ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN — POLONIA
VOL. LIV, 24 SECTIO D 1999

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The influence of ethanol and different free radical scavengers on the lipid peroxidation process and antioxidant status in the rats' gastric mucosa

Wpływ alkoholu etylowego oraz zmiataczy wolnych rodników
na proces peroksydacji lipidów oraz wydolność antyoksydacyjną
błony śluzowej żołądka szczurów

It is known that some irritating exogenous agents such as alcohol or non–steroid antiinflammatory drugs (NSAID) disrupt the gastric surface epithelium and cause the decline of the secretion of gastric mucus which reduces the protective effect of the gastric mucus barrier. The integrity of the mucosal layer of the upper gastrointestinal tract depends on a balance between its defensive ability and aggressive factors. Mucosal defence is connected with the anatomic structure of the gastric wall. The first defence agent is mucus, secreted by the surface epithelial cells and mucous neck cells. Mucus with bicarbonate creates "mucus–bicarbonate" barrier. The other ones are the surface–active phospholipid layer that resides at the luminal surface of the mucus overlying the epithelium and the dense network of capillaries in the epithelium. It is very important that lamina propria contains many types of cells, such as mast cells, resident macrophages and neutrophils which play the role in the response to superficial and profound injury. These cells can release many inflammatory mediators such as histamine, serotonin, PAF (plateled activating factor), leucotriens, tromboxane, endothelin which affect mucosal blood flow, vascular permeability and the process of chemotaxis and phagocytosis. Due to these cells and their mediators many toxic substances can be excluded but on the other hand released mediators can alter microvasculature tone and permeability. The process of phagocytosis, arachidonic acid pathway and also changes in the mucosal blood flow, especially reperfusion after ischemia cause the production of cytotoxic free radicals. These active oxygen metabolites, can play the important role in the pathogenesis of stomach ulcer. On the other hand some prostaglandines such PGE2 and PGI2 show the protective role in relation to the gastric mucosa, causing the increase in the mucosal secretion, vasodilatation and activation of bicarbonates secretion to the gastric lumen. The action of alcohol is connected with changes of the arachidonic acid pathway. The administration of

ethanol results in the increase in gastric mucosal leucotriene synthesis and causes the inhibition of prostaglandine synthetase activity. This disbalance between the concentrations of the different mediators mentioned above results in the gastrointestinal tract injury.

Thus the aim of our study was to investigate the influence of some arachidonic acid inhibitors and free radical scavengers on lipid peroxidation process and antioxidant ability of the rat gastric mucosa after ethanol administration.

MATERIAL AND METHODS

All experiments were carried out on 220 male Wistar rats weighing 190–200 g, housed at the room temperature. The animals were starved for 24 hours before experiments, but they were allowed to drink 10% sucrose in 0.96% v/v NaCl solution which was stopped 1 hour before investigation. The animals stayed in cages at room temperature of 20–22 C and humidity ca. 70%. There was a 12–hour cycle of day light. All studies were carried in the same room where the rats were kept. The rats were divided into groups as follows: group I – negative control pretreated with saline in the dose 5 ml per kg b.w. per os, group II – positive control group pretreated with only 50% w/v ethanol in the dose 5 ml per kg b.w. per os, group III – the animals pretreated with dimethylsulfoxide (DMSO) – hydroxyl radical scavenger; 2% solution of DMSO was given orally in the dose 5 ml per kg of b.w., group IV – rats pretreated with mannitol, also hydroxyl radical scavenger; 5% solution was given intraperitoneally – 5 ml per kg b.w., group V – pretreated with uric acid – hydroxyl radical scavenger; 2% solution was given intraperitoneally in the dose 5 ml per kg b.w., group VI – rats pretreated with 1,4–-diazo /2.2.2./bicyclooctane (DABCO). This singlet oxygen scavenger was given intraperitoneally, 10 mg/kg b.w., group VII – animals pretreated intraperitoneally with allopurinol – xantine oxidase inhibitor, in the dose 10 mg/kg b.w., group VIII – pretreated intraperitoneally with the compound AA 861 – lipooxygenase inhibitor (Chem. Pharm. Inst. Tokyo Japan), in the dose 100 μg per kg b.w., group IX – pretreated intraperitoneally with the compound BW 775C – 5–lipooxygenase–cyclooxygenase dual inhibitor (Wellcom Res. Lab. Beckenham, England) in the dose 100 μg/kg b.w., group X – the rats pretreated with CGS 13080 – TXA2 synthtetase inhibitor (Ciba Geigy Summit USA) – 1 mg/kg b.w. s.c.

Each experimental group consisted of 20 animals. The animals from the groups I–X were administered with drugs described above and 30 minutes later they were administered orally with 50% ethanol solution (5ml per kg of b.w.) using a stainless steel stomach tube. Ethyl alcohol solution was prepared by diluting 96% alcohol in 0.96% NaCl to achieve the required 50% concentration, each time directly before the use. All rats were killed by decapitation 2 hours after the last ethanol administration. After decapitation their stomachs were resected and cut along the greater curvature. The extent of injury to the gastric mucosa was estimated. Each injury was measured along its largest dimension and in the case of extravasations each five petechies were treated as 1 mm mucosal injury. Then arithmetic mean was calculated from the sum of injury lenghts in each group separately. The ulceration index achieved in this way was assumed as the measure of severity of mucosal injury.

The gastric mucosa was separared from the muscular layer and used for biochemical estimations. Part of the mucosa was homogenized in three volumes of 0.1 m. Tris–HCl of pH 7.4. The homogenate was centrifuged at 3000 G for 10 minutes and in the supernatant the level of malonyl dialdehyde (MDA) was determined according to the method of Ledwożyw et al. and expressed in nM per 1 mg of protein (4). The concentrations of hydroperoxides (HPETE) and conjugated dienes (CD) in the

supernatant were determined according to Buege and August's method in Ward's modification and expressed in OD (Optical Density) per 1mg of protein (16).

The other part of the mucosa was homogenized in 10 volumes of 50 mM buffer Tris–HCl, pH 8.9 and then the homogenate was centrifuged at 2000G for 10 minutes. Supernatant was used for enzymatic studies. Catalase (CAT) activity (EC 1.11.1.7) was measured according to Cohen et al. (2)., glutathione peroxidase (GPx) activity (EC 1.11.1.9) according to Paglia and Valentine (11), peroxidase (POX) activity (EC 1.11.1.7) according to Putter (13), glutathione (GR) reductase activity (EC 1.6.4.2) according to Mizuno (8) and superoxide dismutase (SOD) activity (EC 1.15.1.1) according to Misra and Fridovich (7). Mn–isoenzyme of superoxide dismutase was determined in the presence of 2 mM KCN in the incubation fluid.

Enzyme activity was expressed in units per 1 mg of protein. The protein was determined according to Lowry et al., using bovine albumin as a standard.

The results of the studies were analyzed statistically by means of Student's t–test for non–junction variables.

RESULTS

QUANTITY OF LIPID PEROXIDATION PRODUCTS IN RAT MUCOSA (Fig. 1, Tab. 1)

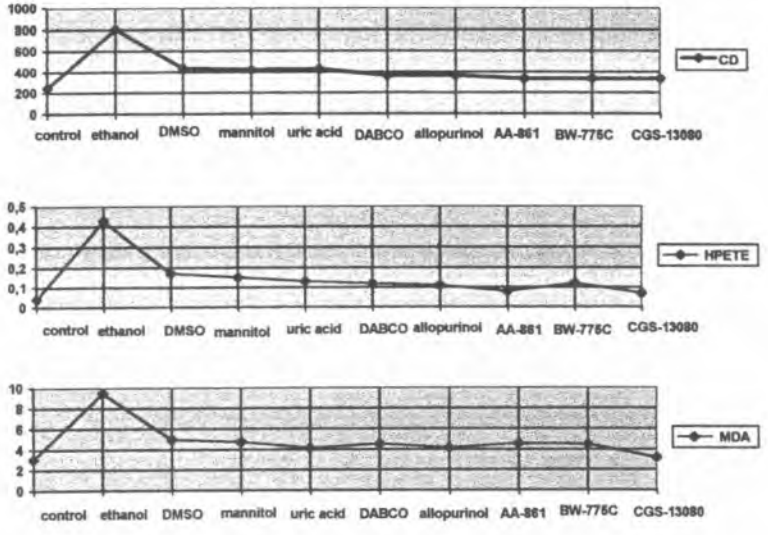

Fig. 1. The levels of conjugated dienes (CD) (OD 233 nm), hydroperoxides (HPETE) (OD 353 nm) and malonyl dialdehyde (MDA) (nM/g tissue) in rats' gastric mucosa after ethanol injury and after administration with some free radical scavengers and arachidonic acid pathway inhibitors

The concentration of conjugated dienes (CD) in mucosa of the rats pretreated with ethanol amounted to 330% of the control level. In each group pretreated with the drugs – free radical scavengers (e.i. DMSO, mannitol, uric acid, DABCO and allopurinol) or with arachidonic acid pathway inhibitors

Tab. 1. The influence of some free radical scavengers and arachidonic acid pathway inhibitors on the levels of malonyl dialdehyde (nM/g tissue), conjugated dienes (OD 233 nm) and hydroperoxides (OD 353 nm) in rats stomach mucosa after ethanol injury. The results are expressed as arithmetical means ± standard deviations (X ± SD). Student's t–test for unpaired data was used for statistical analysis. $p < 0.05$ was considered statistically significant

	Control	0.96% NaCl + ethanol	DMSO	Mannitol	Uric acid	DABCO	Allopurinol	AA-861	BW-755C	CGS-13080
CD	245±17	810±73 ***	435±33 **/##	422±33 **/##	430±41 **/##	364±34 */##	365±32 */##	333±29 */##	337±27 */##	333±28 */##
HPETE	0.04±0.03	0.43±0.039 ***	0.17±0.012 **/##	0.15±0.013 **/###	0.13±0.011 **/##	0.12±0.009 **/##	0.11±0.009 **/##	0.08±0.007 */#	0.12±0.01 **/##	0.07±0.005 */#
MDA	3.05±0.21	9.5±0.83 **	5.0±0.39 */##	4.75±0.31 */##	4.15±0.24 */##	4.55±0.21 */##	4.15±0.21 */##	4.6±0.25 */##	4.5±0.22 */##	3.2±0.26 **

[*] – statistically significant difference between the saline and the ethanol group and also between the saline and each of the group pre–treated with AA pathway inhibitors or with the drugs–free radical scavengers; [#] – statistically significant difference between the ethanol group and each of the group pre–treated with AA pathway inhibitors or free radical scavengers;
* – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$, # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$

(AA 861, BW–755 C and CGS–13080) prior to ethanol administration, the levels of CD were significantly higher than in the control ones but in each case significantly lower than in only ethanol preteated group.

The levels of hydroperoxides (HPETE) and malonyl dialdehyde (MDA) also increased significantly after ethanol in comparison to the control rats and were also higher in the groups pretreated with the drugs described above than the control values. The levels of HPETE and MDA decreased significantly in relation to the only ethanol pretreated group.

ACTIVITY OF ANTIOXIDANT ENZYMES IN RAT MUCOSA (Fig. 2, Tab. 2)

The activity of each examined enzymatic free radical scavengers in rat mucosa significantly increased when ethanol was given.The activity of Cu–Zn SOD amounted to about 170% of the control value in the ethanol pretreated group. After pretreatment with free radical scavengers and arachidonic acid pathway inhibitors Cu–Zn SOD significantly decreased in comparison to the ethanol group but it was still higher than the control value. The activity of Mn–SOD amounted to about 250% of the control activity after ethanol was given and decreased after scavengers pretreatment just as Cu–Zn SOD. The activity of CAT was about 50% higher after ethanol in relation to the activity of the control group, significantly decreased when free radical scavengers were given but it was still higher than the control value. The activity of GPx increased by about 300% after ethanol and was also higher than the control value after scavengers pretreatment. When the uric acid, DABCO and allopurinol were given the activity of GPx decreased in comparison to the ethanol group.The activities of GR and POX also

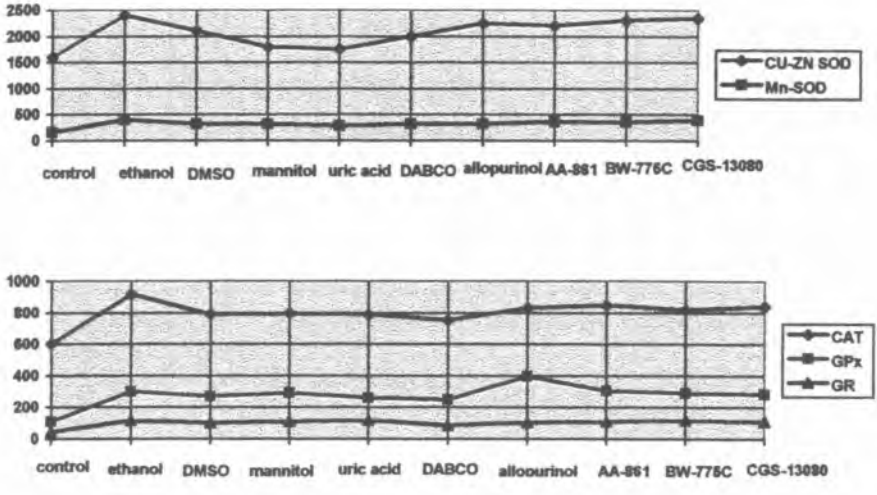

Fig. 2. The influence of some free radical scavengers and arachidonic acid pathway inhibitors on the activities of enzymes: Cu–Zn SOD and Mn–SOD (superoxide dismutase) (1u = 50% inhibition of pyrogallol autooxidation), GPx (glutathione peroxidase) (1u. = nM NADPH x min $^{-1}$ x mg protein $^{-1}$), GR (glutathione reductase) (1u. = nM NADPH x min $^{-1}$ x mg protein $^{-1}$), CAT (catalase) (1u. = 1 μmol H_2O_2 metabolised x min $^{-1}$ x mg protein $^{-1}$), POX – 1u. = μM. of guaiacol x mg protein $^{-1}$) in the rats' gastric mucosa injured by ethanol

Tab. 2. The influence of some free radical scavengers and arachidonic acid pathway inhibitors on the activity of the antioxidant enzymes in rat stomach mucosa. The enzymes activity are expressed in units pet mg protein: SOD (superoxide dismutase) –1u. = 50% inhibition of pyrogallol autooxidation, GPx (glutathione peroxidase) –1u. = nM NADPH x min $^{-1}$ x mg protein $^{-1}$, GR (glutathione reductase) – u. = nM NADPH x min $^{-1}$ x mg protein $^{-1}$, CAT (catalase) $^{-1}$ u. = 1 (mol H2O2 metabolised x min $^{-1}$ x mg protein $^{-1}$, POX $^{-1}$ u. = (M. of guaiacol x mg protein –1. The results are expressed as arithmetical means ± standard deviations (X ± SD). Student's t–test for unpaired data was used for statistical analysis. $p < 0.05$ was considered statistically significant

	Control	0.96% NaCL + ethanol	DMSO	Mannitol	Uric acid	DABCO	Allopurinol	AA-861	BW-755C	CGS-13080
Cu-Zn SOD	1600±145	2400±210 **	2100±200 **/#	1800±170 */##	1750±135 */##	2000±195 */#	2250±221 **/#	2200±190 **/#	2300±221 **/#	2350±221 **
Mn-SOD	160±7	407±30 **	328±20 **/#	320±25 **/#	289±19 */#	324±17 **/#	328±18 **/#	368±22 **/#	360±22 **/#	395±23 **
CAT	605±40	916±58 **	790±41 */#	795±38 */#	790±38 */#	750±31 */#	830±40 */#	850±41 */#	820±41 */#	840±39 */#
GPx	110±16	300±20 **	270±15 *	290±13 **	260±14 **/#	250±13 **/#	395±21 **/#	305±15 **	290±17 **	285±14 **
GR	45±3	115±7 **	102±6 *	110±7 **	117±8 **	85±5 **/#	103±7 *	110±8 **	117±8 **	108±7 **

[*] – statistically significant difference between the saline and the ethanol group and also between the saline and each of the group pre–treated with AA pathway inhibitors or with the drugs– free radical scavengers; [#] – statistically significant difference between the ethanol group and each of the group pre–treated with AA pathway inhibitors or free radical scavengers.

* – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$, # – $p < 0.05$, ## – $p < 0.01$, ### – $p < 0.001$

increased in the ethanol given group. We did not observe any significant decrease of GR and POX acitivities after free radical scavengers pretreatment in comparison to the ethanol group.

ULCER INDEX (Fig. 3, Tab. 3)

The ulcer index significantly increases in the ethanol group in relation to the control one. After pretreatment with AA pathway inhibitors it was still higher than the control value but lower in comparison to the ethanol group. After DMSO, uric acid, allopurinol and DABCO pretreatment ulcer index was not different from the control one.

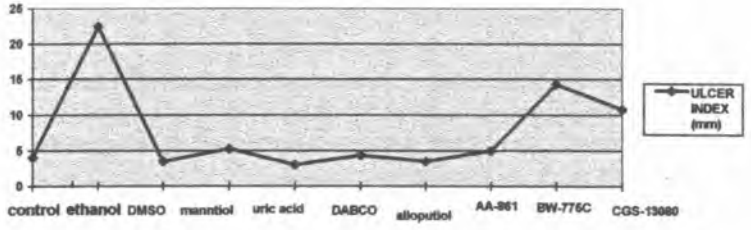

Fig. 3. The influence of some free radical scavengers and arachidonic acid pathway inhibitors on the ulcer index (mm) in rat gastric mucosa

DISCUSSION

Oxygen free radicals are formed in many conditions, i.e. during phagocytosis, ischemic conditions or arachidonic acid pathway. Nowadays it is known that free radicals act as the secondary messengers inside the cells. They activate genes responsible for enzymatic antioxidants production (SOD, GPx, CAT, GR), interleukines and their receptors release and for some adhesive molecules production. Although oxidative stress results in the activation of the defence mechanisms, sometimes free radicals production is very intensive, the balance between development of reactive oxygen forms and antioxidants activity is disturbed and this in turn causes the disease. Many clinical observations and experiment data suggest that oxygen free radicals can play the important role in the pathogenesis of alcohol induced gastric ulcers.

In our investigations we observed that after ethanol exposure the levels of lipid peroxidation products in gastric mucosa increased significantly. Simultaneously the activity of oxygen enzymatic scavengers increased but nevertheless the ulcer index was higher than in the control conditions. It clearly means that acute ethanol exposure causes the oxidative stress in the gastric mucosa and increased enzymatic activity cannot prevent the damage of the gastric tissues.

We noticed that after pretreatment with free radical scavengers the levels of lipid peroxidation products increased and enzymes activities also increased in comparison to the control values but after DMSO, uric acid, allopurinol and DABCO pretreatment we did not notice any differences in the ulcer index between the control group and pretreated ones. This fact demonstrates that nonenzymatic scavengers effectively cooperate with the enzymes in the protection of gastric mucosa against the ethanol damage. The results obtained after allopurinol show that ethanol–induced gastric mucosal damage is

Tab. 3. The influence of some free radical scavengers on the ethanol-induced injury of rat's stomach mucosa. The results are expressed as arithmetical means ± standard deviations (X ± SD). Student's t-test for unpaired data was used for statistical analysis. $p < 0.05$ was considered statistically significant

Group of animals	Control	0.96% NaCL + ethanol	DMSO	Mannitol	Uric acid	DABCO	Allopurinol	AA-861	BW-755C	CGS-13080
ulcer index (mm) X ± SD	4.0±0.5	22.5±15 ***	3.5±1.5 ###	5.25±2.7 */###	3.0±1.9 ###	4.33±2.3 ###	3.5±2.2 ###	14.3±4.99 **/##	10.8±4.1 **/##	5.0±2.8 **/###

[*] – statistically significant difference between the saline and the ethanol group and also between the saline and each of the group pre–treated with AA pathway inhibitors or with the drugs–free radical scavengers. [#] – statistically significant difference between the ethanol group and each of the group pre–treated with AA pathway inhibitors or free radical scavengers.

* – $p < 0.05$, ** – $p < 0.01$, *** – $p < 0.001$, # – $p < 0.05$, ## – $p < 0.01$, ### - $p < 0.001$

dependent on the xantine oxidase system. It is interesting that arachidonic acid pathway inhibitors caused the decrease of ulcer index in comparison to the ethanol group but this index was staying significantly higher than in the control group.

The results described above show that gastric mucosa damage after acute ethanol exposure may be connected with free radicals action and these free radicals are formed during ischemic conditions, inflammatory reactions and arachidonic acid pathway.

Numerous experimental data also suggest the role of oxygen free radicals in the ethanol–induced gastric injury.

Mutoh et al. (10) showed in their investigations that cultured rat gastric mucosal cells exposed to ethanol, produced superoxide anions directly proportionally to the ethanol dose and SOD and CAT activity maintained their enzymatic activities in the presence of 15% ethanol. They also showed that ethanol damage of the gastric cells is closely linked with the intensity of superoxide anion production.

Hirokawa et al. (3) investigating the details of ethanol–induced gastric mucosal damage showed that ethanol administration induced intracellular oxidative stress and produced mitochondrial permeability transition and mitochondrial depolarization, which resulted in cell death in mucos. They also noticed that glutathione – intracellular antioxidant had the protective action against ethanol.

Suzuki et al. (14) noticed in their investigations that oral administration of ethanol caused increase in the content of thiobarbituric acid–reactive substances in the injured mucosa in rats. Pretreatment with compounds scavenging both superoxide anions and hydroxyl radicals (querticin, alpha–tocopherol, nifedipine and tetracycline) markedly prevented ethanol gastric mucosal injury and the increase in MDA level.

Ligumsky et al. (5) and Matsumoto et al. (6) suggest that gastric mucosal damage after ethanol exposure is connected with the generation of oxygen–derived radicals, but independent of xantine oxidase system. Ligumsky et al. showed using gross and microscoping scoring that radical scavengers as Mn^{2+}, glycine, carotenes, catalase and dimethylohydroxyurea (Dmtu) given simultaneously with ethanol administration, caused gastroprotection, but allopurinol did not. Matsumoto et al. also noticed that gastric lesions induced by ethanol were not reduced in mice treated with allopurinol. Matsumoto concluded that the main source of oxygen free radicals after ethanol exposure are neutrophils. He also showed that oral administration of SOD and CAT reduced ethanol gastric lesions formation.

Also Szelenyi and Brune's (15) experiments show that oral administration of superoxide dismutase reduces the ethanol–induced mucosal lesions like some compounds with scavenging properties such as thiourea, dimethyl sulfoxide and sulfhydryl–containing substances. In their investigations antioxidants such as alpha–tocopherol, beta–carotene, coenzyme Q or even glutathione peroxidase and catalase were not able to inhibit ethanol–induced mucosal lesions.

Cho's et al. (1) and Moghadasian's et al. (9) experiments show that ethanol–induced injury of the antioxidant status in the gastric mucosa is dependent on the concentration of alcohol. Cho showed that oral administration of absolute ethanol caused the increase in the CAT–activity and did not influence the SOD activity. Moghadasian noticed that 8% ethanol increased the activity of glutathione peroxide and superoxide dismutase in the gastrointestinal tract but undiluted alcohol only increased glutathione peroxide activity in the gastric mucosa.

It is known that free radicals are also formed during arachidonic acid pathway. Peskar et al. (12) investigated connections between ethanol exposure, arachidonic acid pathway and gastric mucosal damage. They noticed that ethanol administration caused the increase in Ltc4 release by gastric mu-

cosa and it was directly proportional to the gastric lesions. Lipooxygenase inhibitor acting as the protector against ethanol caused damage.

Our own and described above investigations clearly show that ethanol–induced gastric mucosal injury is connected with the oxygen free radicals action and different radical scavengers have got gastroprotectional role during ethanol exposure.

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Otrz.: 1999.11.10

STRESZCZENIE

Alkohol etylowy jest czynnikiem sprzyjającym powstawaniu owrzodzeń przewodu pokarmowego, zaś ważną rolę w patogenezie tego zjawiska mogą odgrywać aktywne metabolity tlenu. Celem pracy było zatem zbadanie wpływu zmiataczy wolnych rodników (DMSO, mannitolu, kwasu moczowego, DABCO i allopurinolu) oraz inhibitorów kaskady kwasu arachidonowego (AA861, BW775C i CGS 13080) na intensywność peroksydacji lipidów, wydolność antyoksydacyjną oraz indeks owrzodzeniowy w błonie śluzowej żołądków szczurzych. Uzyskane wyniki ukazują, iż ostra ekspozycja na etanol powoduje wzrost stężenia sprzężonych dienów (CD), hydronadtlenków lipidowych (HPETE) oraz aldehydu malonowego (MDA) w błonie śluzowej żołądka, zaś zastosowane zmiatacze wolnych rodników i inhibitory kaskady kwasu arachidonowego istotnie ograniczają ten proces. Jednocześnie aktywność enzymów: Cu–Zn SOD, Mn–SOD, CAT, GPx i GR wzrasta bardziej po podaniu etanolu niż po jednoczesnej ekspozycji na wymienione zmiatacze i inhibitory, lecz zawsze jest wyższa niż w grupie kontrolnej. Indeks owrzodzeniowy, wysoki po etanolu, ulega w różnym stopniu obniżeniu po zastosowaniu zmiataczy wolnych rodników oraz inhibitorów kaskady kwasu arachidonowego.