Gastroprotective effect of simvastatin against experimentally induced gastric ulcers in rats: Role of ATP-sensitive K⁺ channels

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Abstract: Simvastatin appeared to have additional benefits beyond their lipid lowering effects, which has led to interest in the use of this class of drugs outside the field of cardiovascular disease. Aim: This study aimed to investigate the possible gastroprotective effect of simvastatin against both indomethacin and cold restraint stress (CRS) induced gastric ulcers in rats and to study its effect on gastric mucosal malonaldehyde (MDA), nitric oxide (NO) and prostaglandin E₂ (PGE₂) levels in both ulcer models. Exploration of the possible contribution of ATP-sensitive K⁺ channels in this action. Design: 72 healthy, adult male albino rats were used. The rats were randomly assigned to vehicle (distilled water or carboxymethylcellulose (0.5%), simvastatin, simvastatin + glibenclamide (ATP-sensitive K⁺ channels blocker), pretreated groups for 7 days then ulcers were induced using oral indomethacin or cold restraint stress. Assessment of gastric lesions was done, gastric juice parameters (total acid output, pepsin activity and mucin content) were determined for each group using pyloric ligation method. Rats from simvastatin pretreated groups in both ulcer models were used for determination of gastric mucosal level of MDA (as indicator of lipid peroxidation), nitrite (as indicator of NO) and PGE₂ levels. Results: Simvastatin displayed significant (P<0.05) protection against gastric lesions induced by either indomethacin or exposure to cold restraint stress by correction of both ulcer score and the measured gastric juice parameters. This effect was partially blocked by coadministration of glibenclamide. Simvastatin significantly (P<0.05) reduced gastric mucosal MDA; significantly (P<0.05) increased in PGE₂ levels and corrected nitrite to near normal levels in both ulcer models. Conclusion: This study confirmed the gastroprotective effect of simvastatin in indomethacin induced ulcer in rats and proved it in CRS induced ulcer. The gastroprotective effect of simvastatin is mediated through opening of ATP sensitive K⁺ channels, free radical scavenging, increase in gastric mucosal PGE₂ and normalization of gastric mucosal NO in both ulcer models.

Keywords: indomethacin; cold restraint stress; NO; simvastatin; ATP-sensitive K⁺ channels and ulcer.

1. Introduction
Gastric ulcer is an illness that affects a considerable number of people worldwide. The etiological factors of this disorder include: stress, smoking, nutritional deficiencies, frequent and indiscriminate use of non steroidal anti-inflammatory drugs (NSAIDs) (Khazaei and Salehi 2006). The pathophysiology of gastric ulcer has generally focused on imbalance between aggressive and protective factors in the stomach (Lima, et al., 2006). The gastric ulcerogenic action of NSAIDs is believed to occur mainly due to their local inhibitory effect on gastric prostaglandin E₂ (PGE₂) and prostaglandin I₂ (PGI₂) that are the main inhibitors of gastric acid secretion (Bhargava, et al., 1973; Ribeiro-Rama., et al., 2009). Hypothermic-restraint stress ulcers (CRS) have been used as an experimental model in the evaluation of antiulcer activity in rats (Murakami et al., 1985). It induces ulcer through disturbance in the gastric mucosal microcirculation, enhancement of acid secretion, reduction in mucus production and abnormal gastric motility (Garrick, et al., 1986), free radicals formation (Bagchi, et al 1999) and decreased in prostaglandin synthesis (Bandyopadhyay, et al., 1999).

Statins (3-hydroxyl-3-methyl glutaryl-CoA reductase inhibitors) are a group of drugs that are originally designed to lower serum cholesterol level and have been recognized as the most efficient drugs for the treatment of hyperlipidemia(Heeba et al., 2009). Previous clinical trials have demonstrated that the therapeutic benefits of statins could not solely be explained by their inhibitory actions on cholesterol synthesis (Werner, et al., 2002; Wainwright, 2005). Clinical trials proved that they exhibit other effects unrelated to their lipid lowering effect (pleotropic effect) (Tamargo, et al., 2007). Simvastatin which has tested in this study is a commonly prescribed statin with antioxidant and anti-inflammatory properties (Ungureanu, et al., 2003; Franzoni, et al., 2003). Accordingly, this study aimed to investigate the possible gastroprotective
effect of simvastatin against indomethacin and CRS induced gastric ulcers in rats with exploration of the possible mechanisms underlying this effect.

2. Materials and methods

Drugs and chemicals

Simvastatin was obtained from (Pharco Egypt) as powder. Indomethacin was obtained from Sigma chemical Co. (St. Louis, MO. USA) and was suspended in carboxymethylcellulose 0.5 % (Na salts, Merck, Darmstadt, Germany). Glibenclamide powder, EIPICO, Egypt). Ether, from SD Fine chemicals (India). All drug solutions and suspensions were freshly prepared.

Animals

Seventy two adult male Albino rats weighing 180-200 grams were purchased from Abu-Rawash animal house (Giza- Egypt). Animals were given tap water ad libitum, fed with standard commercial rat chow and were left to accommodate for one week before dosing, kept 12 hours light / 12 hours dark regular cycle in partially humid and well aerated room. Protocol was approved by the local animal care committee at Zagazig University (Egypt). All experimental procedures were carried out in accordance with international guidelines for care and use of laboratory animals.

Experimental design

The rats were fasted for 24 hours prior to the experiment in meshbottomed cages to minimize corporophagia. The animals had free access to water except the last hour before the experiments. All experiments were performed during the same time of the day to avoid variations due to diurnal rhythms of putative regulators of gastric functions. The animals were randomly classified into nine groups (8 rats per each): (1) control group: in which the animals received distilled water orally for 7 days. (2) control indomethacin group(indom): the rats received oral indomethacin in a dose of 20 mg/kg in 2.5ml/kg of 0.5% of carboxymethylcellulose after daily administration of distilled water for 7 days. (3) Indomethacin + carboxymethylcellulose: in which ulcers were induced by indomethacin after 7 days of oral administration of carboxymethylcellulose 0.5% (the vehicle of both indomethacin and glibenclamide). (4) indomethacin + simvastatin (indom+ sim): in which animals were pretreated with 40 mg/kg simvastatin orally for 7 days then, gastric ulceration was induced by indomethacin administration. (5)indomethacin + simvastatin+ glibenclamide (indom+sim+giben): in which animals were concurrently pretreated with 40 mg/kg simvastatin and 5 mg/kg glibenclamide(KATP channels blocker) orally for 7 days then gastric ulcer was induced by indomethacin. (6) CRS: cold-restrained stress to induce gastric ulcer , the rats were immobilized in individual restraint boxes without possibility of visual contact (popovic’ et al.1997) and subjected to cold (4± 1) stress for 3.5 hours. This regimen of cold-restraint stress has been reported to produce gastric ulcers reliability in food-deprived rats (Senay and Levine 1967) (7) CRS+ carboxymethylcellulose: the rats received carboxymethylcellulose 0.5% orally for 7 days then ulcer was induced by CRS.(8) CRS+ simvastatin(CRS+sim): in which the ulcer was induced by CRS after 7 days of daily oral administration of 40 mg/kg simvastatin. (9) CRS+ simvastatin+ glibenclamide (CRS+ sim+ giben): in which the animals concurrently pretreated with simvastatin 40 mg/kg and 5 mg/kg of glibenclamide orally for 7 days then gastric ulcer was induced by CRS. It should be noted that all drugs, vehicle, distilled water were administered in a volume of 2.5 ml/kg via gavage. Doses of drugs were in homogeneity with previous reports (Tariq, et al., 2007; Aziz, 2009)

Pyloric ligation

Pyloric ligation was carried out before either indomethacin administration or exposure to CRS in order to collect gastric secretion (Alumets et al 1982). This was done under ether anesthesia, a midline abdominal incision was performed, the pyloric portion of the stomach was gently mobilized and carefully ligated with a silk ligature around the pyloric sphincter taking care not to interfere with gastric blood supply. Abdominal incision was sutured and the animals were allowed to recover from anesthesia.

Assessment of gastric mucosal lesions

Three hours later after administration of indomethacin or exposure of rats to CRS, rats of all groups were killed with an overdose of ether, their stomachs were rapidly removed, opened by an incision along the greater curvature and the gastric juice were collected, the stomachs rinsed with saline. Gastric tissues were pinned out flat on a cork board, the number and the severity of discrete areas of damage in the mucosa were scored by two trained independent observers who were unaware of the drug treatment, the ulcer score was determined according to the 1 to 5 scoring system devised by Wilhelm and Menasse-Gdynia 1972. (1) 1 or 2 minute, sporadic, punctuate lesion (2) several small lesion (3) one extensive lesion or multiple moderate sized lesions(4) several large lesions (5)several large lesions with stomach perforation.

Analysis of gastric juice

Gastric juice from each animal was centrifuged at 1000 g for 10 minutes to remove any solid debris and the volume of the supernatant was

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measured. The supernatant was then assayed for total acid concentration (Hara et al. 1991), the total acid output was calculated by multiplying the volume of gastric juice by the total acid concentration also pepsin activity (Sanyal et al. 1971) and mucin content (Winzler, 1955) were determined in the obtained supernatant.

**Biochemical analysis of gastric mucosa**

The stomach of each animal was divided into two parts. Gastric mucosa of one part was scrapped and was immersed in indomethacin (10μg/ml) and was immediately stored at -80 °C, afterwards, homogenized in 2 ml normal saline containing 0.1 M dithiothreitol and centrifuged at 2000g for 10 minutes at room temperature. The supernatant was used for determination of prostaglandin E2 (PGE2) level by ELISA using PGE2 immunoassay kit (R&D systems, USA). The mucosa of the other part of the stomach was also scrapped, homogenized in cold potassium phosphate buffer (0.05 M, PH7.4) and centrifuged at 2000g for 10 minutes at 4°C; the supernatant was then kept at -80°C for measurement of malonaldehyde (MDA) (Mihara and Uchiyama 1978). Also the total nitrate/nitrite in the gastric mucosal homogenate was assayed after reduction of nitrate to nitrite using the cadmium reduction method (Sastry et al., 2002).

**Statistical analysis:**

Analyzed by One-way analysis of variance (ANOVA) followed by LSD test using SPSS for windows version 11.5. Differences were considered to be significant at P< 0.05.

**3. Results**

It is noted that carboxymethylcellulose 0.5% pretreated groups did not show any significant difference as compared to indomethacin group or CRS group in any of the parameters investigated in this study.

(A) Investigation of the involvement of ATP sensitive K⁺ channels in the gastroprotective effect of simvastatin on indomethacin and CRS induced gastric lesions

- **Fig (1):** histogram shows that either administration of indomethacin or exposure of rats to CRS induced high ulcer score 4.1±0.3 & 3.1±0.3 respectively when compared to control group. Pretreatment with simvastatin significantly reduced the ulcer scores in both group to 0.5±0.2 & 0.3±0.2 respectively. Co-administration of simvastatin and glibenclamide increased the ulcer score to 2.5±0.2 & 2.1±0.2 in both ulcer models respectively.

- **Fig (2, 3):** gross appearance of mucosal lesions on exposure to indomethacin or CRS (a), pretreatment with simvastatin (b) and coadministration of simvastatin and glibenclamide (c) respectively.

(B) Effect of simvastatin on changes in gastric juice contents induced by indomethacin:
Table (1) shows that Indomethacin significantly increased gastric juice total acid output as compared to control group 92.5±4.2mEq/3h versus 56.1±3.2mEq /3h. Pretreatment with simvastatin significantly reduced total acid output to 61.2±4.5 mEq /3h while concurrent use of simvastatin and glibenclamide raised the above mentioned value to 74.2±2.7mEq/3h.

Pepsin activity was significantly increased by indomethacin 208.4±10.7 µg/ml tyrosine versus 122±3.2 µg/ml tyrosine for the control group. Rats pretreated with simvastatin showed significant reduction in pepsin activity with mean ±S.E. 144.9±4.3µg/ml tyrosine, this reduction was attenuated by coadministration of glibenclamide with simvastatin with value 174.9±4.5µg/ml tyrosine.

Indomethacin significantly reduced gastric juice mucin content from 89.3±2.8mg% hexose for the control group to 46.2± 2.3 mg% hexose. In simvastatin pretreated rats, this value significantly raised to 83.3±1.8mg% hexose while concurrent administration of simvastatin and glibenclamide significantly decreased this value to 61.8± 2.1 mg % hexose.

Table (1): Effect of indomethacin, simvastatin, simvastatin + glibenclamide on the total acid output, pepsin activity and mucin content of gastric juice in rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total acid output (meq/3h)</th>
<th>Pepsin activity (µg/ml tyrosine)</th>
<th>Mucin content (mg%hexose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>56.1±3.2</td>
<td>122±3.2</td>
<td>89.3±2.8</td>
</tr>
<tr>
<td>Indom</td>
<td>92.5±4.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>208.4±10.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46.2±2.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indom+sim</td>
<td>61.2±4.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>144.9±4.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>83.3±1.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indom+sim+gliben</td>
<td>74.2±2.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>174.9±4.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>61.8±2.1&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a significantly different from control group at P < 0.05  
b significantly different from CRS group at P < 0.05  
c significantly different from CRS + simvastatin group at P < 0.05

(C) Effect of simvastatin on changes in gastric juice contents induced by CRS:

Table (2): shows that CRS significantly increased gastric juice total acid output as compared to control group 88.2±2.8 mEq/3h versus 56.1±3.2 mEq/3h. Pretreatment with simvastatin significantly reduced total acid output with mean ±S.E.62.2±2.9 mEq /3h while concurrent use of simvastatin and glibenclamide raised the above mentioned value to 77.7±3.2 mEq/3h.

CRS significantly raised the pepsin activity to 220.4±5.2µg/ml tyrosine versus 122±3.2 µg/ml tyrosine for the control group. Rats pretreated with simvastatin showed significant reduction in pepsin activity with mean ±S.E.152±4.3 µg/ml tyrosine. Concurrent administration of simvastatin and glibenclamide increased this value to 201±5.1 µg/ml tyrosine. Gastric juice mucin content was significantly reduced by CRS .It decreased from 89.3±2.8 mg% hexose for the control group to 48.3±1.8 mg% hexose. In CRS, simvastatin pretreated rats showed significant elevation in mucin content to 83.5±2 mg % hexose. Concurrent administration of simvastatin and glibenclamide significantly decreased this value to 59.8±2 mg% hexose.

Table (2): Effect of CRS, simvastatin, simvastatin + glibenclamide on the total acid output, pepsin activity and mucin content of gastric juice in rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total acid output (meq/3h)</th>
<th>Pepsin activity (µg/ml tyrosine)</th>
<th>Mucin content (mg%hexose)</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>56.1±3.2</td>
<td>122±3.2</td>
<td>89.3±2.8</td>
</tr>
<tr>
<td>CRS</td>
<td>88.2±2.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>220±5.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48.3±1.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>CRS+sim</td>
<td>62.2±2.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>152±4.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>83.5±2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CRS+sim+gliben.</td>
<td>77.7±3.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>201±5.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>59.8±2&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a significantly different from control group at P < 0.05  
b significantly different from CRS group at P < 0.05  
c significantly different from CRS + simvastatin group at P < 0.05

(2) Effect of simvastatin on gastric mucosal MDA level in both ulcer models: Figure (4): shows that both indomethacin and CRS significantly elevated the gastric mucosal MDA) to 61.05±1.9 and 62.5±1.3
(nmol/g wet tissue) respectively as compared to control group 20.1±0.8 nmol/g wet tissue. Simvastatin significantly caused reduction in the gastric mucosal MDA in both ulcer models to 35.3±0.1 and 30.2±1.3 nmol/g wet tissue respectively.

(3) Effect of simvastatin on gastric mucosal nitrite level in both ulcer models: Figure (5): shows that indomethacin significantly reduced gastric mucosal nitrite level from 169.9±3.7 nmol/g wet tissue for the control group to 80.3±2.6 nmol/g wet tissue. Rats pretreated with simvastatin showed significant increased in the gastric mucosal nitrite content to 152.7±4 nmol/g wet tissue. In contrast, CRS significantly increased it from 171.5±1.7 nmol/g wet tissue in control group to 371.5±4.5 nmol/g wet tissue. Rats pretreated with simvastatin showed marked reduction in gastric mucosal nitrite concentration to 219.6±4.8 nmol/g wet tissue.

(4) Effect of simvastatin on gastric mucosal PGE$_2$ level in both ulcer models: Figure (6): shows that both indomethacin and CRS significantly reduced the gastric mucosal PGE$_2$ content from 318±4.9 ng/g wet tissue for the control group to 102±5 ng/g wet tissue and 125.4±6 ng/g wet tissue for indomethacin group and CRS group respectively. Simvastatin significantly increased the gastric mucosal PGE$_2$ levels to 262.6±8.1 and 256±4.7 ng/g wet tissue for both groups respectively.

4. Discussion
The diversity of etiological factors underlying gastric ulcers and the complex nature of pathways participating in healing always make peptic ulcers treatment a complicated challenge (El-Moselhy et al., 2009). Maintaining equilibrium between aggressive and defensive factors is always a critical objective in peptic ulcer management (Glavin and Szabo, 1992).

The results of the present study showed either oral administration of indomethacin in rats or their exposure to cold restraint stress resulted in severe mucosal ulceration associated with significant increase in total acidity and pepsin activity and significant reduction in gastric juice mucin content.

Our work showed that simvastatin administered orally in a dose of 40 mg/kg for 7 days reversed all the deleterious effects induced by either indomethacin or CRS on both gastric mucosa and gastric juice contents. Tariq, et al. (2007) demonstrated that oral administration of simvastatin in doses of 20, 40, 60 mg/kg for 7 days significantly and dose dependently reduced gastric lesions induced by indomethacin and ethanol in rats, an effect accompanied by reduction in total acidity and volume of gastric juice. Heeba et al., 2009 illustrated that simvastatin in a dose of 10 mg/kg for two weeks decrease the ulcer index induced by indomethacin in rats with concomitant elevation in gastric juice mucin content. They found that neither total acidity nor pepsin activity were affected.

The present study found that the beneficial effects mediated by simvastatin on ulcer score or on...
the measured parameters of gastric juice in both ulcer models were partially blocked by co administration of glibenclamide (ATP sensitive K^+ channel blocker) which indicates that some of the gastroprotective effect of simvastatin is mediated through activation of ATP sensitive K^+ channels.

Different researches have demonstrated antulcer activity of some K_{ATP} channel openers like cromakalim (Goswami et al., 1997), diazoxide (Toroudi et al., 1999) and nicorandil (Patel et al., 2001). Zhao et al., 2006 and Yang, et al., 2007 illustrated that simvastatin was able to reduce the myocardial no reflow after ischemia and reperfusion through activation of K_{ATP} channels. The suggested protective effect of ATP sensitive K^+ channels on ulcerative lesions mediated by simvastatin may be attributed to increase gastric mucosal blood flow offering more resistance to ulcer (Ismail et al., 2007). Furthermore, K_{ATP} channels openers decreased the gastric hypermotility induced by activation of vagus nerve in CRS (Garrick et al., 1986).

The ability of glibenclamide to partially block the inhibitory effect of simvastatin on total acidity may be due to the fact that some of the potent gastric acid inhibitors as prostaglandins (Peskar et al., 2002), adrenomedullin and CGRP (Rossowski et al., 1997; Sakai, et al., 1999), act through K_{ATP} channels. The results of the present work revealed that glibenclamide partially abolished the reduction in pepsin activity mediated by simvastatin. CGRP which acts through K_{ATP} channels was found to inhibit pepsin secretion (Kraenzlin, 1985). K_{ATP} channel openers were known to interfere with Ca^{++} ion influx and to antagonize mobilization of Ca^{++} bound to intracellular stores leading to reduction in free cytosolic Ca^{++} ion important for gastric acid and pepsin secretion (Miyamoto., et al., 1992; Bose et al., 2003). The decreased gastric acidity may be a cause as its presence is essential for cleavage of pepsinogen to active pepsin (Morsy and Fouad 2008).

The ability of glibenclamide to block the stimulatory effect of simvastatin on gastric juice mucin is compatible with a previous report which illustrated that eugenol (active ingredient of Clove oil) increased gastric mucin through ATP sensitive K^+ channels (Morsy and Fouad 2008)

The result of the present work showed significant elevation in MDA level , an indicator for lipid peroxidation which is a well established mechanism for cellular injury (Kwiecien et al., 2001), in both ulcer models. This was in accordance with Vaananen ., et al.,1991 who proved that the gastrotoxic effect of NSAID was mediated through induction of reactive oxygen metabolites which promote lipid peroxidation , Tandon et al.( 2004) who stated that there are positive correlation between the level of gastric mucosal lipid peroxidation products (marker of oxidative stress) and stomach damage in CRS in rats.

The result of the present study showed that simvastatin pretreatment caused significant reduction in MDA level in both ulcer models as compared to non treated control groups and it was reported that simvastatin possesses free radicals scavenger activity (Haendeler et al., 2004). This suggests that simvastatin afforded part of its gastroprotective effect in both ulcer models via antioxidant activity.

NO is a double edge weapon exerting either protective or destructive effects depending on the extent on NO synthesis (Tariq et al., 2007). It has been reported that NO generated from eNOS play an important role in gastric ulcer formation and healing (Ma and Wallace 2000) whereas NO generated from iNOS participate in ulcer formation through the production of oxygen derived radical formation and their cytotoxic action (Cho 2001).

The result of the present work showed marked reduction in nitrite level (as indicator of NO) in indomethacin treated group. This is attributed to the ability of indomethacin to upregulate the endothelin-1 leading to decrease production of gastric mucosal NO (Slomiany and Slomiany 2000) while nitrite level is markedly elevated in CRS which occurred due to stimulation of iNOS which reacts with superoxide to form peroxynitrite (potent cytotoxic oxidant) causing gastric damage (Lanas 2008). Simvastatin was able to normalize the nitrite levels in both ulcer models. It increased NO level in indomethacin treated group. Similar finding was observed by Heeba et al. (2009), while it deceased NO level in CRS group. Madonna et al., 2005 illustrated that simvastatin attenuates expression of cytokine iNOS in embryonic cardiac myoblasts.

Earlier researches demonstrated that PGE_2 influence virtually every component of the mucosal defense ; stimulate mucus, bicarbonate ; maintaining of mucosal blood flow ; enhancing the resistance of the epithelial cells to injury induced by cytokines (Miller., 1983)

In the present study , oral administration of indomethacin resulted in significant reduction in gastric mucosal PGE_2 level , through non selective inhibition of cyclooxygenase (Schmassmann et al., 1998) and the same in CRS rats. Bandyopadhyay et al. (1999) attributed this effect to accumulation of hydrogen peroxide (a potent PG biosynthesis inhibitor). Rats pretreated with simvastatin showed significant increase in PGE_2 level in both types of ulcers. NO was reported to increase PGE_2 biosynthesis in vivo through CGMP independent mechanism and it is
possible to assume that NO might regulate the release and or the biosynthesis of PGE2 in the stomach after damage (Takeuchi et al., 1999). Chen, et al., 2004 proved that statins induce cyclooxygenase -2 gene expressions and PGE2 release in murine macrophage.

**Conclusion:** the results obtained from this study confirmed the gastroprotective effect of simvastatin in indomethacin induced ulcer and proved it in CRS induced ulcer. This effect is mediated through ATP sensitive K+ channel opening activity, free radical scavenging, decrease in total acid output and proteolytic activity, increase in gastric juice mucin content, increase in gastric mucosal PGE2, returning of gastric mucosal NO to normal values in both ulcer models.

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