksi AP. Effect of ginger & garlic on DNA content of gastric aspirate. Indian J. Med. Res 1990;92:139–141. [PubMed: 2370094]

Fuhrman B, Rosenblat M, Hayek T, Coleman R, Aviram M. Ginger extract consumption reduces plasma cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E-deficient mice. J. Nutr 2000;130:1124–1231. [PubMed: 10801908]

Han LK, Gong XJ, Kawano S, Saito M, Kimura Y, Okuda H. Antiobesity actions of *Zingiber officinale* Roscoe. Yakugaku Zasshi 2005;125:213–217. [PubMed: 15684576]

Huang QR, Iwamoto M, Aoki S, Tanaka N, Tajima K, Yamahara J, Takaishi Y, Yoshida M, Tomimatsu T, Tamai Y. Anti-5-hydroxytryptamine3 effect of galanolactone, diterpenoid isolated from ginger. Chem. Pharm. Bull. (Tokyo) 1991;39:397–399. [PubMed: 2054863]

Jiang H, Xie Z, Koo HJ, McLaughlin SP, Timmermann BN, Gang DR. Metabolic profiling and phylogenetic analysis of medicinal Zingiber species: tools for authentication of ginger (*Zingiber officinale* Rosc.). Phytochemistry 2006;67:232–244. [PubMed: 16376957]

Kamtchouing P, Mbongue Fandio GY, Dimo T, Jatsa HB. Evaluation of androgenic activity of *Zingiber officinale* and *Pentadiplandra brazzeana* in male rats. Asian J. Androl 2002;4:299–301. [PubMed: 12508133]

Koo K, Ammit A, Tran V, Duke C, Roufogalis B. Gingerols and related analogues inhibit arachidonic acid-induced human platelet serotonin release and aggregation. Thromb. Res 2001;103:387–397. [PubMed: 11553371]

Nicoll R, Henein MY. Ginger (*Zingiber officinale* Roscoe): a hot remedy for cardiovascular disease? Int. J. Cardiol 2009;131:408–409. [PubMed: 18037515]

Nurtjahja-Tjendraputra E, Ammit A, Roufogalis B, Tran V, Duke C. Effective anti-platelet and COX-1 enzyme inhibitors from pungent constituents of ginger. Thromb. Res 2003;111:259–265. [PubMed: 14693173]

Ramakrishna Rao R, Platel K, Srinivasan K. In vitro influence of spices and spice-active principles on digestive enzymes of rat pancreas and small intestine. Nahrung 2003;47:408–412. [PubMed: 14727769]

Shukla Y, Singh M. Cancer preventive properties of ginger: a brief review. Food Chem. Toxicol 2007;45:683–690. [PubMed: 17175086]

Soudamini KK, Unnikrishnan MC, Sukumaran K, Kuttan R. Mutagenicity and anti-mutagenicity of selected spices. Indian J. Physiol. Pharmacol 1995;39:347–353. [PubMed: 8582746]

Thomson M, al-Qattan K, al-Sawan S, Alnaqeeb M, Khan I, Ali M. The use of ginger (*Zingiber officinale* Rosc.) as a potential anti-inflammatory and antithrombotic agent. Prostaglandins Leukot. Essent. Fatty Acids 2002;67:475–478. [PubMed: 12468270]

Unnikrishnan MC, Kuttan R. Cytotoxicity of extracts of spices to cultured cells. Nutr. Cancer 1988;11:251–257. [PubMed: 3217263]

Van Toorenenbergen AW, Dieges PH. Immunoglobulin E antibodies against coriander and other spices. J. Allergy Clin. Immunol 1985;76:477–481. [PubMed: 2411778]

Verma SK, Singh M, Jain P, Bordia A. Protective effect of ginger, Zingiber officinale Rosc on experimental atherosclerosis in rabbits. Indian J. Exp. Biol 2004;42:736–738. [PubMed: 15339040]

Weidner MS, Sigwart K. The safety of a ginger extract in the rat. J. Ethnopharmacol 2000;73:513–520. [PubMed: 11091007]

Weidner MS, Sigwart K. Investigation of the teratogenic potential of a Zingiber officinale extract in the rat. Reprod. Toxicol 2001;15:75–80. [PubMed: 11137381]

Wilkinson JM. Effect of ginger tea on the fetal development of Sprague-Dawley rats. Reprod. Toxicol 2000;14:507–512. [PubMed: 11099876]

Yoshikawa M, Hatakeyama S, Chatani N, Nishino Y, Yamahara J. Qualitative and quantitative analysis of bioactive principles in *Zingiberis rhizoma* by means of high performance liquid chromatography

and gas liquid chromatography. On the evaluation of *Zingiberis rhizoma* and chemical change of constituents during *Zingiberis rhizoma* processing. Yakugaku Zasshi 1993;113:307–315. [PubMed: 8492294]

Table 1

Summary of hematology and clinical chemistry parameters measured.

Hematology	
Erythrocyte count (RBC)	Hemoglobin concentration (HGB)
Hematocrit (HCT)	Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)	mean corpuscular hemoglobin concentration (MCHC)
Platelet count (PLT)	Absolute reticulocyte count (RET)
Total white blood cell (WBC) and differential leukocyte count	
Lymphocyte (LYM)	Segmentedleukocyte (S)
Monocyte (MON)	Eosinophilic granulocyte (EOS)
Basophile granulocyte (BAS)	Stab form leukocyte (ST)
Clinical chemistry	
Serum total protein (TP)	Serum albumin (ALB)
Serum lactate dehydrogenase (LDH)	Serum aspartate aminotransferase (AST)
Serum alanine aminotransferase (ALT)	Serum total bilirubin (TBil)
Serum alkaline phosphatase (ALP)	Serum glucose (GLU)
Serum triglycerides (TG)	Serum total cholesterol(TCHO)
Serum high density lipoprotein-cholesterol (HDL-C)	Serum low density lipoprotein-cholesterol (LDL-C)
Serum urea nitrogen (BUN)	Serum creatinine (CREA)
Serum uric acid (UA)	Serum sodium (NA)
Serum potassium (K)	Serum calcium (CA)
Serum magnesium (Mg)	Serum chloride (CL)

Table 2

Body weight (BW) (*g*).

Day	Gender	Ginger (mg/kg)			
		0	**500**	**1000**	**2000**
Day 0	M	140.4 ± 3.2	144.4 ± 3.8	139.0 ± 4.2	136.6 ± 2.4
	F	128.2 ± 1.5	128.2 ± 2.8	127.4 ± 4.7	128.0 ± 3.2
Day 7	M	204.8 ± 5.5	215.2 ± 5.2	209.8 ± 2.6	203.8 ± 5.4
	F	168.6 ± 13.3	168.4 ± 6.1	159.2 ± 6.7	163.4 ± 3.4
Day 14	M	268.6 ± 4.0	279.2 ± 3.3	274.0 ± 3.6	261.8 ± 6.1
	F	199.8 ± 10.1	182.0 ± 8.8	189.8 ± 4.7	195.2 ± 7.9
Day 21	M	322.4 ± 8.4	323.4 ± 6.3	331.6 ± 10.9	311.4 ± 18.3
	F	226.0 ± 16.5	223.0 ± 14.5	222.6 ± 6.7	217.6 ± 12.8
Day 28	M	363.0 ± 5.5	376.6 ± 13.6	376.0 ± 14.3	351.2 ± 10.3
	F	248.2 ± 13.5	244.8 ± 18.0	245.2 ± 10.8	241.4 ± 13.8
Day 35	M	372.6 ± 6.7	387.6 ± 15.5	387.4 ± 19.0	362.6 ± 15.5
	F	257.2 ± 10.1	252.6 ± 17.0	248.8 ± 13.6	249.2 ± 11.5
BW gain	M	232.2 ± 9.9	243.2 ± 15.5	248.4 ± 21.7	226.0 ± 11.9
	F	129.0 ± 10.3	124.4 ± 17.3	131.4 ± 12.1	121.2 ± 11.5

M, male; F, female.

Table 3

Food and water consumption (g/day).

Item		Ginger (mg/kg)			
		0	500	1000	2000
Day 0	M	18.1 (22.70)	17.1 (21.8)	17.1 (23.5)	17.0 (21.5)
	F	14.9 (19.9)	15.2 (20.6)	14.6 (18.8)	13.9 (19.1)
Day 7	M	22.1 (26.4)	20.9 (25.5)	21.5 (26.4)	20.8 (25.5)
	F	15.5 (19.4)	15.2 (20.4)	14.6 (18.0)	14.4 (19.2)
Day 14	M	22.4 (32.4)	21.9 (32.7)	22.9 (33.8)	22.5 (31.0)
	F	15.2 (20.3)	16.9 (22.8)	16.3 (23.2)	15.3 (20.5)
Day 21	M	26.3 (33.4)	25.2 (32.4)	26.5 (32.6)	25.2 (29.9)
	F	18.3 (22.5)	20.2 (23.1)	18.4 (24.4)	19.0 (22.8)
Day 28	M	23.1 (33.5)	22.5 (31.0)	24.0 (34.2)	23.9 (32.4)
	F	18.5 (22.1)	19.0 (24.8)	17.4 (24.9)	17.5 (24.9)
Day 35	M	25.0 (35.0)	24.8 (37.0)	25.4 (38.9)	23.9 (36.5)
	F	18.8 (23.1)	18.0 (24.1)	19.8 (24.4)	18.0 (24.4)

(), water intake; M, male; F, female.

Table 4

Hematology parameters (n = 5).

Item	Gender	Ginger (mg/kg)			
		0	500	1000	2000
(A)					
RBC ($\times 10^6$/μl)	M	800.8 ± 39.9	789.0 ± 21.0	781.0 ± 44.6	773.8 ± 42.3
	F	774.4 ± 23.7	734.4 ± 54.8	739.0 ± 26.9	757.4 ± 25.6
HGB (g/dl)	M	16.3 ± 0.9	16.1 ± 0.5	16.2 ± 0.8	15.8 ± 0.7
	F	15.7 ± 0.26	15.4 ± 0.9	15.7 ± 0.7	15.7 ± 0.4
HCT (%)	M	49.8 ± 2.7	48.6 ± 1.8	48.7 ± 2.2	47.5 ± 2.4
	F	48.0 ± 0.8	46.2 ± 3.1	46.5 ± 2.3	46.6 ± 1.0
MCV (fL)	M	62.2 ± 2.4	62.0 ± 1.6	62.4 ± 2.1	61.4 ± 1.7
	F	62.0 ± 2.6	63.0 ± 1.9	63.0 ± 1.2	61.6 ± 1.1
MCH (pg)	M	20.3 ± 0.8	20.4 ± 0.6	20.8 ± 0.6	20.5 ± 0.3
	F	20.3 ± 0.7	21.0 ± 0.4	21.2 ± 0.5	20.8 ± 0.4
MCHC (g/dl)	M	32.7 ± 0.3	33.1 ± 0.4	33.3 ± 0.6	33.3 ± 0.5
	F	32.8 ± 0.3	33.4 ± 0.7	32.7 ± 0.2	32.8 ± 0.3
PLT ($\times 10^3$/μl)	M	81.0 ± 5.8	75.5 ± 5.1	80.4 ± 9.8	86.8 ± 5.6
	F	76.3 ± 6.5	77.8 ± 13.7	71.3 ± 5.6	72.0 ± 14.8
RET ($\times 10^3$/μl)	M	48.2 ± 14.0	54.4 ± 9.7	50.4 ± 10.1	55.2 ± 9.6
	F	53.6 ± 16.3	49.2 ± 6.8	43.2 ± 5.6	47.2 ± 9.8
(B)					
WBC ($\times 10^3$/μl)	M	4.52 ± 0.54	4.26 ± 3.85	4.62 ± 6.14	4.36 ± 5.90
	F	2.64 ± 0.80	3.28 ± 0.44	2.74 ± 0.25	2.96 ± 1.18
LYM (%)	M	94.2 ± 2.2	89.2 ± 5.1	93.6 ± 1.1	88.4 ± 6.5
	F	89.2 ± 6.6	90.0 ± 6.8	92.6 ± 1.9	91.2 ± 2.6
S (%)	M	4.4 ± 1.5	5.8 ± 4.4	5.6 ± 1.3	5.8 ± 3.4
	F	8.8 ± 6.3	8.6 ± 7.1	5.8 ± 1.3	8.0 ± 1.9
MON (%)	M	0.8 ± 0.5	0.6 ± 0.6	0.8 ± 0.8	0.8 ± 0.5
	F	0.8 ± 0.8	0.4 ± 0.6	0.4 ± 0.6	0.6 ± 0.9
EOS (%)	M	0.2 ± 0.5	0.2 ± 0.5	0 ± 0	0.6 ± 0.6
	F	0.8 ± 0.8	1.0 ± 1.2	1.0 ± 1.2	0.2 ± 0.6
BAS (%)	M	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	F	0 ± 0	0 ± 0	0 ± 0	0 ± 0
ST (%)	M	0.4 ± 0.6	0.2 ± 0.5	0 ± 0	0.4 ± 0.6
	F	0.4 ± 0.6	0 ± 0	0.2 ± 0.5	0 ± 0

M, male; F, female.

Table 5

Blood biochemical parameters (n = 5).

Item	Gender	Ginger (mg/kg)			
		0	500	1000	2000
(A)					
TP (g/dl)	M	6.26 ± 0.18	6.18 ± 0.15	6.30 ± 0.20	6.34 ± 0.13
	F	6.78 ± 0.15	6.62 ± 0.30	6.60 ± 0.30	6.62 ± 0.16
ALB (g/dl)	M	3.94 ± 0.09	3.94 ± 0.09	4.04 ± 0.11	4.01 ± 0.08
	F	4.42 ± 0.23	4.24 ± 0.13	4.16 ± 0.25	4.26 ± 0.15
A/G	M	1.70 ± 0.13	1.76 ± 0.13	1.78 ± 0.08	1.80 ± 0.09
	F	1.88 ± 0.21	1.95 ± 0.13	1.85 ± 0.11	1.89 ± 0.19
LDH (U/L)	M	1032.0 ± 282.7	712.8 ± 227.9	402.2 ± 235.8*	328.8 ± 214.7*
	F	445.0 ± 71.2	452.2 ± 101.2	526.8 ± 244.7	592.0 ± 134.1
AST (U/L)	M	114.4 ± 19.4	98.4 ± 13.2	100.2 ± 17.4	104.6 ± 24.4
	F	95.6 ± 3.1	100.6 ± 14.9	104.6 ± 15.8	98.8 ± 5.2
ALT (U/L)	M	33.2 ± 5.6	37.2 ± 2.9	37.0 ± 11.1	33.8 ± 10.9
	F	30.0 ± 3.9	33.0 ± 4.0	35.2 ± 5.7	29.6 ± 2.3
TBil (mg/dl)	M	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	F	0 ± 0	0 ± 0	0 ± 0	0 ± 0
ALP (IU/L)	M	713.0 ± 139.8	623.4 ± 128.9	644.8 ± 138.8	693.8 ± 85.7
	F	262.6 ± 68.8	333.6 ± 62.7	307.0 ± 41.4	275.2 ± 71.1
GLU (mg/dl)	M	129.8 ± 16.4	123.0 ± 13.5	121.6 ± 4.6	124.4 ± 4.0
	F	99.6 ± 7.5	106.0 ± 8.2	91.0 ± 5.3	93.4 ± 10.1
TG (mg/dl)	M	76.4 ± 17.7	77.6 ± 22.7	98.0 ± 23.1	63.8 ± 17.5
	F	94.0 ± 49.7	79.2 ± 32.9	76.2 ± 30.1	55.6 ± 24.5
TCHO (mg/dl)	M	60.4 ± 7.9	68.2 ± 11.2	72.2 ± 8.5	70.6 ± 9.5
	F	78.2 ± 14.7	74.2 ± 9.3	82.2 ± 14.4	83.2 ± 8.6
HDL-C (mg/dl)	M	47.6 ± 5.9	55.2 ± 7.8	55.4 ± 5.0	54.8 ± 7.1
	F	61.0 ± 9.4	56.4 ± 5.5	65.2 ± 8.8	65.4 ± 5.9
LDL-C (mg/dl)	M	3.6 ± 0.6	3.6 ± 1.1	3.6 ± 0.6	3.6 ± 0.6
	F	3.4 ± 0.9	2.8 ± 0.8	3.4 ± 0.6	3.8 ± 0.5
(B)					
BUN (mg/dl)	M	14.4 ± 1.7	15.2 ± 0.4	16.0 ± 3.1	16.0 ± 3.5
	F	25.8 ± 5.4	20.6 ± 2.3	21.0 ± 1.6	20.6 ± 3.4
CREA (mg/dl)	M	0.42 ± 0.08	0.46 ± 0.06	0.46 ± 0.06	0.44 ± 0.06
	F	0.52 ± 0.08	0.48 ± 0.05	0.50 ± 0.00	0.54 ± 0.06
UA (mg/dl)	M	1.34 ± 0.33	1.26 ± 0.27	1.32 ± 0.23	1.52 ± 0.22
	F	0.88 ± 0.11	1.18 ± 0.22	0.86 ± 0.09	0.84 ± 0.11
Na (mEq/L)	M	142.8 ± 0.4	142.4 ± 1.5	143.4 ± 0.5	142.6 ± 0.5
	F	142.0 ± 0.7	141.2 ± 1.1	142.2 ± 1.1	141.8 ± 0.8
K (mEq/L)	M	4.5 ± 0.2	4.4 ± 0.2	4.4 ± 0.3	4.6 ± 0.2
	F	3.9 ± 0.1	3.9 ± 0.1	3.9 ± 0.0	3.9 ± 0.2
Ca (mg/L)	M	10.6 ± 0.5	10.5 ± 0.4	10.8 ± 0.3	10.8 ± 0.2
	F	10.6 ± 0.3	10.5 ± 0.1	10.4 ± 0.3	10.2 ± 0.2
Mg (mg/L)	M	2.5 ± 0.2	2.3 ± 0.2	2.6 ± 0.2	2.6 ± 0.1
	F	2.5 ± 0.3	2.5 ± 0.2	2.5 ± 0.1	2.5 ± 0.2
Cl (mEq/L)	M	98.4 ± 1.1	97.4 ± 1.1	98.2 ± 1.3	99.2 ± 0.8
	F	101.0 ± 0.7	101.6 ± 1.1	101.4 ± 0.9	100.6 ± 1.5

M, male; F, female.

*$P < 0.05$.

Table 6

Organ weights (n = 5).

Item	Gender	Ginger (mg/kg)			
		0	500	1000	2000
BW (g)	M	345.2 ± 4.3	359.0 ± 14.1	360.8 ± 17.8	335.0 ± 25.7
	F	233.6 ± 29.3	237.4 ± 20.5	224.8 ± 11.7	224.0±12.5
Lungs (g)	M	1.54 ± 0.40	1.44 ± 0.13	1.45 ± 0.07	1.43 ± 0.19
	F	1.03 ± 0.14	1.03 ± 0.06	1.13 ± 0.09	1.01 ± 0.07
Lungs/BW (g/kg)	M	4.48 ± 1.20	4.01 ± 0.31	4.04 ± 0.30	4.28 ± 0.59
	F	4.40 ± 0.22	4.34 ± 0.34	5.04 ± 0.39*	4.52 ± 0.19
Heart (g)	M	1.01 ± 0.06	1.09 ± 0.08	1.05 ± 0.08	0.99 ± 0.06
	F	0.69 ± 0.06	0.69 ± 0.07	0.70 ± 0.03	0.69 ± 0.04
Heart/BW (g/kg)	M	2.93 ± 0.20	3.02 ± 0.19	2.91 ± 0.20	2.95 ± 0.08
	F	2.96 ± 0.14	2.91 ± 0.25	3.14 ± 0.19	3.07 ± 0.24
Spleen (g)	M	0.90 ± 0.16	0.83 ± 0.07	0.89 ± 0.11	0.90 ± 0.16
	F	0.56 ± 0.07	0.57 ± 0.09	0.63 ± 0.12	0.57 ± 0.08
Spleen/BW (g/kg)	M	2.61 ± 0.44	2.31 ± 0.21	2.46 ± 0.31	2.67 ± 0.39
	F	2.42 ± 0.18	2.39 ± 0.28	2.77 ± 0.43	2.55 ± 0.30
Kidneys (g)	M	2.45 ± 0.16	2.61 ± 0.15	2.62 ± 0.16	2.40 ± 0.25
	F	1.59 ± 0.11	1.62 ± 0.14	1.54 ± 0.16	1.61 ± 0.15
Kidneys/BW (g/kg)	M	7.09 ± 0.38	7.27 ± 0.33	7.29 ± 0.65	7.17 ± 0.69
	F	6.87 ± 0.62	6.85 ± 0.50	6.90 ± 0.68	7.17 ± 0.51
Testes (g)	M	3.53 ± 0.23	3.59 ± 0.25	3.69 ± 0.17	3.02 ± 0.17*
Testes/BW (g/kg)	M	10.22 ± 0.66	10.01 ± 0.56	10.24 ± 0.61	9.04 ± 0.70*
Ovaries + uterus (g)	F	0.55 ± 0.06	0.52 ± 0.05	0.57 ± 0.18	0.52 ± 0.05
Ovaries + uterus/BW (g/kg)	F	2.41 ± 0.49	2.18 ± 0.23	2.52 ± 0.68	2.31 ± 0.23

M, male; F, female.

*$P < 0.05$.