UNIVERSA MEDICINA

January-April, 2013 *Vol.32 - No.1*

Combination of three species of *Zingiberaceae* prevents doxorubicin-induced hepatotoxicity

Heny Ekowati*, Sarmoko*, and Retno Widiastuti**

ABSTRACT

BACKGROUND

Doxorubicin as an anticancer drug has hepatotoxic side effects. *Curcuma xanthorrhiza, Curcuma longa* and *Zingiber officinale* are commonly used as herbals in Indonesia and around the world. Several compounds in these plants have antioxidant activities and are known to exhibit protection against doxorubicin-induced toxicities. This study aimed to observe the hepatoprotective effect of a combination of *C. xanthorriza, C. longa,* and *Z. officinale* extract on doxorubicin-induced hepatotoxicity in rats.

METHODS

A total of 28 Wistar male rats were divided into four groups: 1) control group (0.9% NaCl); 2) doxorubicin 5 mg/kg intraperitoneally (ip) four times in 14 days (days 1, 5, 9, 13); 3) doxorubicin + combination of *C. xanthorriza, C. longa,* and *Z. officinale (temulawak, kunyit,* and *jahe merah,* designated as Tekuja) 250 mg/kg/day orally for 14 days; and 4) doxorubicin + Tekuja extract 500 mg/kg/day orally for 14 days. Measurements of parameters based on liver histopathology and the parameters of serum alanine amino transferase (ALT) and aspartate amino tranferase (AST).

RESULTS

Doxorubicin caused significant elevation in serum ALT and AST enzymes after 14 days of treatment. Rats treated with doxorubicin + Tekuja extract 250 mg/kg/day showed no histological changes, but had decreased levels of ALT and AST.

CONCLUSION

This study indicates that the combination of *C. xanthorriza, C. longa,* and *Z. officinale* has a protective effect in rats against liver damage induced by doxorubicin.

Key words : Doxorubicin, *Curcuma xanthorriza, Curcuma longa, Zingiber officinale,* hepatotoxicity, rats

*Pharmacy Department,
Faculty of Medicine and Health Sciences
Jenderal Soedirman University
**Medical Department,
Faculty of Medicine and Health Sciences
Jenderal Soedirman University

Correspondence
Heny Ekowati, M.Sc., Apt.
Pharmacy Department
Medicine and Health Sciences Faculty
Jenderal Soedirman University
Jl. Dr. Soeparno
Karangwangkal
Purwokerto 53123
Fax. +62281-642840
E-mail :
heny240377@gmail.com

Univ Med 2013;32:11-9

Kombinasi tiga spesies Zingiberacea mencegah hepatotoksitas yang diinduksi doksorubisin

ABSTRAK

LATAR BELAKANG

Doksorubisin adalah antikanker yang memiliki efek samping hepatotoksik. Curcuma xanthorrhiza (Temulawak), Curcuma longa (kunyit), dan Zingiber officinale (jahe), adalah herbal yang biasa digunakan di Indonesia dan di dunia. Senyawa-senyawa yang terkandung dalam ketiga herbal tersebut dilaporkan dapat menurunkan toksisitas yang disebabkan penggunaan doksorubisin. Penelitian ini bertujuan untuk menilai efek hepatoprotektif dari kombinasi ekstrak C. xanthorriza, C. longa, and Z. officinale (Temulawak, kunyit dan jahe merah) pada tikus yang diinduksi doksorubisin.

METODE

Hewan tikus galur Wistar jantan sejumlah 28 ekor dibagi dalam empat kelompok: 1) kelompok kontrol (0.9% NaCl); 2) doksorubisin 5 mg/kg intraperitoneal, empat kali selama 14 hari (hari 1, 5, 9, 13); 3) doksorubisin + kombinasi ekstrak temulawak, kunyit dan jahe merah (Tekuja) 250 mg/kg/hari per oral selama 14 hari; dan 4) doksorubisin + kombinasi ekstrak Tekuja 500 mg/kg/hari per oral selama 14 hari. Pengukuran parameter berdasarkan gambaran histopatologi organ hati dan parameter alanine amino transferase *(ALT) dan* aspartate amino tranferase *(AST).*

HASIL

Doksorubisin menyebabkan peningkatan yang signifikan pada enzim ALT dan AST setelah 14 hari perlakukan. Hewan yang diberikan ekstrak tidak menunjukkan perbedaan pada gambaran histopatologi namun memberikan gambaran penurunan level ALT dan AST. Doksorubisin menyebabkan kenaikan jumlah yang signifikan enzim ALT dan AST serum.

KESIMPULAN

Studi ini menunjukkan bahwa kombinasi ekstrak Tekuja memiliki efek protektif pada organ hati yang diinduksi doksorubisin.

Kata kunci : *Doksorubisin, Curcuma xanthorriza, Curcuma longa, Zingiber officinale, hepatotoksisitas, tikus*

INTRODUCTION

Natural products and their active constituents as a source of new drugs for the treatment of disease have attracted attention in recent years. Medicinal applications of spices or herbs have been gradually increasing in developed countries. *Curcuma xanthorriza*, *Curcuma longa* and *Zingiber officinale* are commonly used as spices as well as herbals in Indonesia and around the world. These spices are an indispensable component of curry, and belong to the *Zingiberaceae* family.[1] Several compounds in these plants have antioxidant activities and are known to exhibit protection against doxorubicin-induced toxicities.[1,2]

C. xanthorrhiza is known as *temulawak* or Javanese turmeric and its extract reportedly possesses anti-inflammatory and antitumor activities, particularly one of its active principles, xanthorrhizol,[3] *Z. officinale* or ginger, is one of the most commonly used spices in Indonesia and around the world. The active compounds of *Z. officinale* are gingerol, paradol, shogaol, and

zingerone.[4] The major chemical constituent of *C. longa* rhizomes is a yellow pigment, 1,7-bis (4-hydroxy-3-methoxyphenyl) -1, 6-heptadiene-3, 5- dione, known as curcumin (diferulolylmethane). Curcumin has shown antioxidant, anti-neoplastic and anti-inflammatory properties.[5]

Doxorubicin (DOX) is an anthracycline glycoside antibiotic that possesses a potent and broad spectrum antitumor activity against a variety of human solid tumors and hematological malignancies.[6] The DOX antitumor effects include mechanisms related to alterations of DNA and the production of free radicals.[7] However its use in chemotherapy has been limited, largely due to its diverse toxicities, including cardiac, hepatic, hematological and testicular toxicity.[6] Several studies have shown that the combination of the inflammatory process, free radical oxidative stress, and lipid peroxidation is frequently associated with liver damage, induced by toxic agents such as DOX.[7] Persistent and irreversible liver damage has been a well-known side effect of DOX therapy. It has been observed that there is an increase in the apoptotic processes in liver tissues after a single dose of DOX.[8,9] It was confirmed that the therapeutic dose of DOX enhanced lipid peroxidation in microsomes and mitochondria in the liver, especially in the presence of Fe3+ ions.[6] DOX-mediated hepatotoxicity includes focal damage in hepatocytes, vascular damage and steatosis.[10]

Although the antioxidant activities of *C. xanthorrhiza*, *Z. officinale* and *C. longa* were well-known, their protective effect against DOX-induced hepatotoxicity has not yet been reported. Several studies have shown that using a combination of plants increases their effectiveness because of synergy with minimal side effects.[11] In our study, we used a combination of three herbs, *C. xanthorriza (temulawak)*, *C. longa (kunyit)* and *Z. officinale (jahe merah)* (which we will designate as Tekuja). A study on the combination of *C. longa* and *C. xanthorrixa* showed that it had a protective effect against doxorubicin-induced liver damage in rats.[3,5] An earlier study, using *Z.officinale* only, suggested that *Z. officinale* protected against nephrotoxicity either by enhancing the renal antioxidant status that had been reduced by DOX, or by exerting a direct antioxidant activity.[12]

Therefore the current study was aimed at evaluating the hepatoprotective activity of an aqueous ethanolic extract of a combination of *C. xanthorrhiza*, *Z. officinale* and *C. longa* (Tekuja) on doxorubicin-induced hepatotoxicity in rats.

METHODS

Study design

An experimental laboratory study was conducted from March to October 2012. A total of 28 male rats was randomized into 4 groups (control and experimental groups) of seven rats each. The minimum group size as derived from the formula (t-1) (r-1) ≥15, where t = number of treatments and r = number of rats, was 4 rats per group. Animals from group I (control group) received NaCl 0.9%; animals from group II received doxorubicin (DOX) (5 mg/kg) intraperitoneally (ip) 4 times in 14 days (on days 1, 5, 9,13); group III was given Tekuja extract 250 mg/kg/day orally for 14 days and DOX (5 mg/kg) intraperitoneally (on days 1, 5, 9,13); animals from group IV were given Tekuja extract 500 mg/kg/day orally for 14 days and DOX (5 mg/kg) intraperitoneally (on days 1, 5, 9, 13). DOX-treated groups received the drug every fourth day, while the other groups instead of DOX received 0.9% sodium chloride (10 mL/kg BW) intraperitoneally. The time intervals between two DOX administrations were similar to the most frequently-used treatment schedules in humans. On day 15 (1 day after the last dose of DOX) all animals were sacrificed.[12,13]

Experimental animals

Laboratory-bred Wistar albino rats (8-week-old and weighing 140 ± 30 g) were

obtained from Medical Faculty, Gadjah Mada University, Yogyakarta, Indonesia and approved by the Animal Care Committee of Gadjah Mada University. The animals were maintained under standard laboratory conditions of 25° C and a photoperiod of 12 h dark and 12 h light. Commercial pellet diet (Clinical Pharmacy Laboratory rat and mouse feed, Purwokerto, Indonesia) and water were provided ad libitum. The animals were allowed to acclimatize for 10 days before beginning the experiments.

Extract preparation

C. xanthorriza, *C. longa* and *Z. officinale* rhizomes were purchased from and authenticated by the Center for Research and Development of Medicinal Plants and Traditional Medicine/ B2P2TO2T, Tawangmangu, Indonesia. The sundried rhizomes were ground separately to a powder, then 500 g each of the powders were combined and macerated in ethanol for 3 days at room temperature. The filtrate was air-dried and concentrated under reduced pressure.

Laboratory determination

Blood samples were withdrawn from the orbital vein using a capillary tube. The blood samples were left to clot at room temperature. The clotted blood was then centrifuged at 3,000 rpm for 15 min to obtain blood serum, and analyzed for the biochemical parameters serum alanine amino transferase (ALT) and aspartate amino tranferase (AST). All serum biochemical testing was conducted at Biofit Laboratory, Purwokerto, Indonesia using a SYSMEX KX 21 serum analyzer.

Histopathologic examination of liver tissues

At autopsy, the liver of each rat was removed and fixed in 10% buffered formalin. After 12–24 h of fixation, 3–5 mm tissue slices were embedded in paraffin, and stained with Hematoxylin (H) and Eosin (E) for histopathologic examination.

Ethical Clearance

Animals were handled according to the rules and regulations of the Animal Care Committee of the Faculty of Medicine, Gadjah Mada University**.**

Data analysis

All results were expressed as mean and standard deviation. Differences between groups were assessed by one-way analysis of variance (ANOVA), followed by Tukey HSD. Statistical significance was defined as $p<0.05$.

RESULTS

Observation was terminated at 14 days after the last DOX treatment. Macroscopic observation of the livers showed no perceptible differences between groups (Figure 1). The histopathological appearance of the livers in rats treated with DOX and DOX + Tekuja extract also showed no differences between groups (Figure 2).

However, we found a significant increase in ALT and AST levels ($p<0.05$) in the group treated with DOX only, compared with the control group (Table 1). Administration of Tekuja (250 and 500 mg/kg BW) plus DOX significantly ($p < 0.05$) attenuated the decrease in ALT and AST levels observed after administration of DOX alone. The ALT levels were restored to normal in the Tekuja plus DOX groups (Tukey HSD Test, $p<0.05$) (Table 2).

DISCUSSION

The results of the present study indicate that the aqueous ethanolic extract of the combination of *C. xanthorrhiza*, *C. Longa* and Z. *officinale* (Tekuja) significantly protected rats against DOX–induced hepatotoxicity. A study on the combination of *C. longa* and *C.xanthorrixa* showed that it had a protective effect against DOX-induced liver damage in rats.[3,5] Another study using *C. longa* alone

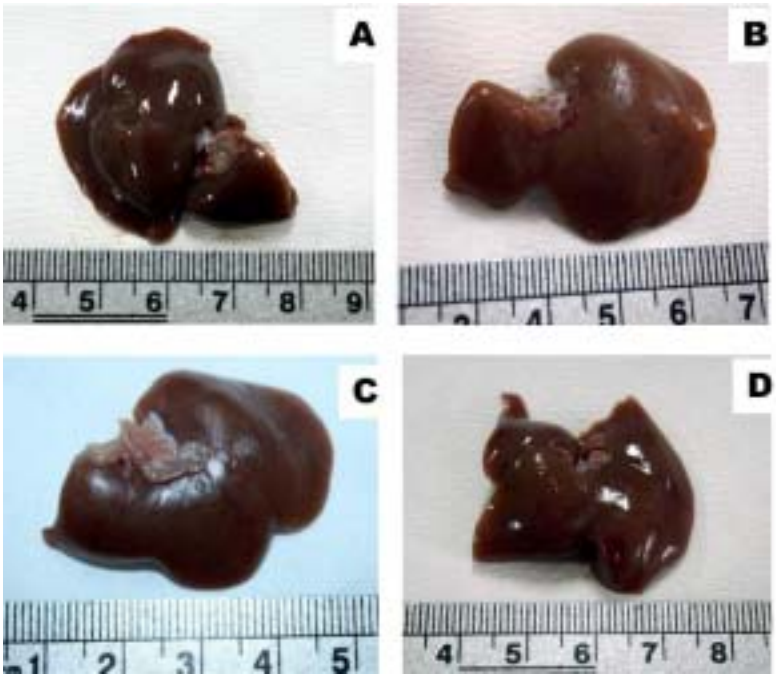

Figure 1. Absence of morphological differences in livers of rats treated with C. *xanthorrhiza, Z. officinale* and *C. longa* combination and doxorubicin
(A) NaCl control group; (B) Doxorubicin group; (C) Doxorubicin+250 mg/kgBW C. *xanthorrhiza, Z. officinale*, and *C. longa* combination; (D) Doxorubicin+500 mg/kgBW *C. xanthorrhiza, Z. officinale*, and *C. longa* combination

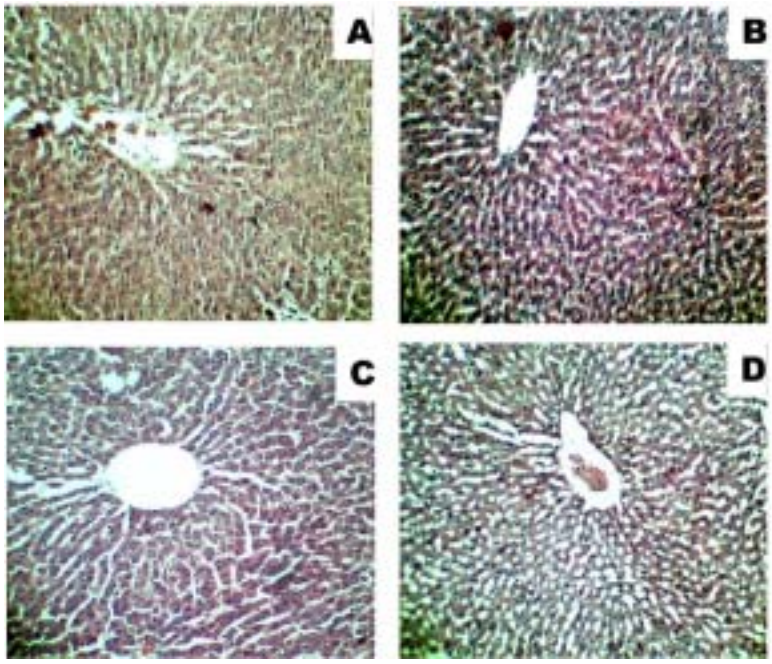

Figure 2. Histological evaluation in liver tissues of control and experimental group. (A) NaCl control group; (B) Doxorubicin group; (C) Doxorubicin + 250 mg/kgBW C. *xanthorrhiza, Z. officinale*, and *C. longa* extract combination; (D) Doxorubicin + 500 mg/kgBW *C. xanthorrhiza, Z. officinale*, and *C. longa* extract combination

Table 1 Mean of on ALT and AST bases on Treatment groups in rats

Groups	ALT (U/l)	AST (U/l)
Control	169.57 ± 7.79	34.43 ± 2.76
DOX	312.14 ± 8.71	73.14 ± 3.58
DOX+Tekuja 250mg	256.14 ± 9.21	60.43 ± 3.95
DOX+Tekuja 500mg	221.86 ± 8.71	53.86 ± 1.86
p	0.000	0.000

Each value represents mean ± S.D. of seven animals

showed that *C. longa* has multiple therapeutic activities by blocking cardiac, hepatic,and renal toxicities induced by doxorubisin.[14] An earlier study using *Z.officinale* only, suggested that *Z. officinale* protected against nephrotoxicity either by enhancing the renal antioxidant status that had been reduced by DOX, or by exerting a direct antioxidant activity.[12]

The present study explored the effect of a combination of *C. xanthorrhiza*, *C. longa* and *Z. officinale* extract (Tekuja) on DOX-induced hepatotoxicity in rats. The Tekuja extract was given during the DOX induction period. Treatment with the combination of *C. xanthorrhiza*, *Z. officinale* and *C. longa* extract was designed to prevent metabolic activation of DOX and suppress liver damage. The liver is the central organ of metabolism and acts as a storage organ. Liver cells metabolize toxic agents, including DOX. The liver is extremely vulnerable to damage by chemical agents, presumably as a result of its central role in the metabolism of foreign substances.[15] In our study, histopathological examination of the livers showed no appreciable differences between groups. These results may be interpreted as indicating that administration of DOX does not result in liver damage, although the serum transaminase was elevated.

DOX in the form of DOX semiquinone has been suggested to play a major role in its hepatotoxic action. Semiquinones are unstable under aerobic conditions, thereby generating superoxide anion radicals by reacting with molecular oxygen.[16] Hepatocytes are the likely targets of attack by reactive oxygen species (ROS) in the failing liver. It is conceivable that free radicals cause damage at their formation. Consequently the mitochondria as the major source of ROS production, could also be the major target susceptible to attack by ROS.[16]

Table 2. Multiple comparison test (Tuckey HSD) of ALT (U/L) and AST (U/L) levels between treatment groups

	Mean Difference	Std. Error	p
ALT levels (U/L)			
Contrd-DOX	-142.57	4.48	0.000
Contrd-DOX+Tekuja 250 mg	-86.57	4.48	0.000
Contrd-DOX+Tekuja 500 mg	-52.28	4.48	0.000
DOX-DOX+Tekuja 250 mg	56.00	4.48	0.000
DOX-DOX+Tekuja 500 mg	90.28	4.48	0.000
DOX+Tekuja 250 mg-DOX+Tekuja 500 mg	34.28	4.48	0.000
AST levels (U/L)			
Contrd-DOX	-38.71	1.73	0.000
Contrd-DOX+Tekuja 250 mg	-26.00	1.73	0.000
Contrd-DOX+Tekuja 500 mg	-19.42	1.73	0.000
DOX-DOX+Tekuja 250 mg	12.71	1.73	0.000
DOX-DOX+Tekuja 500 mg	19.28	1.73	0.000
DOX+Tekuja 250 mg-DOX+Tekuja 500 mg	6.57	1.73	0.006

Serum transaminases have long been considered a sensitive indicator of hepatic injury. Injury to the hepatocytes alters their transport function and membrane permeability, leading to leakage of enzymes from the cells, causing a decrease in the levels of ALT and AST in hepatic cells but an increase of these enzymes in serum.[17] In this study, administration of DOX to rats significantly increased serum ALT and AST levels. AST is a more liver- specific enzyme. On the other hand, an increase in ALT activity is usually proportional to the extent of cardiac damage.

Treatment with the combination of *C. xanthorrhiza*, *Z. officinale* and *C. longa* (250 and 500 mg/kg) resulted in a significant decrease in enzyme activities in DOX-treated animals, thus offering considerable protection against hepatotoxicity. The data presented in this study demonstrate that DOX increased serum indices of liver function including ALT and AST. These elevations of ALT and AST are attributable to hepatocellular damage and decreased liver functions.[15,18] These elevated levels of serum indices for hepatocellular damage have been previously reported in a DOX-induced hepatoxicity model.[18,19]

The effectiveness of *C. xanthorrhiza* in lowering the serum enzyme levels of AST, ALT, and glutamate transferases demonstrates the hepatoprotective effect of this plant against cisplastin induced hepatotoxicity.[20,21] The plant also acts to prevent fatty degeneration of the liver, which can cause irreversible functional breakdown, inevitably leading to death.[22]

Yemitan et al.[23] tested the effect of an ethanol extract *Z. officinale* rhizomes against carbon tetrachloride (CCl_4) and acetaminophen-induced liver toxicities in rats. Carbon tetrachloride and acetaminophen induced many histopathological changes and increased the activities of ALT, AST, ALP, LDH and SDH in serum. The protective effect of *Z. officinale* extract against carbon tetrachloride- and acetaminophen-induced damage was confirmed by histopathological examination of the liver.

C. xanthorriza, *C. longa* and *Z. officinale* all contain the active compounds curcumin, xanthorrizhol and oleoresin.[3-5] Curcumin has shown antioxidant, anti-neoplastic and anti-inflammatory activity.[5,24,25] Many of the activities associated with curcumin relate to its ability to suppress acute and chronic inflammation.[26] An in vivo study showed that rats fed curcumin for 7 days prior to being treated with cyclophosphamide to induce lung injury, exhibited an increase in antioxidant defense mechanisms. Thus, curcumin exhibits substantial antioxidant properties in a wide variety of experimental settings.[25]

The antioxidant properties of [6]-gingerol, which is a very effective agent for anticipation of ultraviolet B (UVB)-induced reactive oxygen species production and COX-2, and a promising therapeutic agent against UVB-induced skin disorders, have been studied both in vitro and in vivo. The compound also has a protective role against the toxicity and lethality induced by agents such as carbon tetrachloride and cisplatin.[27,28]

The present study provides the information that Tekuja extract protected against the hepatotoxicity of DOX. Tekuja was shown to protect liver tissue, as indicated by the histopatological profile, and ALT and AST levels. These results suggest the possible use of Tekuja as a novel agent against DOX-induced organ toxicities and a potential candidate to be further evaluated. However, the parameters in our present study could not explore the activity of DOX in DOX-induced decline in hepatic antioxidant status or its direct antioxidant activity. Therefore further studies should be conducted to explore hepatic antioxidant status and direct antioxidant activity.

CONCLUSION

The results of the present study indicate that the combination of *C. xanthorriza, C. longa,* and *Z. officinale* has a protective effect against liver damage induced by DOX.

ACKNOWLEDGEMENTS

The authors wish to express their sincere gratitude to the Directorate of Higher Education, Ministry of Education and Culture, and to the Jenderal Soedirman University for financial support by Institutional Research Grant 2011-2012.

REFERENCES

1. 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;46:409-20.
2. Ghosh AK, Banerjee S, Mullick HI, Banerjee J. Zingiber officinale: a natural gold. Int J Pharma Bio Sci 2011;2:283-94
3. Deasywaty, Mangunwardoyo W, Usia T. Antimicrobial and identification of active compound in *Curcuma xanthorrhiza* Roxb. IJBAS-IJENS 2012;12:69-78
4. Ravindran PN, Babu KN. Ginger the genus *Zingiber.* New York: CRC Press; 2005.
5. Mohanty IR, Arya DS, Gupta SK. Dietary *Curcuma longa* protects myocardium against isoproterenol-induced hemodynamic, biochemical and histopathological alternations in rats. Int J Appl Res Nat Prod 2008;1:19-28.
6. Balmer CM, Valley AM, Iannucci A. Cancer treatment and chemotherapy in pharmacotherapy: a pathophysiologic approach. New York: The McGraw-Hill Companies; 2005.
7. Yagmurca M, Bas O, Mollaoglu H, Sahin O, Nacar A, Karaman O. Protective effects of erdosteine on doxorubicin-induced hepatotoxicity in rats. Arch Med Res 2007;38:380-5.
8. Pedrycz A, Wieczorski M, Czerny K. Increased apoptosis in the rat liver after a single dose of adriamycin administration. Annales UMCS Sect D 2004;59:313-8.
9. Pedrycz A, Boratynski Z, Wieczorski M, Visconti J. Ultrastuctural and immunohistochemical evaluation of apoptosis in fetal rat liver after adriamycin administration. Bull Vet Inst Pulawy 2005;49:475-9
10. Pedrycz A, Wieczorski M, Czerny K. The influence of a single dose of adriamycin on the pregnant rat female liver histological and histochemical evaluation. Ann Univ Mariae Curie Sklodowska 2004;59:319-23.
11. Beinfield H, Kornglod E. Chinese medicine and cancer care. Altern Ther 2005;9:38-52.
12. Ajith TA, Aswathy MS, Hema U. Protective effect of *Zingiber officinale* Roscoe against anticancer drug doxorubicin-induced acute nephrotoxicity. Food Chem Toxicol 2008;46:3178–81.
13. Kolarovic J, Popovic M, Mikov M, Mitic RGL. Protective effects of celery juice in treatments with doxorubicin. Molecules 2009;14:1627-38.
14. Mohamad RH, El-Bastawesy AM, Zekry ZK, Al-Mehdar HA, Al-Said MG, Aly SS, et al. The role of *Curcuma longa* against doxorubicin (Adriamycin)-induced toxicity in rats. J Med Food 2009;12:394-402.
15. Ibrahim SS, Barakat MA. and Helmy HTS. Modulating effect of carvedilol on doxorubicin-induced cardiomyopathy and hepatic damage. J Am Sci 2010;6:20-32.
16. Kalender Y, Yel M, Kalender S. Doxorubicin hepatotoxicity and hepatic free radical metabolism in rats: the effects of vitamin E and catechin. Toxicology 2005;209:39-45.
17. Yadav NP, Dixit VK. Hepatoprotective activity of leaves of *Kalanchoe pinnata* Pers. J Ethnopharmacol 2003;86:197-202.
18. Injac R, Perse M, Boskovic M, Djordjevic-Milic V, Djordjevic A, Hvala A. Cardioprotective effects of fullerenol C60(OH)24 on a single dose doxorubicin induced cardiotoxicity in rats with malignant neoplasm. Technol Cancer Res Treat 2008;7:15–26.
19. Alshabanah OA, Hafez MM, Al-Harbi MM, Hassan ZK, Al Rejaie SS, Asiri YA, et al. Doxorubicin toxicity can be ameliorated during antioxidant L-carnitine supplementation. Oxid Med Cell Longev 2010;3:428-33.
20. Sakr SA, Mahran HA, Lamfon HA. Protective effect of ginger *(Zingiber officinale)* on adriamycin-induced hepatotoxicity in albino rats. J Med Plants Res 2010;5:133-40.
21. Seong HK, Kyoung OH, Won YC, Jae KH, Kwang KP. Abrogation of cisplatin-induced hepatotoxicity in mice by xanthorrhizol is related to its effect on the regulation of gene transcription. Toxicol Appl Pharmacol 2004:196: 346–55.
22. Devaraj S, Ismail S, Ramanathan S, Marimuthu S, Fei YM. Evaluation of the hepatoprotective activity of standardized ethanolic extract of *Curcuma xanthorrhiza* Roxb. J Med Plants Res 2010;4:2512-17.
23. Yemitan OK, Izegbu MC. Protective effects of *Zingiber offcinale (Zingiberaceae)* against carbon tetrachloride and acetaminopheninduced

hepatotoxucity in rats. Phytother Res 2006;20:997-1002.

24. Kelkel M, Jacob C, Dicato M, Diederich M. Potential of the dietary antioxidants resveratrol and curcumin in prevention and treatment of hematologic malignancies. Molecules 2010;15: 7035-44.
25. Hatcher H, Planalp R, Cho J, Torti MF, Torti SV. Curcumin: from ancient medicine to current clinical trials. Cell Mol Life Sci 2008;65:1631-52.
26. Shishodia S, SethiG, Aggarwal BB. Curcumin: getting back to the roots. Ann N Y Acad Sci 2005; 1056 :206-17.
27. Jagetia GC, Baliga MS, Venkatesh P, Ulloor JN. Influence of ginger rhizome (*Zingiber officinale* Rosc.) on survival, glutathione and lipid peroxidation in mice after whole-body exposure to gamma radiation. Radiat Res 2003;160:584-92.
28. Kim HW, Murakami A, Abe M, Ozawa Y, Morimitsu Y, Williams MV, et al. Suppressive effects of mioga ginger and ginger constituents on reactive oxygen and nitrogen species generation, and the expression of inducible pro-inflammatory genes in macrophages. Antioxid Redox Signal 2005;7:1621-29.