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Intraperitoneal curcumin decreased lung, renal and heart injury in abdominal aorta ischemia/reperfusion model in rat

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ABSTRACT

Background: Previous studies have demonstrated that curcumin (CUR) has protective effects against ischemia reperfusion injury to various organs. We aimed to determine whether CUR has favorable effects on tissues and oxidative stress in abdominal aorta ischemia-reperfusion injury.
Materials and methods: Thirty rats were divided into three groups as sham, control and treatment (CUR) group. Control and CUR groups underwent abdominal aorta ischemia for 60 min followed by a 120 min period of reperfusion. In the CUR group, CUR was given 5 min before reperfusion at a dose of 200 mg/kg via an intraperitoneal route. Total antioxidant capacity (TAC), total oxidative status (TOS), and oxidative stress index (OSI) in blood serum were measured, and lung, renal and heart tissue histopathology were evaluated with light microscopy.
Results: TOS and OSI activity in blood samples were statistically decreased in sham and CUR groups compared to the control group ($p < 0.001$ for TOS and OSI). Renal, lung, heart injury scores of sham and CUR groups were statistically decreased compared to control group ($p < 0.001$ for all comparisons). Histopathological examination revealed less severe lesions in CUR group than in the control group.
Conclusion: CUR administered intraperitoneally was effective in reducing oxidative stress and histopathologic injury in an acute abdominal aorta I/R rat model.
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1. Background

It has been accepted that multiple organ dysfunction is a major cause of morbidity and mortality after abdominal aortic aneurysm surgery [1]. Aortic cross-clamping during open abdominal aortic surgery may cause ischemia–reperfusion (I/R) injury, leading to translocation of bacteria and endotoxiemia, with the systemic release of reactive oxygen species (ROS) and inflammatory cytokines. This may result in end organ injury, including heart, renal, and lung damage [2–4].

Curcumin (CUR), undoubtedly one of the natural bioactive molecules [5,6], is a polyphenolic compound that is mainly present in the dried rhizomes of *Curcuma longa* L. (commonly known as turmeric). It has been reported that CUR has several pharmacological properties, including antioxidant, anti-inflammatory [7], antiviral [8], antimicrobial [9], antifungal [10] and anticancer [11] activities. It has also been reported that CUR attenuated several types of organ injury (lung, renal, hepatic, heart, ovary and intestine) in different I/R models [12–17].

Techniques focusing on diminishing I/R injury via different mechanism might affect morbidity and mortality in abdominal aortic surgery and we think that CUR as a hopeful natural bioactive molecule might play a protective role in several organ injuries while in aortic I/R with its' unique pharmacological properties. The

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aim of this study was to determine the efficacy of CUR in prevention of injury to vital organs (lung, heart and renal) in an acute abdominal aorta ischemia-reperfusion model in rats.

2. Materials and methods

A total of 30 three-month-old Wistar-Albino rats weighing 200–250 g were included in the study and divided into three groups. All animals were maintained under standard conditions and treated in compliance with National Institutes of Health guidelines. They were housed on a 12-h dark/light cycle schedule with lights on at 06.00 h. Rats were deprived of food, though not water, for 12 h before surgery. Experiments were done in the Harran University Experimental Research Center.

2.1. Ischemia reperfusion injury model

The rats were randomly assigned to three experimental groups: sham, control (I/R; non-treated), and CUR groups (CUR-treated I/R). Rats were anesthetized using ketamine hydrochloride 50 mg/kg i.p. ketamine and additional 25 mg/kg i.p. was applied when needed in all experiments. Total study time was equal for all groups. The abdomen was explored through a midline incision after shaving and disinfection. In the sham group only laparotomy was performed. In the control group, I/R injury was induced by clamping the aorta under both renal vascular pedicles for 60 min, followed by 2 h of reperfusion. In the CUR group, I/R injury was also induced by clamping the aorta under both renal vascular pedicles for 60 min and CUR was given 5 min before reperfusion at a dose of 200 mg/kg via the intraperitoneal route [18], and again reperfusion was established for 2 h. At the end of the procedures, the rats were sacrificed after blood sampling and then renal, lung, and heart tissues were obtained from all of the rats.

CUR was dissolved in 1% dimethyl sulfoxide for intraperitoneal injection. CUR was purchased from Sigma Aldrich (Saint Louis, MO, United States).

2.2. Histopathological evaluation

The renal, lung and heart of each animal were obtained for histological evaluation. Samples of these organs were placed in formalin and embedded in wax according to standard protocols. They were subsequently sectioned at 5 μm slice thickness and stained with hematoxylin and eosin. Magnification of ×20 was used (Olympus BX51 TF, USA). Samples were then graded histologically according to the severity of injury using a predetermined scoring system [19]. The predetermined scoring system by Solez et al. included tubular necrosis, interstitial edema, loss of brush border, and cast formation [19](19), in which the score was 0 for absent, 1 for mild to moderate, and 2 for marked renal involvement. The histological parameters for lung evaluation were alveolar congestion, intra-alveolar hemorrhage and interstitial-perivascular infiltration of neutrophils, in which the score was 0 for absent, 1 for mild focal, 2 for moderate focal and 3 for severe marked lung involvement. Interstitial edema, inflammatory cell infiltration and coagulation necrosis were assessed for heart examination, in which the score was 0 for absent, 1 for mild focal, 2 for moderate focal and 3 for severe marked heart involvement. Histological analysis was performed by a blinded expert.

2.3. Biochemical analyses

2.3.1. Measurement of the total antioxidant capacity

TAC of supernatant fractions was determined using a novel automated measurement method developed by Erel [20]. Hydroxyl radicals, the most potent biological radicals, are produced with this method. In the assay, a ferrous ion solution present in Reagent 1 is mixed with hydrogen peroxide, which is present in Reagent 2. The subsequently produced radicals, such as brown-colored dianisidinyl radical cations produced by the hydroxyl radicals, are also potent radicals. Using this method, the antioxidative effect of the sample was measured against the potent-free radical reactions initiated by the hydroxyl radicals produced. The assay has excellent precision values lower than 3%. The results were expressed as nmol Trolox Equiv./mg protein.

2.3.2. Measurement of total oxidant status

TOS of supernatant fractions was determined using a novel automated measurement method developed by Erel [21]. Oxidants present in the sample oxidize the ferrous ion–o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundant in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide, and the results were expressed in terms of nmol H_2O_2 Equiv/mg protein.

2.3.3. Oxidative stress index

The percent ratio of TOS level to TAC level was accepted as OSI. OSI values were calculated according to the following formula [21]: OSI (arbitrary unit) = TOS (nmol H_2O_2 Equiv/mg protein.)/TAC (nmolTroloxEquiv/mg protein).

2.3.4. Statistical analysis

Statistical analyses were performed using SPSS 11.5 (SPSS for Windows 11.5, Chicago, IL). Continuous data are expressed as mean ± SD whereas categorical variables are presented as number (count) and percentage. Distribution of continuous variables was assessed with one-sample Kolmogorov–Smirnov test and indicated that all variables were abnormally distributed. Therefore, nonparametric independent group comparisons were made: for multiple comparisons, the Kruskal–Wallis test was used, and for comparisons between groups, the Mann–Whitney test was used if any statistical significance was found. A two-sided p value of <0.05 was considered statistically significant.

3. Results

All animals survived the experimental protocol. Sham, Control and CUR group TAC, TOS and OSI concentrations are summarized in Table 1. TAC activity in blood samples was significantly higher in the sham group than in the CUR and control groups ($p < 0.001$) but there were no statistically significant differences between the CUR group and control group for TAC activity ($p > 0.05$). TOS and OSI activity in blood samples were statistically decreased in sham and CUR groups compared to the control group ($p < 0.001$ for TOS and OSI) (Fig. 1).

Histopathologic injury scores of renal, lung and heart tissues are also summarized in Table 2. Renal, lung, heart injury scores of sham and CUR groups were statistically decreased compared to control group ($p < 0.001$ for all comparisons). Upon histopathological evaluation, renal, lung and heart tissues were found to be normal with no pathological changes in the sham group. Histopathological examination of the tissues in the control group revealed neutrophil and leukocyte infiltration with alveolar congestion in the lung. Histopathological examination of the tissues in the control group revealed severe lesions, such as tubular damage characterized by cast formation, the loss of brush border and interstitial edema in

Table 1
Oxidative and antioxidative parameters in Sham, Control and Curcumin rats.

	Sham ($n = 10$)	Control ($n = 10$)	Curcumin ($n = 10$)	P Kruskal–Wallis
TAC (nmol Trolox Eqv./mg protein)	$1.29 \pm 0.16^{*}$	0.45 ± 0.13	0.48 ± 0.14	$p < 0.001$
TOS (nmol H_2O_2 Eqv./mg protein)	26.3 ± 2.4	$43.1 \pm 7.9^{+}$	29.8 ± 3.2	$p < 0.001$
OSI (arbitrary units)	2 ± 0.44	$8.35 \pm 1.23^{+}$	5.46 ± 1.3	$p < 0.001$

$p < 0.05$ was considered as statistically significant.
*: $p < 0.001$ compared to control and Curcumin groups.
+: $p < 0.001$ compared to sham and Curcumin groups.

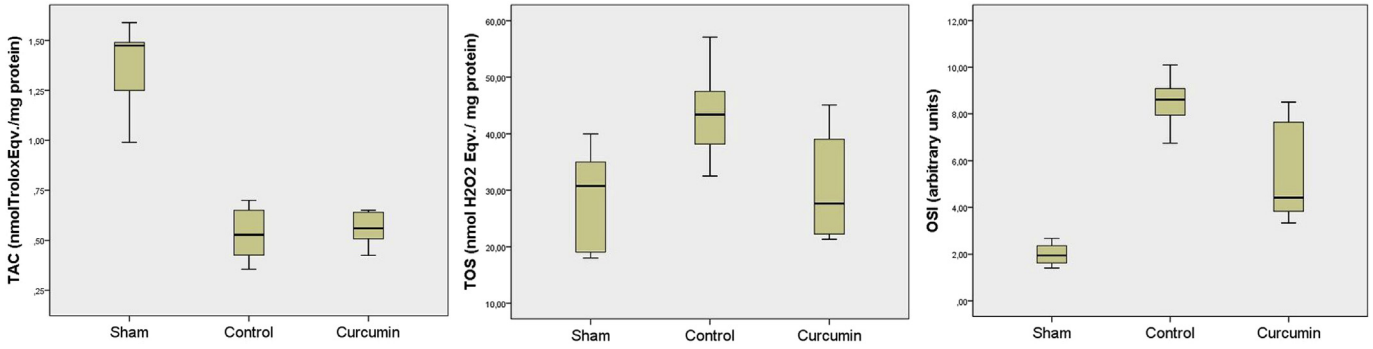

Fig. 1. Serum TAC, TOS and OSI levels of Sham, Control and CUR Groups.

the renal. Histopathological examination of the tissues in the control group revealed interstitial edema in the heart. In rats receiving CUR intraperitoneally, these lesions were less severe than in the control group in lung, renal and heart tissues. Lung and renal tissues of sham, control and CUR groups are shown in Figs. 2–4.

4. Discussion

In our experimental study, we hypothesized that abdominal aorta ischemia for 60 min followed by reperfusion for 2 h would cause renal and lung pathology which would –possibly- be prevented with CUR and we have shown that (i) abdominal aorta ischemia for 60 min followed by reperfusion for 2 h caused significant pathology in lung, renal and heart, (ii) TOS and OSI levels were statistically decreased in sham and CUR groups compared to the control group (iii) histopathological injury scores (in lung, renal and heart) were statistically decreased in the sham and CUR groups.

Abdominal aortic surgery may cause ischemia reperfusion due to clamping of the aorta and might cause mortality and morbidity. One of the main reasons could be the systemic inflammatory response and multiple organ dysfunctions occurring during the reperfusion phase. Reperfusion of the acutely ischemic aorta against long odds may lead to systemic complications, morbidity and mortality [17]. In previous studies, reperfusion of the acutely ischemic aorta was shown to increase reactive oxygen species (ROS) and proinflammatory molecules, and the subsequent inflammatory response is thought to be one of the most essential underlying mechanisms of damage [22], especially in lungs and vital organs such as renal and heart [23,24].

Table 2
Histopathological evaluation in Sham, Control and Curcumin rats.

	Sham ($n = 10$)	Control ($n = 10$)	Curcumin ($n = 10$)	P Kruskal–Wallis
Renal pathology score	1.6 ± 1.15	$3.9 \pm 0.65^{+}$	2 ± 1.56	$p < 0.001$
Lung pathology score	1.8 ± 1.15	$4.1 \pm 0.51^{+}$	2.7 ± 1.25	$p < 0.001$
Heart pathology score	0.4 ± 0.52	$1.1 \pm 0.45^{+}$	0.5 ± 0.44	$p < 0.001$

$p < 0.05$ was considered as statistically significant.
+: $p < 0.001$ compared to sham and Curcumin groups.

The polyphenol, curcumin, is the active component of turmeric, a common Indian spice, derived from the rhizome of the *C. longa* plant [25]. Clinical studies with curcumin (500 mg) have shown a decrease of lipid peroxides and total serum cholesterol, and an increase in serum HDL levels. It has also been reported to reduce LDL and to increase HDL levels in acute coronary syndrome [26,27]. Several studies focused on the antioxidant effects of curcumin against lipid peroxidation showed that curcumin considerably inhibited formation of thiobarbituric acid reactive substances in the liver tissues of diabetic rats [28]. Curcumin was also found to attenuate lipid peroxidation in cisplatin-treated rats [29], and in another study it was reported to be an effective inducer of detoxifying enzymes in toxicity induced by chemical carcinogens [30]. In our study, significant oxidative stress in the control group compared to sham and CUR groups also emphasized that the antioxidant properties of CUR might be the probable protective mechanism in lung, renal and heart tissues in an acute abdominal aorta ischemia-reperfusion model in rats.

Several studies demonstrated the protective effects of curcumin in the lung by different mechanisms. The protective effect in restrictive lung disease is reported to be associated with decreased hydroxyl radicals, lipid peroxidation, and inflammation in the lungs [13]. In intestinal I/R injury models, CUR was shown to reduce both intestinal and lung injury in rats [16,31,32]. In contrast, some studies did not report positive results [17].

The renal protective effects of CUR have also been evaluated in several studies focusing on preservation of antioxidant enzymes and prevention of oxidative stress, as well as inhibition of mitochondrial dysfunction and attenuation of inflammatory response [33–35]. A limited number of studies showed that CUR pretreatment enhanced cardiac contractility and prevented myocardial injury with inhibition of lipid peroxidation and augmentation of endogenous antioxidants, and was found to improve myocardial metabolism [12,36–38]. Similar to the mentioned studies, the

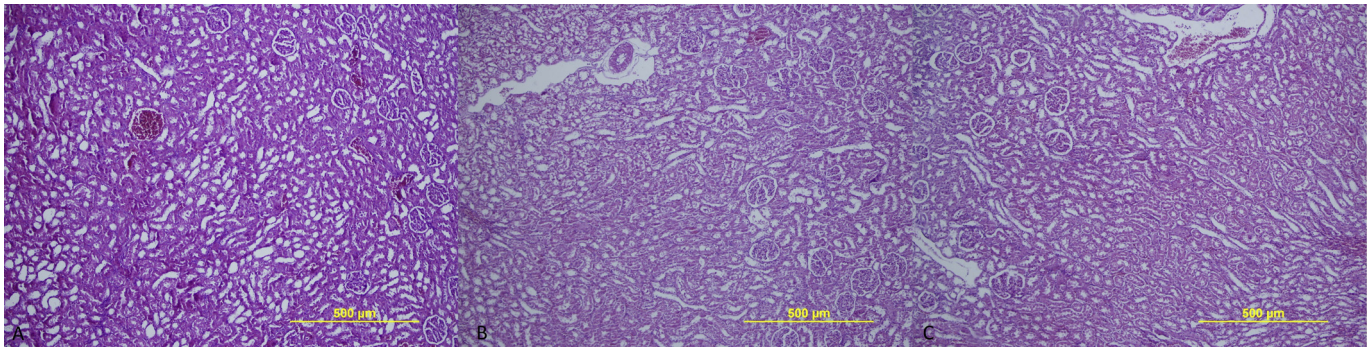

Fig. 2. A-Renal tissue samples of the sham group and there were no pathological changes. B-Renal tissues samples of control group and tubular damage characterized by cast formation, the loss of brush border and interstitial edema were observed. C-Renal tissue sample of CUR group and there were less severe lesions than in the control group.

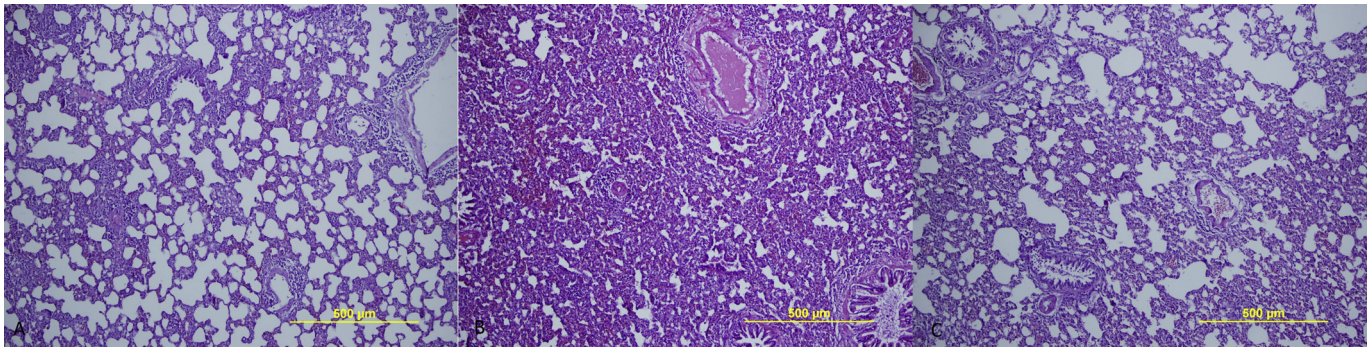

Fig. 3. A-Lung tissue samples of the sham group and there were no pathological changes. B-Lung tissues samples of control group and neutrophil and leukocyte infiltration with alveolar congestion were observed. C-Lung tissue sample of CUR group and there were less severe lesions than in the control group.

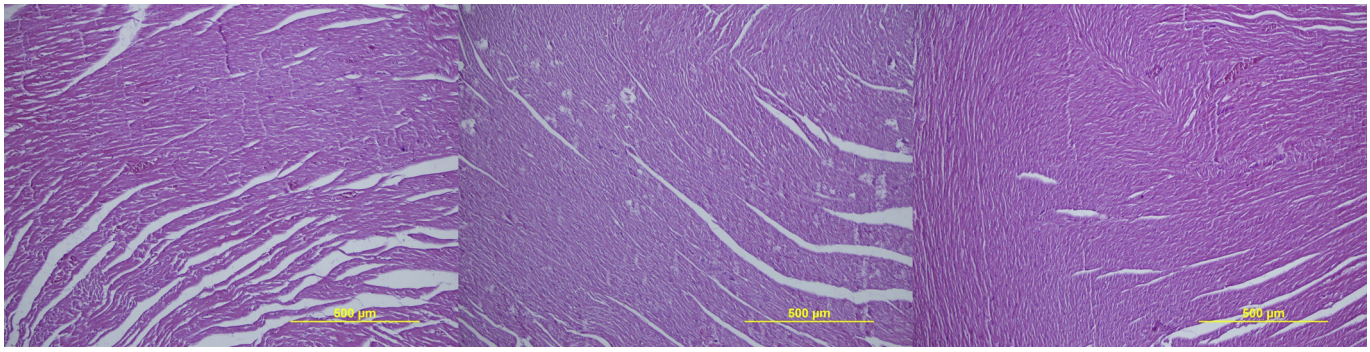

Fig. 4. A-Heart tissue samples of the sham group and there were no pathological changes. B-Heart tissues samples of control group and interstitial edema were observed. C-Heart tissue sample of CUR group and there were less severe lesions than in the control group.

current data showed the protective effects of CUR in lung, renal and heart and antioxidant properties of CUR might be the main protective mechanism.

Several limitations of this study should be considered. One of the potential limitations is the absence of oral administration of CUR versus an intraperitoneal route. Another limitation is the absence of biochemical analysis of different lung, renal and heart biochemical parameters. Further studies focusing on IR injury of other end organs such as intestine, brain and medulla spinalis injury are needed.

In conclusion, CUR administered intraperitoneally was effective in reducing oxidative stress and histopathological injury of lung, renal and heart in an acute abdominal aorta I/R rat model. Oxidative stress indices and tissue injuries might be modified with CUR treatment in different clinical settings though further large scale studies are needed to verify/exclude the possible favorable effects of CUR in clinical settings.

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Ethical approval

The study protocol was approved (2013-06) by the Committee of Experimental Animals of Dicle University.

Author contribution

MSA, AC and AK participated in the design of this study, and AY and FY performed the statistical analysis. S.K. evaluated the pathology of specimen and E.S. evaluated biochemistry parameters SG carried out the study, together with AH and MSA and AC collected important background information, and MSA and AC drafted the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

[1] R.D. Sayers, M.M. Thompson, A. Nasim, P. Healey, N. Taub, P.R. Bell, Surgical management of 671 abdominal aortic aneurysms: a 13 year review from a single centre, Eur. J. Vasc. Endovasc. Surg. 13 (3) (1997) 322–327.

[2] M.J. Bown, M.L. Nicholson, P.R. Bell, R.D. Sayers, Cytokines and inflammatory pathways in the pathogenesis of multiple organ failure following abdominal aortic aneurysm repair, Eur. J. Vasc. Endovasc. Surg. 22 (6) (2001) 485–495.

[3] L. Willoughby, P. Dark, G. Warhurst, Investigation of systemic and mesenteric inflammatory signaling and gut-derived endothelial toxicity in patients undergoing high-risk abdominal aortic surgery, Shock 36 (2) (2011) 121–127.

[4] H.S. Khaira, S.R. Maxwell, H. Thomason, G.H. Thorpe, M.A. Green, et al., Antioxidant depletion during aortic aneurysm repair, Br. J. Surg. 83 (3) (1996) 401–403.

[5] A. Sahebkar, Molecular mechanisms for curcumin benefits against ischemic injury, Fertil. Steril. 94 (5) (2010) e75–e76.

[6] A. Sahebkar, Baicalin as a potentially promising drug for the management of sulfur mustard induced cutaneous complications: a review of molecular mechanisms, Cutan. Ocul. Toxicol. 31 (2012) 226–234.

[7] G. Yılmaz Savcun, E. Ozkan, E. Dulundu, U. Topaloğlu, A.O. Sehirli, O.E. Tok, F. Ercan, G. Sener, Antioxidant and anti-inflammatory effects of curcumin against hepatorenal oxidative injury in an experimental sepsis model in rats, Ulus. Travma Acil Cerrahi Derg. 19 (6) (2013) 507–515.

[8] Anggakusuma, C.C. Colpitts, L.M. Schang, H. Rachmawati, A. Frentzen, S. Pfaender, P. Behrendt, R.J. Brown, D. Bankwitz, J. Steinmann, M. Ott, P. Meuleman, C.M. Rice, A. Ploss, T. Pietschmann, E. Steinmann, Turmeric curcumin inhibits entry of all hepatitis C virus genotypes into human liver cells, Gut (2013 Jul 31), http://dx.doi.org/10.1136/gutjnl-2012-304299.

[9] H. Magesh, A. Kumar, A. Alam, Priyam, U. Sekar, V.N. Sumantran, R. Vaidyanathan, Identification of natural compounds which inhibit biofilm formation in clinical isolates of *Klebsiella pneumoniae*, Indian J. Exp. Biol. 51 (9) (2013) 764–772.

[10] A. Kumar, S. Dhamgaye, I.K. Maurya, A. Singh, M. Sharma, R. Prasad, Curcumin targets cell wall integrity via calcineurin-mediated signaling in *Candida albicans*, Antimicrob. Ag. Chemother. 58 (1) (2014) 167–175.

[11] M. Mollazade, K. Nejati-Koshki, A. Akbarzadeh, N. Zarghami, M. Nasiri, R. Jahanban-Esfahlan, et al., PAMAM dendrimers augment inhibitory effects of curcumin on cancer cell proliferation: possible inhibition of telomerase, Asian Pac. J. Cancer Prev. 14 (11) (2013) 6925–6928.

[12] T.H. Chen, Y.C. Yang, J.C. Wang, J.J. Wang, Curcumin treatment protects against renal ischemia and reperfusion injury-induced cardiac dysfunction and myocardial injury, Transplant. Proc. 45 (10) (2013) 3546–3549.

[13] J.H. Yeh, Y.C. Yang, J.C. Wang, D. Wang, J.J. Wang, Curcumin attenuates renal ischemia and reperfusion injury-induced restrictive respiratory insufficiency, Transplant. Proc. 45 (10) (2013) 3542–3545.

[14] H.F. Zaki, R.M. Abdelsalam, Vinpocetine protects liver against ischemia-reperfusion injury, Can. J. Physiol. Pharmacol. 91 (12) (2013) 1064–1070.

[15] M.E. Sak, H.E. Soydinc, S. Sak, M.S. Evsen, U. Alabalik, F. Akdemir, T. Gul, The protective effect of curcumin on ischemia-reperfusion injury in rat ovary, Int. J. Surg. 11 (9) (2013) 967–970.

[16] N. Okudan, M. Belviranlı, H. Gökbel, M. Oz, A. Kumak, Protective effects of curcumin supplementation on intestinal ischemia reperfusion injury, Phytomedicine 20 (10) (2012) 844–848.

[17] A. Oguz, M. Kapan, A. Onder, E. Kilic, M. Gumus, et al., The effects of curcumin on the liver and remote organs after hepatic ischemia reperfusion injury formed with Pringle manoeuvre in rats, Eur. Rev. Med. Pharmacol. Sci. 17 (4) (2013) 457–466.

[18] W.C. Zhao, B. Zhang, M.J. Liao, W.X. Zhang, W.Y. He, et al., Curcumin ameliorated diabetic neuropathy partially by inhibition of NADPH oxidase mediating oxidative stress in the spinal cord, Neurosci. Lett. 560 (2014 7) 81–85, http://dx.doi.org/10.1016/j.neulet.2013.12.019.

[19] K. Solez, L. Morel-Maroger, J.D. Sraer, The morphology of "acute tubular necrosis" in man: analysis of 57 renal biopsies and a comparison with the glycerol model, Medicine 58 (2) (1979) 362–376.

[20] O. Erel, A novel automated method to measure total antioxidant response against potent free radical reactions, Clin. Biochem. 37 (2) (2004) 112–119.

[21] O. Erel, A new automated colorimetric method for measuring total oxidant status, Clin. Biochem. 38 (12) (2005) 1103–1111.

[22] M.M. Yassin, D.W. Harkin, A.A. Barros D'Sa, M.I. Halliday, B.J. Rowlands, Lower limb ischemia-reperfusion injury triggers a systemic inflammatory response and multiple organ dysfunction, World J. Surg. 26 (1) (2002) 115–121.

[23] D.W. Harkın, A.A. Barros D'sa, K. Mccallıon, M. Hoper, M.I. Hallıday, et al., Circulating neutrophil priming and systemic inflammation in limb ischaemia-reperfusion injury, Int. Angiol. 20 (1) (2001) 78–89.

[24] A.B. Groeneveld, P.G. Raıjmakers, J.A. Rauwerda, C.E. Hack, The inflammatory response to vascular surgery-associated ischaemia and reperfusion in man: effect on postoperative pulmonary function, Eur. J. Vasc. Endovasc. Surg. 14 (5) (1997) 351–359.

[25] S. Khurana, K. Venkataraman, A. Hollingsworth, M. Piche, T.C. Tai, Polyphenols: benefits to the cardiovascular system in health and in aging, Nutrients 5 (10) (2013) 3779–3827.

[26] G. Kapakos, V. Youreva, A.K. Srivastava, Cardiovascular protection by curcumin: molecular aspects, Indian J. Biochem. Biophys. 49 (5) (2012) 306–315.

[27] K.B. Soni, R. Kuttan, Effect of oral curcumin administration on serum peroxides and cholesterol levels in human volunteers, Indian J. Physiol. Pharmacol. 36 (4) (1992) 273–275.

[28] P. Suryanarayana, A. Satyanarayana, N. Balakrıshna, P.U. Kumar, G.B. Reddy, Effect of turmeric and curcumin on oxidative stress and antioxidant enzymes in streptozotocin-induced diabetic rat, Med. Sci. Monit. 13 (12) (2007) 286–292.

[29] G. Kaur, N. Tirkey, S. Bharrhan, V. Chanana, P. Rishi, et al., Inhibition of oxidative stress and cytokine activity by curcumin in amelioration of endotoxin-induced experimental hepatoxicity in rodents, Clin. Exp. Immunol. 145 (2) (2006) 313–321.

[30] C. Kalpana, A.R. Sudheer, K.N. Rajasekharan, V.P. Menon, Comparative effects of curcumin and its synthetic analogue on tissue lipid peroxidation and antioxidant status during nicotine-induced toxicity, Singap. Med. J. 48 (2) (2007) 124–130.

[31] A. Onder, M. Kapan, M. Gümüş, H. Yüksel, A. Böyük, et al., The protective effects of curcumin on intestine and remote organs against mesenteric ischemia/reperfusion injury, Turk. J. Gastroenterol. 23 (2) (2012) 141–147.

[32] A. Guzel, M. Kanter, A. Guzel, A.F. Yucel, M. Erboga, Protective effect of curcumin on acute lung injury induced by intestinal ischaemia/reperfusion, Toxicol. Ind. Health 29 (7) (2013) 633–642.

[33] J. Trujillo, Y.I. Chirino, E. Molina-Jijón, A.C. Andérica-Romero, E. Tapia, et al., Renoprotective effect of the antioxidant curcumin: recent findings, Redox. Biol. 1 (1) (2013 17) 448–456.

[34] F.T. Hammad, S. Al-Salam, L. Lubbad, Curcumin provides incomplete protection of the kidney in ischemia reperfusion injury, Physiol. Res. 61 (5) (2012) 503–511.

[35] O. Bayrak, E. Uz, R. Bayrak, F. Turgut, A.F. Atmaca, et al., Curcumin protects against ischemia/reperfusion injury in rat kidneys, World J. Urol. 26 (3) (2008) 285–291.

[36] Z. Brosková, K. Drábiková, R. Sotníková, S. Fialová, V. Knezl, Effect of plant polyphenols on ischemia-reperfusion injury of the isolated rat heart and vessels, Phytother. Res. 27 (7) (2013) 1018–1022.

[37] A. González-Salazar, E. Molina-Jijón, F. Correa, G. Zarco-Márquez, M. Calderón-Oliver, E. Tapia, et al., Curcumin protects from cardiac reperfusion damage by attenuation of oxidant stress and mitochondrial dysfunction, Cardiovasc. Toxicol. 11 (4) (2011) 357–364.

[38] H. Cheng, W. Liu, X. Ai, Protective effect of curcumin on myocardial ischemia reperfusion injury in rats, Zhong. Yao Cai 28 (10) (2005) 920–922.