# Effects of fluoroquinolone antibiotics on hepatic superoxide dismutase and glutathione peroxidase activities in healthy and experimentally induced peritonitis mice*

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**SUMMARY**

In this study, effects of fluoroquinolone antibiotics were investigated on hepatic superoxide dismutase and glutathione peroxidase activities in healthy and experimentally induced peritonitis mice. One hundred thirty two mice randomly divided into six groups. Group 1 served as control, group 2 was injected enrofloxacin, group 3 was injected danofloxacin, group 4 was injected *E. coli*, and group 5 and group 6 were injected enrofloxacin and danofloxacin, respectively, after the injection *E. coli*. Hepatic superoxide dismutase and glutathione peroxidase activities were measured by spectrophotometer.

As results, enrofloxacin caused a decrease glutathione peroxidase activity at 24, 48 and 72 hours, and danofloxacin caused an increase superoxide dismutase activity at 24 and 48 hours after the injection. Danofloxacin and *E. coli* caused a decrease glutathione peroxidase activity during all experimental period after the injection.

**KEY-WORDS : enrofloxacin - danofloxacin - *E. coli* - superoxide dismutase - glutathione peroxidase.**

**RÉSUMÉ**

**Effet des fluoroquinolones antibactériennes sur les activités superoxyde dismutase et glutathion peroxydase hépatique chez la souris témoin ou atteinte de péritonite expérimentale. Par E. YAZAR et B. TRAS.**

Les effets des fluoroquinolones ont été étudiés sur les activités hépatiques : superoxide dismutase, glutathion péroxydase, chez des souris saines et chez des souris porteuses de péritonite expérimentale.

Cent trente deux souris ont été réparties, de façon aléatoire, en six groupes.

Le groupe 1 est le groupe témoin.

Les autres groupes reçoivent différentes injections :

— groupe 2 : enrofloxacine
— groupe 3 : danofloxacine
— groupe 4 : *E. coli*
— groupe 5 : *E. coli* + enrofloxacine
— groupe 6 : *E. coli* + danofloxacine.

Les enzymes hépatiques ont été dosées par spectrophotométrie.

L'enrofloxacine entraîne une diminution de la glutathion péroxydase à 24, 48 et 72 heures.

La danofloxacine provoque une augmentation de la superoxyde dismutase à 24 et 48 heures après l'injection.

L'injection de danofloxacine et *E. coli* entraîne une diminution de la glutathion péroxydase pendant toute la durée de l'expérimentation.

**MOTS-CLÉS : enrofloxacine - danofloxacine - *E. coli* - superoxyde dismutase - glutathion peroxydase.**

## 1. Introduction

The fluoroquinolone antibiotics, metabolized by liver, are structurally related to nalidixic acid and posses potent antimicrobial activity against a wide range of bacteria (gram (-) and (+), and mycoplasma) [16, 29]. Enrofloxacin (ENR) and danofloxacin (DAN) have developed exclusively for veterinary use [4].

It is stated that fluoroquinolones produce reactive oxygen species (ROS) (singlet oxygen ; $^1O$, superoxide radical ; $O_2^-$, hydroxyl radical ; $^-OH$ and hydrogen peroxide ; $H_2O_2$) in phagocytic cells [6, 13, 19, 21], also, side effects of these drugs such as phototoxicity [3, 30, 31] and cartilage damage [35] may related to producing of ROS.

Acute peritonitis, either bacterial or non-bacterial, is a common source of sepsis the main cause of multiple organ failure [18, 42]. The pathogenesis of septic shock has focused on phagocytic cells (neutrophils and Kupffer cell) mediators such as ROS [5, 18, 27]. In sepsis and endotoxic shock, ROS cause hepatocelluler damage being initiated by induced activation of neutrophils and Kupffer cells. These metabolites may also become toxic to tissues by initiating lipid peroxidation. Cells are protected from ROS damage by a chemical and superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase enzymes called antioxidant enzymes [27, 28]. SOD catalyzes the dismutation of two superoxide radicals to $O_2$ and $H_2O_2$ [33]. GPX detoxifies $H_2O_2$ to $H_2O$ and $O_2$, and converts lipid hydroperoxides to nontoxic alcohols [9, 40]. The liver has been selected because it is one of the tissues showing high rate of ROS, which has an effect on hepatic SOD and GPX activities in peritonitis, and liver metabo-

* This study was summarised from PhD thesis (SUAF 98/094).

lizes these antibiotics, and ENR and DAN achieve the high concentrations in liver more than plasma concentrations.

Although it is reported that fluoroquinolone antibiotics produce ROS, however, there are no found any data about directly effect of ENR and DAN on hepatic SOD and GPX activities. The aim of this study is to investigate the effects of fluoroquinolone antibiotics on hepatic SOD and GPX activities in healthy and experimentally induced peritonitis mice.

# 2. Materials and methods

One hundred thirty two Balb/C (approximately 3 months, different sex, 23-32 gram) mice were used as materials (Selcuk University, Experimental Medicine, Research and Application Center, Konya). Mice were fed on the standard pellet diet and tap water *ad libitum* all experimental period. The animals were randomly divided into six groups. Group 1 consisted of six mice. Groups 2, 3 and 4 consisted of thirty mice. Groups 5 and 6 consisted of eighteen mice. Thus, each sampling time consisted of six mouse. Group 1 was served as control. Group 2 was injected ENR (Baytril 10 % inj. Bayer, Istanbul) at recommended doses (10 mg/kg body wt, SC, twice daily) [1]. Group 3 was injected DAN (Advocin inj, Pfizer, Istanbul) at experimental doses (10 mg/kg body wt, SC, twice daily). Group 4 was injected *E. coli* K99 ($1x10^9$ cfu/mice, intraperitoneally), which was obtained from department of microbiology, Faculty of Veterinary Medicine, University of Selcuk. Since developing peritonitis, suitable *E. coli* K99 number was determined as $1x10^9$ cfu/mice. Group 5 was injected ENR at recommended doses after the injection *E. coli* K99 ($1x10^9$ cfu/mice, intraperitoneally). Group 6 was injected DAN at experimental doses after the injection *E. coli* K99 ($1x10^9$ cfu/mice, intraperitoneally). In groups 5 and 6, first ENR and DAN administration was began at 24 hours after the injection *E. coli* K99 because of developing the peritonitis, and these groups were monitored only at 48, 72 and 96 hours.

Each sampling time, six mice were killed at 24, 48, 72, 96 and 120 hours after the injection of ENR, DAN and *E. coli* K99, respectively, and killed at 48, 72 and 96 hours after the injection of *E. coli* K99+ENR and *E. coli* K99+DAN, respectively. Whole livers were removed and washed with cold saline solution. Three hundred milligrams of livers (lobus sinister) were homogenized (1000 rpm, 1 minute) with 1500 µl of cold homogenate solution (0.25 M sucrose (Sigma) + 10 mM Tris (Sigma) + 1 mM EDTA (Pharmacia Biotech), pH 7.4) into ice [8, 38]. The homogenates were centrifuged (10.000 rpm, 15 minute, +4 °C). The supernatants were carefully removed and saved for analysis (-20 °C). Hepatic SOD (Randox-Ransod SD 125) and GPX (Randox-Ransel RS 505) activities and total protein (Sigma 541-2) level were assayed in supernatants by using commercially available kits at spectrophotometer (Schimadzu UV 2100). Determination of SOD was based on the generation of superoxide radical produced by xanthine and xanthine oxidase, which react with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium choride to form a red formazan dye. GPX estimation was based on the following principle : GPX catalyses the oxidation of glutathione by cumen hydroperoxide. In the presence of glutathione reductase and NADPH the oxidised glutathione is immediately converted to the reduced form with a concominant oxidation of NADPH to $NADP^+$. The decrease in absorbance at 340 nm was measured. Hepatic SOD and GPX activities were expressed as U $mg^{-1}$ tissue protein.

All values are expressed as mean ± SE. The results were analyzed by Tukey HSD multiple range test (SPSS for windows, release 6.0). In all cases, probability of error of less than 0.05 was selected as the criterion for statistical significance from the control values.

# 3. Results

Hepatic SOD activity was given in Table I, and hepatic GPX activity was given in Table II, respectively.

Hepatic SOD activity increased significantly ($p < 0.05$) at 24 and 48 hours in group 3, and decreased significantly ($p < 0.05$) at 48 hours in group 6 when compared to the control group.

Hepatic GPX activity decreased significantly ($p < 0.05$) all sampling time in groups 3, 4 and 6, and decreased significantly ($p < 0.05$) at 24, 48 and 72 hours in group 2, decreased significantly ($p < 0.05$) at 72 and 96 hours in group 5 when compared to the control group.

# 4. Discussion and conclusions

Recent studies suggested that some antibiotics could effect SOD and GPX activities and ROS production. It was reported that gentamicin decreased cardiac SOD and GPX activities and renal GPX activity in guinea pigs [14, 25], tetracycline decreased hepatic SOD activity in rats [39], cephaloridine produced ROS in kidney [41], roxithromycin [20], chloramphenicol [26] and tetracyclines [22] inhibited ROS production in phagocytic cells, bleomycin, a antineoplastic agent, produced ROS in lung and caused pulmonary fibrosis [10].

In our knowledge, nothing has been published that any data concerning the effect of fluoroquinolone antibiotics on hepatic SOD and GPX activities. However, it was reported that fluoroquinolones could enhance ROS production in phagocytic cells [13, 24] such as enoxacin, norfloxacin, fleroxacin, levofloxacin, ofloxacin and enrofloxacin [6, 12, 19, 21].

In this study, SOD activity increased ($p < 0.05$) at 48 and 72 hours after the injection DAN and decreased significantly ($p < 0.05$) at 48 hours after the injection *E. coli* K99 + DAN. ENR and DAN may enhance the production of ROS in phagocytic cells or liver cells, and these antibiotics accumulate and metabolized by liver [5, 37]. Present study, DAN caused statistically ($p < 0.05$) changes SOD and GPX activities, but ENR caused statistically ($p < 0.05$) change only GPX activity. It is may be due to high dose of DAN. DAN is used (1.25 mg/kg body wt) half doses of ENR (2.5 mg/kg body wt) in veterinary medicine. Experimental dose of DAN may cause ROS production, it is stated that superoxide radicals may directly inactivate GPX activity [7, 32, 36], and SOD activity is may induced by produced ROS [7, 11, 15]. In addition to this, FRIDOVICH [7] reported that prior induction of ROS could cause an increase intracellular SOD activity. Hence first induction of ROS may cause changes in SOD activity and then SOD activity may return to the normal level.

| | Control | 24 hour | 48 hour | 72 hour | 96 hour | 120 hour |
|---|---|---|---|---|---|---|
| ENR | 6.712±0.50 | 8.233±2.10 | 6.518±1.30 | 5.785±0.89 | 6.947±1.80 | 6.550±1.00 |
| DAN | 6.712±0.50 | 35.45±4.00 *p < 0.05* | 56.82±10.0 *p < 0.05* | 3.630±0.55 | 6.410±0.67 | 6.460±0.67 |
| *E. coli* K99 | 6.712±0.50 | 5.490±0.37 | 6.140±0.48 | 6.630±-0.79 | 6.558±0.68 | 5.603±0.77 |
| *E. coli* K99+ENR | 6.712±0.50 | P | 5.218±0.46 | 7.133±0.33 | 6.002±0.40 | — |
| *E. coli* K99+DAN | 6.712±0.50 | P | 4.997±0.32 *p < 0.05* | 6.108±0.38 | 6.565±0.34 | — |

*p < 0.05* ; significantly different from control group, P ; 24 hours were waited for developing the peritonitis.

TABLE I. — Effects of enrofloxacin (ENR), danofloxacin (DAN), *E. coli* K99, E. coli K99+ enrofloxacin (ENR) and *E. coli* K99+ danofloxacin (DAN) on hepatic superoxide dismutase (U/mg protein) activity (Mean ± SE).

| | Control | 24 hour | 48 hour | 72 hour | 96 hour | 120 hour |
|---|---|---|---|---|---|---|
| ENR | 1.550±0.150 | 0.427±0.100 *p < 0.05* | 0.440±0.120 *p < 0.05* | 0.742±0.180 *p < 0.05* | 1.863±0.290 | 1.490±0.120 |
| DAN | 1.550±0.150 | 0.636±0.130 *p < 0.05* | 0.240±0.037 *p < 0.05* | 0.720±0.087 *p < 0.05* | 0.265±0.043 *p < 0.05* | 0.760±0.060 *p < 0.05* |
| *E. coli* K99 | 1.550±0.150 | 0.920±0.097 *p < 0.05* | 1.075±0.089 *p < 0.05* | 0.828±0.07 *p < 0.05* | 1.030±0.065 *p < 0.05* | 1.076±0.74 *p < 0.05* |
| *E. coli* K99+ENR | 1.550±0.150 | P | 1.293±0.090 | 0.772±0.130 *p < 0.05* | 0.767±0.130 *p < 0.05* | — |
| *E. coli* K99+DAN | 1.550±0.150 | P | 0.537±0.110 *p < 0.05* | 0.718±0.120 *p < 0.05* | 0.720±0.093 *p < 0.05* | — |

*p < 0.05* ; significantly different from control group, P ; 24 hours were waited for developing the peritonitis.

TABLE II. — Effects of enrofloxacin (ENR), danofloxacin (DAN), *E. coli* K99, *E. coli* K99+ enrofloxacin (ENR) and *E. coli* K99+ danofloxacin (DAN) on hepatic glutathione peroxidase (U/mg protein) activity (Mean ± SE).

Activated phagocytic cells are involved in antibacterial defense but also produce tissue injury associated with production of ROS [2,20]. PERALTA *et al* [27] reported that activated phagocytic cells produce ROS and cause hepatic injury in gram (-) bacteremia. ROS toxic to liver by initiating lipid peroxidation. The inhibition of lipid peroxidation improved survival rates in bacteremia. SOD enzyme is widely distributed in various tissues, but it can be found especially in the liver [34].

TAKAHASHI *et al* [34] reported that from three to nine days after injection with *S. typhimurium* LT-2, SOD activity was decreased to about 50 % of that in the control mice. But authors found, in mice given *S. typhimurium* SL-1181, SOD activity remained at the same level as in the control mice, and in mice infected with *P. aeruginosa* ATCC 27853, SOD activity increased 3 days after injection. KIM *et al* [17] reported that hepatic SOD activity increased on two days in infected guinea pigs after the injection *L. interrogans*, and this was followed by a 20 % decrease (from 3 to 14 days) resulting in levels comparable to healthy guinea pigs. On the other hand, PERALTA *et al* [27] reported that SOD and GPX activities decreased early in endotoxemic mice livers, and KONUKOGLU *et al* [18] reported that GPX activity decreased and SOD activity increased in peritoneal tissue in *E. coli* induced peritonitis rats. In this study, SOD activity was not affected ($p > 0.05$) while GPX activity decreased ($p < 0.05$) all experimental period after the injection DAN. Also GPX activity was found statistically different ($p < 0.05$) in DAN injected group from *E. coli* K99+ENR and *E. coli* K99+DAN injected groups at 48 and 96 hours. It is may be due to differences of bacteria and laboratory animals. It is reported that the capacity of SOD induction to ROS is different from species to species [42].

Interestingly, in this study, DAN caused an increase SOD activity in healthy mice at 24 and 48 hours but this effect was not found in peritonitis mice. This controversially result may be due to the peritonitis change the pharmacokinetic, particularly metabolism of DAN, and differences of sampling time between these groups. In *E. coli* K99+DAN injected group, 48 hours passed before first sampling time. In this period, some changes could occur in SOD and GPX activities.

In conclusion, it was observed that DAN effected both SOD and GPX activities, and ENR and *E. coli* K99 effected only GPX activity. It is may be related to either DAN and ENR may directly effect SOD and GPX activities in healthy mice or DAN and ENR may produce ROS, and so ENR and DAN may indirectly effect SOD and GPX activities. For this reason, further investigations are required, particularly malondialdehyde, indicator of lipid peroxidation [23], level must be measured and pharmacokinetics of ENR and DAN were determined in peritonitis mice.

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# References


1. — ALLEN D.G., PRINGLE J.K. and SMITH D.A. : Common dosages for rodents and rabbits in «*Handbook of Veterinary Drugs*», 605-627, second edition, Lippincott-Raven Publisher, 1998, New York.
2. — BRONER C.W., SHENEP J.L., STIDHAM G.L., STOKES D.C. and HILDNER W.K. : Effect of scavengers of oxygen-derived free radicals on mortality in endotoxin-challenged mice. *Crit. Care Med.*, 1988, **9**, 848-851.
3. — BULERA S.J., THEISS J.C., FESTERLING T.A. and DE LA IGLESIA F.A. : *In vitro* photogenotoxic activity of clinafloxacin : a paradigm predicting photocarcinogenecity. *Toxicol. Appl. Pharmacol.*, 1999, **156**, 222-230.
4. — COOPER A.C., FULLER J.R., FULLER M.K., WITTLESTONE P. and WISE D.R. : *In vitro* activity of danofloxacin, tylosin and oxytetracycline against *Mycoplasma* of veterinary importance. *Res. Vet. Sci*., 1993, **54**, 329-334.
5. — DECKER K. : Biologically active products of stimulated liver macrophages (Kupffer cells). *Eur. J. Biochem*., 1990, **192**, 245-261.
6. — DUNCKER D. and ULLMAN U. : Influence of various antimicrobial agents on the chemiluminescence of phagocytosing human granulocytes. *Chemother*, 1986, **32**, 18-24.
7. — FRIDOVICH I. : Biological effects of the superoxide radical. *Arch. Biochem. Biophys*., 1986, **247**, 1, 1-11.
8. — GELLER B.L. and WING D.R. : Subcellular distribution of superoxide dismutase in rat liver. *Method Enzymol*,1991, **105**, 105-114
9. — GUEMOURI L., ARTUR Y., HERBETH B., JEANDEL C., CUNY G. and SIEST G. : Biological variability of superoxide dismutase, glutathion peroxidase and catalase in blood. *Clin. Chem.*, 1991, **37**, 1932-1937.
10. — HABIB M.P., LACKEY D.L., LANTZ R.C., SOBONYA R.E., GRAND R., EARNEST D.L. and BLOOM J.H. : Vitamin A pretreatment and bleomycin induced rat lung injury. *Res. Commun. Chem. Pathol. Pharmacol.*, 1993, **81**,199-208.
11. — HASEGAWA T., KANEKO F. and NIWA Y. : Changes in lipid peroxide levels and activity reactive oxygen scavenging enzymes in skin, serum and liver following UVB irradiation in mice. *Life Sci*., 1992, **50**, 1893-1903.
12. — HOEBEN D., DOSOGNE H., HEYNEMAN R. and BURNEVICH C. : Effect of antibiotics on the phagocytotic and respiratory burst activity of bovine granulocyte. *Eur. J. Pharmacol*., 1997, **332**, 289-297.
13. — JANSEN VAN RENSBURG C.E., JOONE G. and ANDERSON R. : Interactions of the oxygen dependent antimicrobial system of the human neutrophil with difloksasin, ciprofloxacin, pefloxacin and fleroxacin in the intraphagocytic eradication of *Staphylococcus aureus*. *J. Med. Microbiol.*, 1990, **32**, 15-17.
14. — KAVUTCU M., CANBOLAT O., ÖZTÜRK S., OLCAY E., ULUTEPE S., EKINCI C., GÖKHUN I.H. and DURAK I. : Reduced enzymatic antioxidant defense mechanism in kidney tissues from gentamicin treated guinea pigs : effects of vitamin E and C. *Nephron*, 1996, **72**, 269-274.
15. — KAWAI S., KOMURA J., ASADA Y. and NIWA Y. : Experimental burn induced changes in lipid peroxide levels, and activity of superoxide dismutase and glutathion peroxidase in skin lesions, serum and liver of mice. *Arch. Dermatol. Res*., 1988, **280**, 171-175.
16. — KAYA S. [Quinolones] in «*Veterinary Applied Pharmacology*», 2nd ed, Ed ; KAYA S, PIRINÇCI I and BILGILI A, p : 364-373, 1997, Medisan, Ankara, Turkey.
17. — KIM Y.G., JEON D.Y. and YANG M.K. : Superoxide dismutase activity and lipid peroxidation in the liver of guinea pig infected with *Leptospira interrogans*. *Free Radic Res.*, 1997, **25**, 1-6.
18. — KONUKOGLU D., IYNEM H. and ZIYLAN E. : Antioxidant status in experimental peritonitis : effects of alpha tocopherol and taurolin. *Pharmacol. Research*, 1999, **39**, 3, 247-251.
19. — KUBO S., MATSUMOTO T., TAKAHASHI K., HARAOKA M., TANAKA M., SAKUMOTO M., SAKAMOTO Y. and KUMAZAWA J. : Enhanced chemiluminescence response of polymorphonuclear leukocytes by new quinolone antimicrobial. *Chemother*, 1994, **40**, 333-336.
20. — LABRO M.T., EL BENNA J. and CHAVAYE C.B. : Comparison of the *in vitro* effect of several macrolides on the oxidative burst of human neutrophils. *J. Antimicrob. Chemother*, 1989, **24**, 561-572.
21. — MATSUMOTO T., TAKAHASHI K., NAGAFUJI T., KUBO S., SAKUMOTO M., MOCHIDA O., SAKAMOTO Y., MIZUNOE Y. and KUMAZAWA J. : Fleroxacin enhancement of superoxide production by polymorphonuclear leukocytes : The role of protein kinase. *Chemother*, 1996, **42**, 280-285.
22. — MIYACHI Y., YOSHIOKA A., IMAMURA S. and NIWA Y. : Effect of antibiotics on generation of reactive oxygen species. *J. Invest. Dermatol.*, 1986, **9**, 86, 449-453.
23. — NEILSEN F., MIKKELSEN B.B., NEILSEN J.B., ANDERSEN H.R. and GRANDJEAN P. : Plasma malondialdehyde as biomarker for oxidative stress : reference interval and effects of life-style factors. *Clinical Chemistry*, 1997, **47**, 3, 1209-1214
24. — NIELSEN S.L., OBEL M., STORGAARD M. and ANDERSON P.L. : The effect of quinolones on the intracellular killing *S.aureus* in neutrophil granulocytes. *J. Antimicrob. Chemother*, 1997, **39**, 617-622.
25. — OZTURK H.S., KAVUTÇU M., KAÇMAZ M., CANBOLAT O. and DURAK I. : The effects of gentamicin on the activities of glutathione peroxidase and superoxide dismutase enzymes and malondialdehyde levels in heart tissues of guinea pigs. *Curr. Med. Res. Opin*, 1997, **14**, 47-52.
26. — PAAPE M.J., MILLER R.H. and ZIV G. : Effects of florfenicol, chloramphenicol and thiamphenicol on phagocytosis, chemiluminescence and morphology of bovine polymorphonuclear neutrophil leucocytes. *J. Dairy Sci*., 1990, **73**, 1734-1744.
27. — PERALTA J.G., LLESUY S., EVELSON P., CARRERAS M.C., FLECHA B.G. and PODEROSO J.J. : Oxidative stress in skeletal muscle during sepsis in rat. *Circ. Shock.*, 1993, **39**, 153-159.
28. — PORTOLES M.T., AINAGA M.J. and PAGANI R. : The induction of lipid peroxidation by *E. coli* lipopolysacharide on rat hepatocytes as an important factor in the etiology of endotoxic liver damage. *Biochim. Biophys. Acta*, 1993, **1158**, 287-292.
29. — ROCHE Y., GOUGEROT-POCIDALO M.A., FAY M., ETIENNE D., FOREST N. and POCIDALD J.J. : Comparative effects of quinolones on human mononuclear leukocyte functions. *J. Antimicrob. Chemother*, 1987, **19**, 781-790.
30. — SANIABADI A.R., WADA K., UMEMURA K., SAKUMA S. and NAKASHIMA M. : Impairment of phagocytic cell respiratory burst by UVA in the presence of fluoroquinolones : an oxygen dependent phototoxic damage to cell surface microvilli. *J. Photochem. Photobiol. B :Biology*, 1996, **33**, 137-142.
31. — SCHMIDT U. and SCHLÜTER G. : Studies on the mechanism of phototoxicity of Bay y3118 and other quinolones. *Adv. Exp. Med. Biol.*, 1996, **96**, 387, 117-120
32. — SODHI C.P., RANA S.V., MEHTA S.K., VAIPHEI K., ATTARI S. and MEHTA S. : Study of oxidative stress in isoniazid-rifampicin induced hepatic injury in young rats. *Drug and Chem. Toxicol*., 1997, **20**, 255-269.
33. — SUN Y., OBERLEY L.W. and LI Y. : A simple method for clinical assay of superoxide dismutase. *Clin. Chem*., 1988, **34**, 3, 497-500.
34. — TAKAHASHI M., USHIJIMA T. and OZAKI Y. : Changes in hepatic superoxide dismutase and xanthine oxidase activity in mice infected with *Salmonella typimurium* and *Pseudomonas aeruginosa*. *J. Med. Microbiol*., 1988, **26**, 281-284.
35. — THUONG-GUYOT M., DOMALE O., POCIDALO J.J. and HAYEM G. : Effects of flouroquinolones on cultured articular condrocytes flow cytometric analysis of free radical production. *J. Pharmacol. Exp. Ther*., 1994, **271**, 1544-1549.
36. — TURRENS J.F. : The potential of antioxidant enzymes as pharmacological agents *in vivo*. *Xenobiotica*, 1991, **8**, 1033-1040.
37. — VANCUTSEM P.M., BABISH J.G. and SCHWARK W.S. : The fluoroquinolone antimicrobials, structure, antimicrobial activity, pharmacokinetics, clinical use in domestic animals and toxicity. *Cornell Vet*., 1990, **80**, 173-186.
38. — VANI M., REDDY G.P., REDDY R., THYAGARAJUK K. and REDANNA P. : Glutathione-S-transferase, superoxide dismutase, xantine oxidase, catalase, glutathione peroxidase and lipid peroxidation in the liver of exercised rat. *Biochem. Int*., 1990, **21**, 17-26.
39. — VIJAYALEKSHMY K.S., MENON V.P. and LEELAMMA S. : Role of antibiotics in lipid peroxidation. *Ind. J. Biochem. Biophys*., 1992, **29**, 371-374.
40. — WATSON A.M., WARREN G., HOWARD G., SHEDLOFSKY S.I. and BLOUIN R.A. : Activities of conjugating and antioxidant enzymes following endotoxin exposure. *J. Biochem. Molecul. Toxicol*., 1999, **2**, 63-69.
41. — YOKOZAWA T. and OWADA S. : Effect of ginsenoside-Rd cephaloridine induced renal disorder. *Nefron*, 1999, **81**, 200-207.
42. — ZHI-YONG S., YUAN-LIN D. and XIAO-HONG W. : Bacterial translocation and multiple system organ failure in bowel ischemia and reperfusion. *J. Trauma*., 1990, **2**, 148-153.