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Sesame Oil Has Gastroprotective And Anti-Oxidative Properties: An Experimental Study In Rats With Indomethacin-Induced Gastric Ulcers

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Abstract

Sesame oil (SO) is a component of the traditional health food in India as well as in oriental countries and has long been thought to possess the ability to prevent various diseases. We examined the protective effects of sesame oil against acute gastric mucosal damage induced in rats by nonsteroidal anti-inflammatory drug indomethacin (IND). We also intended to determine the relation between antiulcer effect of SO and its antioxidant properties by biochemical evaluation. In this study a total of 5 rat groups were used for ulcer experiment. Antiulcer effects of SO have been investigated on 24 hour fasted 5 rat groups with indomethacine (IND)-induced ulcer model in the presence of positive (Famotidine, FAM), negative (untreated IND group) and intact control groups. In ulcer experiments, two doses of SO exerted significant anti-ulcerogenic effects. In gastric tissues, sesame oil administration decreased the level of LPO and activities of CAT, GR, MPO which were increased after IND application. Furthermore, SO increased the level of GSH which decreased in ulcerous stomach tissues when compared to healthy rat group. We determined that SO has anti-ulcerative effect and this effect are related to antioxidative properties of sesame oil.

Keywords: Sesame oil, Indomethacin, Gastroprotective effect, Myeloperoxidase, Vegetable oil

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INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAID) are the mostly used in cases of pain and fever. There are side effects as well as widespread used. The most common side effect of which is gastric lesions. Gastric lesions are a condition caused by inhibiting prostaglandin biosynthesis. The reactive oxygen species (ROS) are expressed to play an important role in ulcer lesions. (Elliott and Wallace, 1997; Kaplan et al., 2012; Tanas et al., 2010). Indomethacin (IND)-induced gastric damage is a good source of ROS. ROS such as hydrogen peroxide (H_2O_2) and the superoxide radical (O_2^-) play a serious role to occur cancer, gastric injury, atherosclerosis, neurodegeneration, and arthritis through various processes, including inhibition of prostaglandin synthesis, infiltration of polymorphonuclear leukocytes, induction of apoptosis, and initiation of lipid peroxidation (Atalay, 2016; Hsseinigouzdagani et al., 2014; Miura et al., 2002; Odabasoglu et al., 2012; Uzkeser et al., 2012). Indomethacin is a commonly used analgesic in humans. But, it causes injury, such as other NSAIDs do on the gastric mucosa. (Polat et al., 2011; Suleyman et al., 2012; Wallace et al., 2000). In many studies have suggested that IND shows prooxidant activity and initiates lipid peroxidation (LPO) by generating ROS, thereby interfering with the mucosal cells' endogenous antioxidant systems (Albayrak et al., 2010; Atalay, 2016; Miura et al., 2002; Takeuchi et al., 1998). The presence of superoxide radicals can be seen as the cause of many illnesses, especially gastric damage. (Karaca, 2013; Kumtepe et al., 2010; Mates et al., 1999).

At the same time, reactive oxygen species can also initiate lipid peroxidation, damaging membranes. Therefore, antioxidant defense systems are important to protect the cells against damage and deterioration that can occur.(Aksakal et al., 2011; Demirci, 2011; Karaca et al., 2009). Antioxidant enzymes in oxygen-using cells can protect cells against oxidative stress. Antioxidant defense systems, both enzymes and non-enzymes, are important in protecting against gastric damage. (Koc et al., 2008; Oral et al., 2011; Turkez et al., 2014). Besides, myeloperoxidase (MPO), which is found in azuraphilic granules of mammalian neutrophils and human monocytes, is involved in microbial killing and inflammatory tissue damage (Matheson et al., 1981; Odabasoglu et al., 2008; Nishida et al., 1997; Wallace and Granger, 1992). Myeloperoxidase is commonly used as an index of neutrophil infiltration in various experimental gastric injuries (Khattab et al., 2001; Nishida et al., 1997; Takeuchi et al., 1998; Wallace and Granger, 1992).

Sesame (*Sesamum indicum* L.) is a plant widely used since ancient times (Hsu, 2011). Sesame oil is especially used in India, atherosclerosis, hypertension and aging retarder (Namiki, 1995). Sesame oil is second in terms of nutritional value after olive oil. Also it plays an important role in oxidation due to tocopherol and endogenous antioxidants.(Khier, 2008). Especially it sources vitamin E and B6. Thanks to its micronutrients, it performs many activities such as lowering blood pressure, preventing hyperlipidemia, reducing lipid peroxidation (Saleem et al., 2012; Sankar et al., 2005). Some properties of sesame oil have been supported by many studies such as; endotoxemia (Hsu et al., 2005), healing following gentamicin-induced kidney injury (Periasamy et al., 2010), heavy metal poisoning (Chandrasekaran et al., 2014), anti-atherosclerotic and anti-inflammatory actions (Hsu et al 2013b; Narasimhulu et al 2015; Periasamy et al., 2013). In some studies, positive results of sesame oil are observed in eliminating the gastric damage caused by various factors (Hsu et al., 2013a; Hsu et al., 2009a; Hsu et al., 2009b; Hsu, 2011). However, neither the effective role of glutathione metabolism's enzymes in gastric tissues nor the gastroprotective action of sesame oil on the indomethacine-induced gastric ulcerations has been established. Therefore, we hypothesized that sesame oil would arrange some abnormal antioxidative parameters in gastric-ulcerogenic tissues, and we tested the effects of sesame oil on indomethacine-induced gastric ulcerations in rats.

MATERIALS AND METHODS

Animals

The 30 Wistar rats, weighing 180–200 g, were obtained from Experimental Animal Laboratory of Ataturk University, Experimental Animal Teaching and Researcher Center. The animals were kept under the same conditions (Care, 1993). The experiment protocol of the Ethics Committee on Experimental Animal Use and Care was approved throughout the research.

Chemicals

All chemicals were bought from Sigma Chemical (Germany). Sesame oils was purchased from a retail market (Ulker A.S.-Bizim, Turkey), famotidine and indomethacin from pharmacy store.

Indomethacin-Induced Gastric Damage

The gastroprotective effect of sesame oil was determined in comparison with famotidine. The animals to be tested were fasted for 24 hours and the necessary groups were separated. 0.5 and 1 ml / kg doses of sesame oil and 20 mg / kg doses of famotidine orally administrated to the rats. After five minutes, indomethacin was administered to induce damage and it was waited for 6 hours. At the end of 6 hours, the animals were sacrificed and the stomachs removed. The stomaches was washed and ulcer areas were identified on the millimeter paper (Halici et al., 2011; Karakus et al., 2009).

BIOCHEMICAL INVESTIGATION OF STOMACH TISSUES

The biochemical enzymes such as catalase, GR, myeloperoxidase and the amounts of GSH, LPO were determined after the macroscopic analysis. The stomach tissues were ground to prepare the tissue homogenates with liquid nitrogen in a mortar. Then, 0.5 g tissue was kept under 4.5 ml of appropriate buffer.

Ultra-turraks homogenizer were used to homogenize the stomach tissues. Filtration and homogenization process were carried out at 4°C. Then, these supernatants were used in order to determine enzymatic activities (catalase, GR, myeloperoxidase) and amounts of GSH, LPO. All biochemichal assays were analyzed by using a UV–VIS spectrophotometer.

Catalase (CAT) activity

Decomposition of H_2O_2 in presence of catalase was at 240 nm (Aebi, 1984). Catalase activity was defined as the amount of enzyme required to decompose 1 nmol of H_2O_2 per minute, at 25°C and pH 7.8. Results were expressed as mmol/min/mg tissue.

Myeloperoxidase (MPO) activity

According to the modified method of (Bradley et al) myeloperoxidase activity was measured (Bradley et al., 1982). The homogenized samples were frozen and thawed three times, and centrifuged at 1500 g for 10 min at 4°C. Myeloperoxidase activity in the supernatant was determined by adding 100 ml of the supernatant to 1.9 ml of 10 mmol/l phosphate buffers (pH 6.0) and 1 ml of 1.5 mol/l o-dianisidine hydrochloride containing 0.0005% (w/v) hydrogen peroxide. The changes in absorbance at 450 nm of each sample were recorded on a UV–VIS spectrophotometer. Myeloperoxidase activity in tissues was expressed as μmol/min/mg tissue.

Glutathione reductase (GR) activity

GR activity was determined by measuring the rate of NADPH oxidation at 340 nm (Carlberg and Mannervik, 1985). Results were expressed as the amount of enzyme that catalyzes the oxidation of 1 μmol/min/mg tissue of NADPH.

Total glutathione (GSH) determination

The amount of GSH in the gastric mucosa was measured according to the method described by (Sedlak and Lindsay, 1968) with slight modifications. The stomach tissues were homogenized in 2 ml of 50 mM Tris–HCl buffer containing 20 mM EDTA and 0.2 M sucrose, pH 7.5. The homogenate was centrifuge at 4200 rpm for 40 min at 4°C. The supernatant was used to determine GSH using 5,5′-dithiobis (2-nitrobenzoic acid) (DTNB). Absorbance was measured at 412 nm. The results of the GSH level in the gastric mucosa were expressed as nmol/g tissue.

Lipid peroxidation (LPO) determination

The level of gastric LPO was determined by estimating MDA using the thiobarbituric acid test (Ohkawa et al., 1979). Namely, the rat stomachs were promptly excised and rinsed with cold saline. To minimize the possibility of interference of hemoglobin with free radicals, any blood adhering to the mucosawas carefully removed. The stomach weighed and homogenized in 10 mL of 100 g/L KCl. The homogenate (0.5 mL) was added with a solution containing 0.2 mL of 80 g/L sodium laurylsulfate, 1.5 mL of 200 g/L acetic acid, 1.5 mL of 8 g/L 2-thiobarbiturate and 0.3 mL distilled water. The mixture was incubated at 98°C for 1 h. Upon cooling, 5 mL of n-butanol: pyridine (15:l) was added. The mixture was vortexed for 1 min and centrifuged for 30 min at 1875 x g. The absorbance of the supernatant was measured at 532 nm. The standard curve was obtained by using 1,1,3,3-tetramethoxypropane. The recovery was over 90%. The results were expressed as nanomol MDA per gram tissue (nmol/g tissue).

Statistical analyses

Data were subjected to one-way variance analyzes (ANOVA) using SPSS 11.0 software. Differences between the results were tested using the LSD option and differences at $P<0.05$, 0.01 and 0.001 were considered significant.

RESULTS

Gastroprotective effect of sesame oil on indomethacin induced gastric damage

The protective effect of both doses of sesame oil was determined. (**Table 1 and Fig. 1**). There were quite a lot of hyperamia in the indomethacin group but this rate was very low in the treatment groups. The ulcer index of sesame oil at doses of 0.5 and 1 ml/kg were 21.0±0.05 and 16.0±0.05, respectively. In the indomethacin and famotidine groups were also found 40.9±0.2 and 7.0±0.05. Famotidine and both doses of sesame oil reduced the ulcer areas at a rate of 82.9% and 48.7% and 60.9%, respectively, compared to the indomethacin group (**Table 1**). These results suggest that it is protective effect of sesame oil such as famotidine.

Comparison of biochemical parameters in rats' stomach tissues

The enzyme activities in rat tissues were determined to determine the effects of antioxidant defense systems. The results are presented in Figs. 2-6 and Table 2. Fig. 3 shows that IND administration increased the LPO level compared to healthy rat tissues. In contrast to IND, all doses of sesame oil and other standard drug, famotidine, reduced the LPO level in

rat stomach tissues. These results showed that sesame oil has a reducing effect on LPO in tissues. Nevertheless, GR enzyme activity and GSH levels were found to be low in the tissue of rats given IND compared to healthy rat tissues (Fig. 2 and Fig. 6).

However, the activities of this enzyme and the level of GSH were increased by the administration of all doses of sesame oil and standard anti-ulcer drug (positive control, famotidine) compared to the stomach tissues of rats given IND. On the other hand, as can be seen from **Fig. 5**, IND increased the CAT activity in comparison to healthy stomach tissues. In contrast to the tissue of rats given IND, all doses of sesame oil and famotidine reduced the activity of this enzyme ($p<0.05$).

The present study also assessed the changes of MPO activity in gastric tissues, which is an index of neutrophil infiltration into inflammatory tissues (**Fig. 4**). As shown in this figure, the injection of IND increased MPO activity compared to healthy rat tissues. All doses of sesame oil and famotidine significantly decreased the MPO activity ($p<0.05$).

DISCUSSION

In the present study, the gastroprotective effects of two doses (0.5 and 1.0 ml/kg body weight) of sesame oil were determined on indomethacin-induced gastric damage in rats. The gastric damage in rats is induced by indomethacin. (**Table 1**). On the other hand, in other studies, the effect of sesame oil on the gastric damage induced by different routes was determined. (Hsu et al., 2009a; Hsu et al., 2009b; Hsu, 2011). (Hsu et al) (Hsu, 2011) reported that daily consumption of a recommended dose of sesame seed oil or sesamol may be beneficial in protecting against gastric mucosal damage induced by alcohol or some non-steroidal anti-inflammatory drugs (diclofenac and aspirin). The protective effect of vegetable oils against gastric damage was determined in various studies. (Cargile et al., 2004; De la Lastra, 2002; Odabasoglu et al., 2008). However, mechanisms by which the vegetable oils yield tissue protective effects in response to gastric ulcer caused by indomethacin need to be elucidated.

It was determined that gastric ulcer occurred due to inhibition of prostaglandins and production of COX 1 and COX 2 (Whittle, 1981). In addition, reactive oxygen species have been implicated in gastric damage caused by IND, ethanol, or other causes. (Carvalho et al., 2007; Halici et al., 2011; Wagner et al., 1995; Yoshikawa et al., 1993). IND initiates lipid peroxidation by producing reactive oxygen in gastric damage and interferes with antioxidant systems. (Albayrak et al., 2010; Atalay, 2016; Muthuraman, 2010; Yoshikawa et al., 1993). In addition, Yadav et al. (Yadav et al., 2013) showed that IND induced oxidative stress, triggering mucosal TNF-α that activated NF-κB and JNK MAPK-signalling in mice. Similarly, our results showed that there was a significant ($p<0.05$) increase in the LPO level in the stomach tissues of rats given IND (**Fig. 3**). In contrast to IND, the administration of sesame oil and famotidine significantly ($p<0.05$) decreased the LPO level in stomach tissues. Similar effects, it was reported by different ulcer models (Hsu et al., 2013a; Hsu et al., 2009a; Hsu et al., 2008).

Organisms have many antioxidant defense mechanisms against reactive oxygen toxicity and tissue damage. GR and CAT are some of these antioxidant enzymes. The increase in CAT activity means that there is an increase in the amounts of H_2O_2. It is reported that superoxide radicals spontaneously convert to H_2O_2 and perhydroxyl ($HO_2^{\bullet}$) radicals in acidic media and this is fastest in pH 4.8 (Mahadik and Scheffer, 1996). In addition, superoxide and perhydroxyl radicals react with each other and H_2O_2 and O_2 occurs (Weiss and LoBuglio, 1982). Increased CAT activity in rat tissues subjected to IND is a consequence of exposure to oxidative stress. the catalase enzyme has the ability to detoxify H_2O_2 through the accumulation of H_2O_2. Thus entering the reaction with H_2O_2 to form water and molecular

oxygen. It can also form methanol, ethanol, formic acid or phenols by donating hydrogen (Bradley et al., 1982; Elliott and Wallace, 1997).

In the present study, we established that all doses of sesame oil and famotidine decreased CAT activity (**Fig. 5**). On the other hand, Chen et al. (Chen et al., 1998) suggested that CAT stimulates the expression of mRNA and the protein for COX-2 in the aortic smooth muscle cells of rats, despite not affecting the expression of either mRNA or the protein for COX-1. That is, CAT exerted a biphasic effect on prostaglandin synthesis and enhanced prostaglandin production at low concentrations. This suggests that, at low concentrations, increased CAT activity may cause inflammation as reflected by increased COX-2 activity. One of the factors causing the IND-induced gastric ulceration process is possibly an augmentation of CAT activity, which was ascertained in the results of the present experiment.

The pleiotropic role of reduced glutathione includes the maintenance of cells in a reduced state, serving as an electron donor for certain anti-oxidative enzymes (e.g., glutathione peroxidase) and the formation of conjugates with some harmful endogenous and xenobiotic compounds via the catalysis of GST (Odabasoglu et al., 2008; Pourahmad et al., 2010). The gastroprotective effects of sesame oil can also be supported by GSH levels in rat gastric tissues containing IND (**Fig. 5**). Furthermore, treatment with sesame at all doses increased GSH levels, which were decreased by IND in the stomach tissues. Likewise, it has been reported that GSH level was decreased by IND (Albayrak et al., 2010; Halici et al., 2011; Kaplan et al., 2012; Polat et al., 2011; Suleyman et al., 2012). Hsu et al. (Hsu et al., 2008) reported that sesamol significantly maintained the reduced mucosal glutathione levels in diclofenac-treated stomachs of rats.

Glutathione levels are maintained by two systems. One is de novo synthesis from building blocks, glutamate, cysteine and glycine, via two ATP-consuming steps involving c-glutamylcysteine synthetase and glutathione synthetase. The other constitutes a recycling system involving glutathione reductase, which is a flavoprotein and reduces oxidized glutathione (GSSG) back to reduced glutathione in an NADPH-dependent manner (Shacter et al., 1991). It is known that indomethacin increases the lipid peroxidation in the gastric tissues (Chattopadhyay et al., 2006; De la Lastra, 2002; Odabasoglu et al., 2008). Sesame seed oil has been regarded as a daily nutritional supplement to increase cell resistance to lipid peroxidation (LPO). The antioxidants in sesame seed oil include sesamin, sesamolin, sesamol, and tocopherol (Hsu, 2011). α-Tocopherol, which is an important constituent of the vegetable oils and sesame oil, is the primary fat-soluble antioxidant and one of its principal functions is thought to be protection of membranes from oxidative damage (Ingold et al., 1987). α-Tocopherol reduces the lipid peroxidation by donating one electron into free radical chains, finally, α-tocopherol radicals occurs in tissues. These radicals are regenerated by GSH in tissues (Niki et al., 1982) and results in an increase in the level of GSSG, oxidized form of GSH in tissues. The companion enzyme GR utilizes NADPH to reduce one molecule of GSSG to two molecules of GSH (Davies, 2000; Mates et al., 1999). Thus, GR indirectly participates in the protection of cells against oxidative stress. Odabasoglu et al (Odabasoglu et al., 2008) showed that α-tocopherol administration increase GR activity in gastric tissues, however, there was found interesting results for vegetable oils on the gastric GR activity. They are recorded that corn oil increased the activity of this enzyme, whereas sunflower and olive oils showed an inhibiting effect on GR activity. In similarly, in the present study, it is determined that the administration of sesame oil and famotidine strongly decreased GR, whereas indomethacin increased the activities of this enzyme (**Table 2 and Fig. 6**). Vegetable oils contain components in different proportions and these components affect biological activities. So that the inhibitory effect of GR activity may be due to these components and may indirectly cause inhibition by suppression of the GR gene. These results may be the basis for research on the effects of sesame oil and its components.

The MPO enzyme is commonly used as an index of neutrophil infiltration in various gastric injuries (Albayrak et al., 2010; Atkuri et al., 2007). As shown in **Fig. 4**, MPO activity was found to be very high in rat tissues administered with IND. This increase is due to neutrophil infiltration into damaged tissue. The administration anti-ulcer drugs decrease the MPO activity (Atalay, 2016; Potrich et al., 2010; Yadav et al., 2013). According to the results of the study, the antiulcer drugs used significantly reduced the increase.

The release of MPO enzyme is another indication of ulcer formation, with NSAIDs such as IND also exerting their effects via inhibition of MPO pathways (Atalay, 2016; Atkuri et al., 2007; Karaca et al., 2009; Karakus et al., 2009; Mizoguchi et al., 2001; Yadav et al., 2013). But, the opposite of IND, sesame oil strongly decreased the MPO activity compared to healthy stomach tissues. This data supports that sesame oil effect on the MPO activity. In similar to the present results, it has been found that sesamol, the lignan of sesame oil, administration decreased the MPO activity in aspirin-induced gastric tissues (Hsu et al., 2009a).

As a result, the damage to the rat stomach was significantly reduced with the treatment group. In the IND-induced ulcer model, the antioxidant systems were adversely affected. The data obtained may be related to the gastroprotective property of sesame oil.

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DISCLOSURE STATEMENT

All authors declare that there are no conflicts of interest.

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FIGURE LEGENDS:

Figure 1. Ulcerous areas in the gastric tissues of indomethacin (IND)-induced rat by orally administrated two doses sesame oil (SO) and single dose of famotidine (FAM). Sections of the gastric tissues after IND-administration were obtained from some experimental groups. The A and B sections show some ulcerative areas: A, the control group (IND, 25 mg/kg body wt.); B, IND-administrated plus SO group (1 ml/kg body wt.).

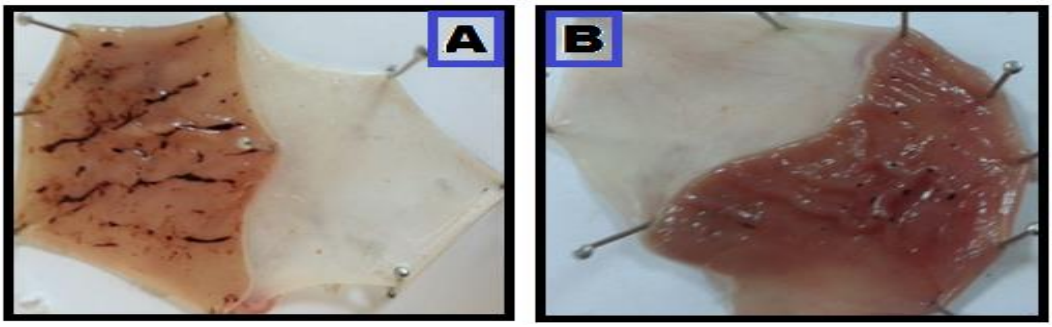
Figure 2. Effects of different doses of sesame oil (SO) and single dose of famotidine (FAM) on the amount of glutathione (GSH) in rat's indomethacin (IND)-induced gastric tissue. Means in the same column by the same letter are not significantly different to the Duncan test ($p<0.05$). Results are means ± SE of three measurements.

Figure 3. Effects of different doses of sesame oil (SO) and single dose of famotidine (FAM) on the amount of lipid peroxidation (LPO) in rat's indomethacin (IND)-induced gastric tissue. Means in the same column by the same letter are not significantly different to the Duncan test ($p<0.05$). Results are means ± SE of three measurements.

Figure 4. Effects of different doses of sesame oil (SO) and single dose of famotidine (FAM) on the activity of myeloperoxidase (MPO) enzyme in rat's indomethacin (IND)-induced gastric tissue. Means in the same column by the same letter are not significantly different to the Duncan test ($p<0.05$). Results are means ± SE of three measurements.

Figure 5. Effects of different doses of sesame oil (SO) and single dose of famotidine (FAM) on the activity of catalase (CAT) enzyme in rat's indomethacin (IND)-induced gastric tissue. Means in the same column by the same letter are not significantly different to the Duncan test ($p<0.05$). Results are means ± SE of three measurements.

Figure 6. Effects of different doses of sesame oil (SO) and single dose of famotidine (FAM) on the glutathione reductase (GR) enzyme in rat's indomethacin (IND)-induced gastric tissue. Means in the same column by the same letter are not significantly different to the Duncan test ($p<0.05$). Results are means ± SE of three measurements.



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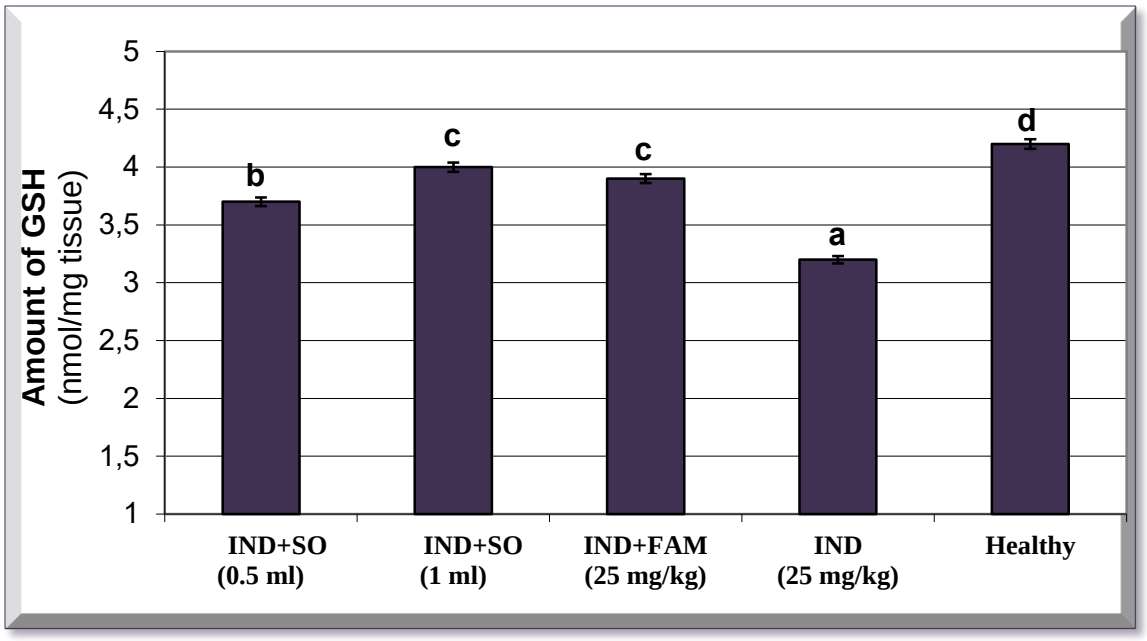

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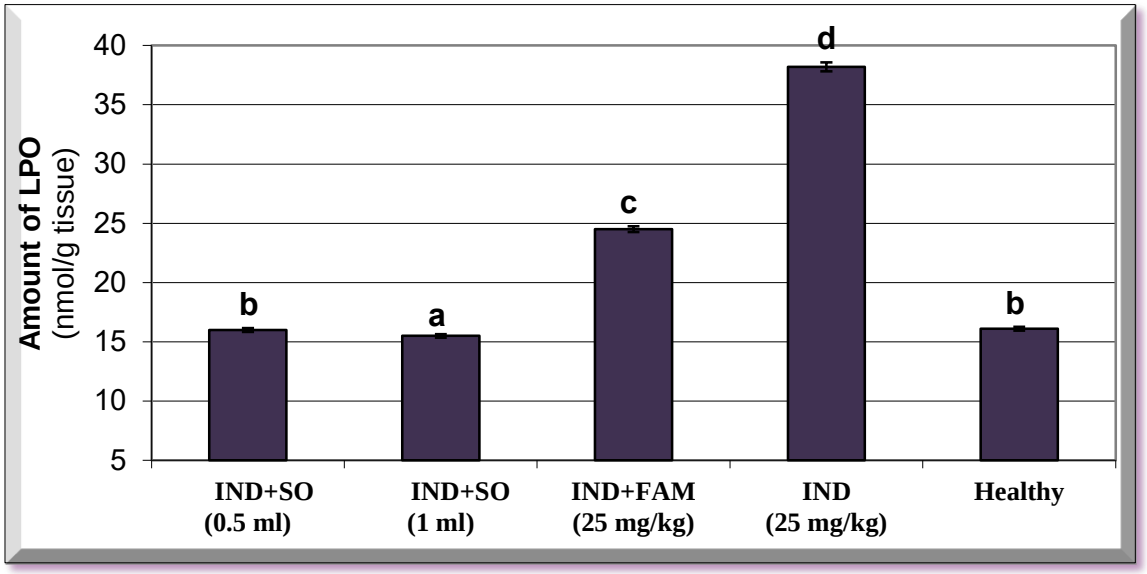

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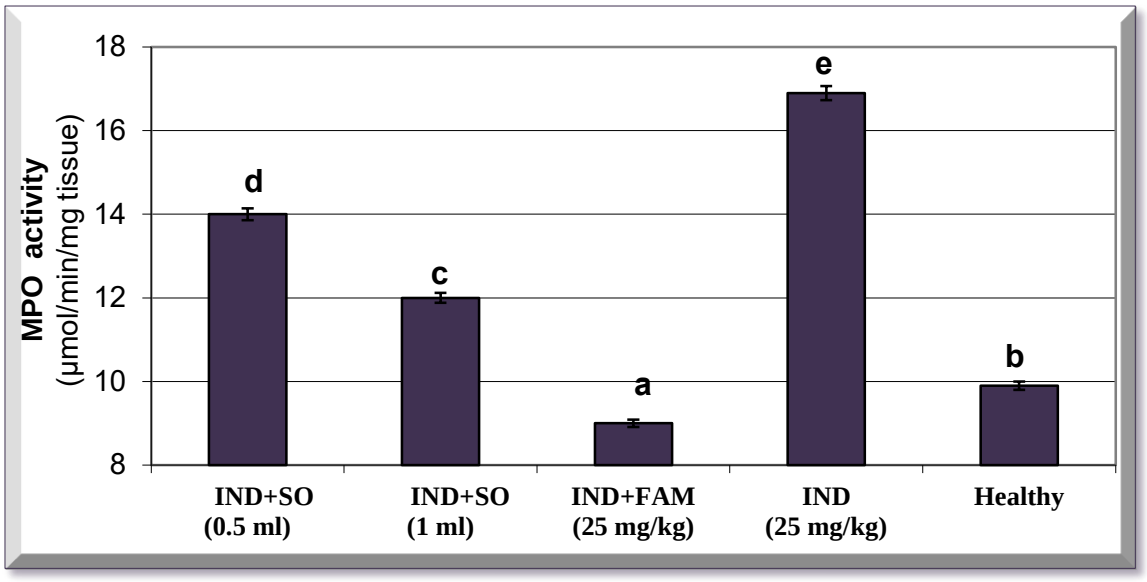

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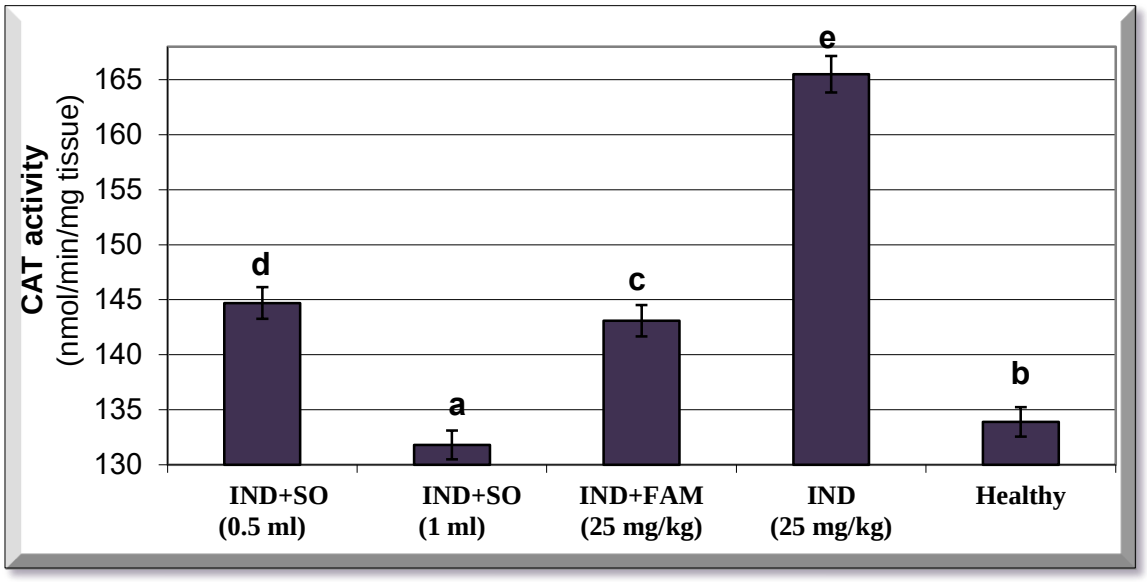

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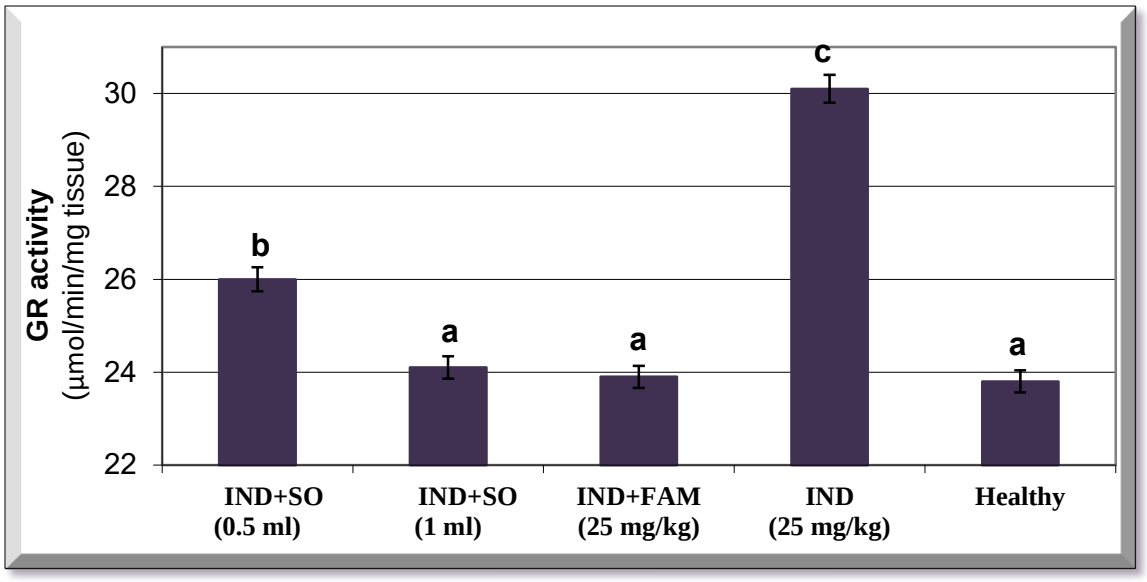

Figure 6. Effects of different doses of sesame oil (SO) and single dose of famotidine (FAM) on the glutathione reductase (GR) enzyme in rat's indomethacin (IND)-induced gastric tissue. Means in the same column by the same letter are not significantly different to the Duncan test ($p<0.05$). Results are means ± SE of three measurements.

Table 1. Effects of different doses of sesame oil (SO) and single dose of famotidine (FAM) on indomethacin (IND)-induced gastric damage in rats.

Treatment	N	Dose	Ulcer index (mm^2/rat)[a]	% Inhibition[b]
IND+SO	6	0.5 ml	21.0±0.05d	48.7
IND+SO	6	1.0 ml	16.0±0.05c	60.9
IND+FAM	6	25 (mg/kg body wt.)	7.0±0.05b	82.9
IND	6	25 (mg/kg body wt.)	40.9±0.2e	0
Healthy[c]	6	-	0.0±0.0a	-

Means in the same column by the same letter are not significantly different to the Duncan test $p<0.05$).
[a] Mean damage index ± SE of six animals in each group.
[b] % Inhibition in ulcer index in relation to indomethacin group.
[c] Nothing administrated. N: The number of rats.

Table 2. Effects of sesame oil (SO) treatments on changes in activities of myeloperoxidase (MPO), catalase (CAT), glutathione reductase (GR) and with levels of lipid peroxidation (LPO) and total glutathione (GSH) in rat's indomethacin (IND)-induced gastric tissue.

Treatment (Lung)	N	Dose	CAT activity (mmol/min/mg tissue)	Amount of LPO (nmol/g tissue)	MPO activity (µmol/min/mg tissue)	GR activity (µmol/min /mg tissue)	Amount of GSH (nmol/mg tissue)
IND+ SO	6	0.5 ml	144.7±0.2d	16.0±0.04b	14.0±0.05d	24.1±0.05a	3.7±0.02b
IND+ SO	6	1.0 ml	131.8±0.3a	15.5±0.02a	12.0±0.05c	26.0±0.2b	4.0±0.04c
IND+ FAM	6	25 (mg/kg)	143.1±0.3c	24.5±0.2c	9.0±0.06a	23.9±0.1a	3.9±0.03c
IND	6	25 (mg/kg)	165.5±0.2e	38.2±0.02d	16.9±0.7e	30.1±0.1c	3.2±0.03a
HEALTHY	6	-	133.9±0.3b	16.1±0.04b	9.9±0.1b	23.8±0.1a	4.2±0.02d

Means in the same column by the same letter are not significantly different to the Duncan test ($P<0.05$). Results are means ± SE of three measurements. N: The number of rats.