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Original Article

A Structural Study of the Protective and Curative Role of Curcumin on Indomethacin Induced Gastric Ulcer in Adult Male Albino Rats: a Light and Scanning Electron Microscope study

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ABSTRACT

Background: The use of medicinal plants or their active components is becoming an increasingly attractive approach for the treatment of various disorders including Peptic ulcers (a group of gastrointestinal erosions with increasing prevalence all over the world). One of these natural derivatives is Curcumin. It proved to have a potent anti-inflammatory and antioxidant capacities at both neutral and acidic pH. Hence, it can be used in treatment of peptic ulcers.

Aim of the Work: The use of Curcumin for the treatment of acute and chronic ulcers still needs further investigations to validate its clinical application. So, this research was planned to clarify the role of Curcumin in both prevention and treatment of Indomethacin- induced gastric ulcer in male albino rats by using the light and scanning electron microscopes.

Material and Methods: Thirty adult male albino rats were used in the present study. They were divided into 5 groups: A control group and a group in which experimental gastric ulcer was induced using the non-steroidal anti-inflammatory drug (NSAID) Indomethacin. This group was further subdivided into group (a) without protection and group (b) receiving Curcumin protection prior to Indomethacin administration. The last group was the healing group in which the rats were further subdivided into: group (a) auto-healing group and group (b) receiving Curcumin for ten days following Indomethacin administration.

Results: In the experimental Indomethacin gastric ulcer induction group, acute forms of gastric ulceration were seen, destruction of the gastric mucosa and loss of mucosal cellular architecture were detected. In the group receiving protection with Curcumin, less severe forms of gastric ulceration either in size or extent were observed; decrease in mucosal congestion was also detected. These findings were analyzed statistically and proved to be significant ($p<0.01$). In the auto healing group, healing appeared unorganized with scar formation, while in the group receiving protection by Curcumin a more organized healing and a well-formed membrane was seen covering the ulcer area with no evidence of scarring. Some animals even showed complete healing. This healing progress was also statistically significant ($p<0.05$) and give an optimistic prospect in decreasing ulcer recurrence.

Conclusion: Curcumin proved to play a role in both prevention and treatment of Indomethacin- induced gastric ulcer through its antioxidant and anti-inflammatory properties.

Key Words: Curcumin, Indomethacin, Gastric ulcer, Prevention, Treatment, Male rats.

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INTRODUCTION

Peptic ulcers (PU) are group of gastrointestinal erosive disorders that may range from just a mild affection of the lining mucosal surface to severe forms that may extend till the serosa or even rupture resulting in severe bleeding *(Tarnawski, 2005)*. For decades it was believed that gastrointestinal ulcerations were caused by the excessive secretion of gastric acid *(Wallace & Granger, 1996)*. However, recent studies demonstrated that they were caused by an imbalance between aggressive factors, such as smoke, anti-inflammatory drugs, alcohol, stress, fatty foods and Helicobacter pylori infection on one hand and the natural gastrointestinal defensive mechanisms on the other hand. Exogenous aggressive factors trigger tissue necrosis through mucosal ischemia, free

radical generation and cessation of nutrient delivery. As the prevalence of PU increases over time, it has a worldwide significant impact on the basic health, economic systems and on patient's life quality *(Yuan et al., 2006)*.

The employ of medicinal plants or their active ingredients has become a progressively more used method for the treatment of various disorders including Peptic ulcers. Among these alternative approaches is the use of food derivatives which have the advantage of being relatively nontoxic *(Sharma et al., 1994 ; Durgaprasad et al., 2005)*. One of these natural derivatives is Curcumin (diferuloylmethane), a polyphenol derived from the herbal remedy and dietary spice turmeric. It has a long history of medicinal use in India and Southeast Asia and is known to exhibit a variety of pharmacological effects including anti-inflammatory, anti-cancer properties, anti-HIV and anti-infectious activities following oral or topical administration *(Jacob et al., 2007; Conteas et al., 2008; Gota et al., 2010)*. Curcumin proved to have a potent antioxidant capacity at neutral and acidic pH. Its mechanisms of action include inhibition of several cell signaling pathways at multiple levels, effects on cellular enzymes such as cyclooxygenase and glutathione S-transferases, immuno-modulation and effects on angiogenesis and cell–cell adhesion *(Harish et al., 2010)*.

Indomethacin, a non-steroidal anti-inflammatory drug (NSAID), has long been used in induction of gastric ulcers in experimental animals *(Aguwa, 1985; Dey et al., 2009)*. It causes gastric lesions through a number of mechanisms including inhibition of prostaglandin synthesis, generation of reactive oxygen species (ROS) and induction of apoptosis. It also increases lipid peroxidation, protein oxidation and depletion of glutathione resulting in oxidative damage of the gastric mucosal cells *(Chattopadhyay et al., 2006)*.

The use of Curcumin for the treatment of acute and chronic ulcers still needs further investigation in order to validate its clinical application as a remedy for peptic ulcer *(Mahattanadul et al., 2006; Itokawa et al., 2008)*. Consequently the aim of the present study was to investigate the structural effects of Curcumin in both prevention and treatment of Indomethacin -induced gastric ulcer in male albino rats by using the light and scanning electron microscopes.

MATERIALS AND METHODS

Thirty Animals: Thirty adult male albino rats of Sprague Dawley strain, aged 5-7months were used in the current study. Their average weight was 150-200 grams. Male rats were chosen because gastric ulcer is more common in males than in females *(Bao et al., 2010)* and also to prevent the effect of sex variation on the experiment's results. The animals were obtained from the Medical Research Center, Faculty of Medicine, Ain Shams University. The rats were housed individually in a plastic cage in the Medical Research Center and maintained on a standard pellet diet where they were allowed free access to water.

Drugs and chemicals: Indomethacin (Indocin SR Merck) was administered in a single oral dose of 50 mg/Kg body weight dissolved in 5 ml saline by using a gastric tube. This dose was sufficient to induce acute gastric ulcer *(Aguwa, 1985)*. A single oral dose of Indomethacin is readily absorbed, attaining peak plasma concentrations of 2 mcg/ml at about 2 hours. Orally administered Indomethacin capsules are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours according to drug information provided by Lexi-Comp. Merck manuals.

Curcumin Extreme™ was used in a daily dose of 40 mg/Kg body weight dissolved in 5ml saline administered by a gastric tube. This dose was chosen according to *Swarnakar et al. (2005)*. This brand was used as it has significantly greater bioavailability and absorption than other Curcumin products.

Experimental Design: The rats were divided into five groups, six animals in each:

Control group: Group I: The rats were only given normal saline orally.

Ulcer induction groups (II-a & b):
Group II-a: Received a single dose of Indomethacin (already mentioned). After six hours, the animals were sacrificed.
Group II-b: Received Curcumin for 10 days and then they were given a single dose of Indomethacin combined with a dose of Curcumin on the 11th day. Six hours later, the rats were sacrificed.

Ulcer healing groups (III-a & b): In these groups, the animals were administered a single

dose of Indomethacin. Ulcer formation was predicted by the apparent fatigue, weight loss and sometimes hematemesis in the experimental rats. Then the animals were further subdivided into 2 subgroups:

Group III-a: Is the auto-healing group in which the animals did not receive any treatment for ten days and were sacrificed on the 11th day of the experiment.

Group III-b: Curcumin was given for 10 days following Indomethacin administration. The animals were also sacrificed on the 11th day of the experiment.

All rats were kept under the same circumstances throughout the experiment. The animals were sacrificed by an overdose of ether anesthesia in the expected date. The anterior abdominal wall was opened and the stomach was collected, sectioned and processed for light and scanning electron microscopy studies.

Light and scanning electron microscopic studies: Some specimens of the stomach were fixed immediately in 10% formalin for seven days. They were processed and embedded in paraffin blocks. Serial sections 5 µm thick were sliced and stained with Hematoxylin and Eosin *(Drury & Wallington, 1980)*. The other specimens were washed twice in sterile phosphate buffer solution PBS. Thereafter, they were fixed in 1% glutraldehyde, 2% paraformaldehyde in phosphate-buffer at room temperature (pH 7.4) for 24 hours. They were then washed twice in buffered sucrose for 5 minutes each (0.1 M phosphate buffer, 5% sucrose solution). Postfixation was performed at 4°C for 60 min in phosphate-buffered 2% osmium. They were dehydrated in a graded series of ethanol (40, 50, 70, 80, 90 and twice in 100%) after rinsing in several changes in cold distilled water. Then the tissues were further dehydrated in ethanol - acetone (1:1) absolute solution for further 30 minutes, afterwards in absolute acetone 100% for additional 30 minutes 3 times 10 minutes each, then critically point dried in CO_2 drying apparatus CPD 030 and mounted on stubs, followed by being coated with gold sputter coater SCD005. The specimens were examined and photographed with Philips Scanning Electron Microscopy XL 3 at 30 kv *(Wahlqvist et al., 1996)*.

Statistical study: Statistical analysis was done by using SPSS statistical package version 16. The description of the categorical variables was done using the Bar chart. Chi square test (X^2) was used for comparison between categorical variables and the level of significance used was $p<0.05$ *(Morton et al., 1990)*.

The severity of Indomethacin- induced gastric ulcers in groups IIa and IIb as regards the ulcer depth, extent, congestion and lymphocytic infiltration was examined in every rat. Comparison was done between rats in each group separately and then between the two groups. Scores were comparatively given as mild=1, moderate=2 or severe=3.The results were further analyzed statistically. The Chi square test (X^2) was then applied.

The two ulcer healing groups (groups III-a & III-b) were also examined and the quality of the gastric ulcer healing was compared as regards the depth of healing, congestion, lymphocytic infiltration and persistent scarring. Every case in each group was examined separately. Comparison between rats of the same group and between both groups was done. Comparative scores were given 1= mild, 2=moderate and 3=severe. The results were then statistically analyzed using The Chi square test (X^2).

RESULTS

On examination, the control male rat gastric mucosa appeared covered with columnar epithelium with no goblet cells. The surface epithelium was interrupted by the openings of the gastric pits which were uniformly arranged parallel to each other, as they conveyed secretion from the gastric glands. The latter were present deep in the gastric mucosa and appeared rounded in the section. Deep in the mucosa was the muscularis mucosa formed of bundles of smooth muscles. The submucosa was found formed of loose areolar tissue with occasional cellular infiltration and blood vessels (Figs. 1-a, b). The mucosa and submucosa showed normal lymphocytic infiltration (Fig. 1-b). By scanning electron microscopy, the mucosal surface showed dome shaped cells with well- defined boundaries, studded with microvilli. The opening of the gastric pits could be identified. Mucus could be seen covering the surface of the gastric mucosa as well (Fig. 2).

In group II-a, in which Indomethacin was given without protection, different forms of acute ulcers were detected. There was either marked destruction of the mucosa, where only its basal zone containing the gastric glands was preserved (Fig. 3), or complete erosion of the mucosa and exposure of the muscularis mucosa to the surface (Fig. 4). Marked congestion and lymphocytic infiltration of the submucosa were observed (Fig. 5). The gastric mucosa of the same group showed different forms of ulceration in the scanning electron microscope. Acute ulcers with sharp edges and deep mucosal cracks were obvious (Figs. 6,7,8). The architecture of the mucosal cells appeared completely lost (Figs. 7,8). Some mucus remnants were noticed in few sections (Fig. 6). The eroded base of the gastric gland could be seen exposed to the surface (Fig. 9).

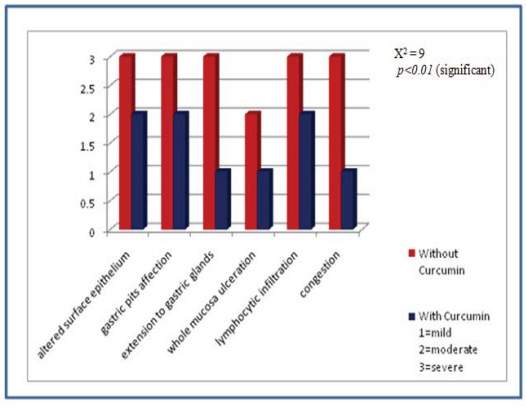
In group II-b, where protection with Curcumin was given to the rats for ten days prior to acute ulcer induction with Indomethacin, ulcers of different grades were also seen but in a less severe form than group II-a. Ulcers in the form of just erosion of the surface epithelium (Fig. 10) or destruction of the gastric gland pits with preservation of the glands at the base of the mucosa were detected (Figs. 11,12). No evidence of congestion or vascular exudates, either in the basal layer of the mucosa or the submucosa was an important observation (Fig. 12). However, lymphocytic infiltration in these layers was discovered (Figs. 10,12). The scanning electron microscope of gastric mucosa confirmed that the grades of ulcerations were less extensive than group II-a either in size or extent (Figs. 13,14,15). No signs of complete mucosal destruction were detected. The lining mucosal cells preserved their normal dome shape contour and their microvilli in some regions nearby the ulcer. The mucus covering could still be identified (Figs. 13,14,16).

The severity scores of Indomethacin- induced gastric ulcer as regards the ulcer depth, extent, congestion and lymphocytic infiltration was examined in every rat and was compared statistically in groups II-a and II-b; without and with Curcumin protection respectively. Statistically significant results were obtained (X^2=8.8, $p<0.05$) (Bar chart 2).

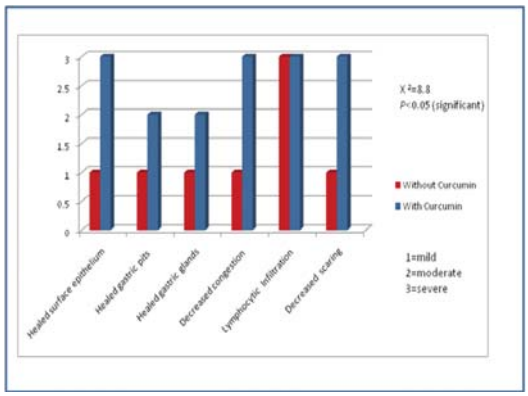
Moving to the healing groups, signs of healing were seen in the form of regeneration of the mucosal epithelium in the auto- healing group (III-a); nevertheless, the regenerated region did not regain a normal architecture (Fig. 17). Congestion and exudation from blood vessels as well as lymphocytic infiltration were still detected in the mucosa and submucosa (Fig. 18). These healing signs were confirmed by the scanning electron microscope where the gastric mucosal glands showed sprouts of regenerating cells from their bases (Fig. 19). Gastric neck cells were regaining their normal dome shape whereas signs of surface epithelium oedema were still observed (Fig. 20). Reappearance of the mucus covering was noticed in some sections (Figs. 21, 22). The ulcer scar could be identified on the surface of the mucosa (Fig. 22).

In the healing group with Curcumin (III-b), more organized healing was detected. A well formed membrane was seen creeping on the mucosal surface (Figs. 23, 24). No evidence of congestion or exudation in the submucosa was identified (Fig. 23). Marked filling and sprouting of regenerating cells from the base of gastric glands was obvious by scanning electron microscope (Fig. 25). The surface epithelium regained its normal architecture with reappearance of mucus covering (Fig. 26). The ulcer region could no longer be identified on the mucosal surface (Fig. 27).

The two ulcer healing groups (groups III-a & b) were also examined as regards the quality of gastric ulcer healing scores: the congestion, lymphocytic infiltration and persistent scarring. Statistically significant results were obtained (X^2=8.8, $p<0.05$) (Bar chart 2).



Bar Chart 1: Comparing the Indomethacin- induced gastric ulcer without and with Curcumin protection; Groups II-a and II-b respectively as regards the ulcer's severity.



Bar Chart 2: Comparing the Indomethacin-induced gastric ulcer healing as regards the quality of ulcer healing, without and with Curcumin; Groups III-a and III-b respectively.

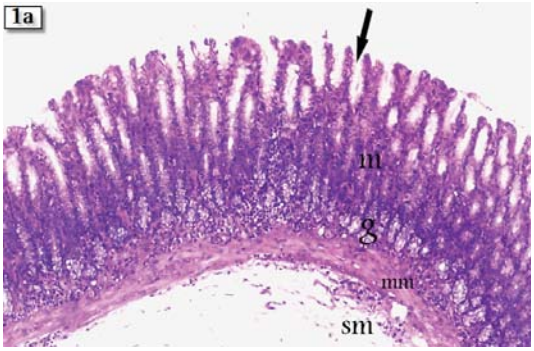


Fig. 1-a: A photomicrograph of a control male rat gastric mucosa, showing the mucosa (m) with its lining epithelium. Gastric glands (g) are seen at the base of the mucosa, with their neck opening to the surface through gastric pits (arrow). These pits are uniformly arranged parallel to each other. Notice that the muscularis mucosa (mm) is formed of smooth muscle fibres and the submucosa (sm) is formed of loose areolar connective tissue. Hx. & E.; X100

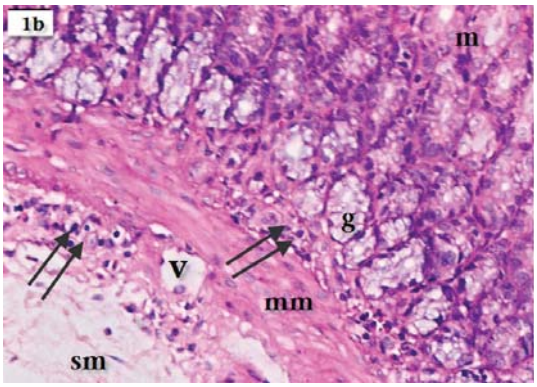


Fig. 1-b: A higher magnification of the previous fig. showing the mucosa (m) with gastric glands (g) at its base where they appear circular in cross section. Notice that the muscularis mucosa (mm) is formed of smooth muscle fibres, the submucosa (sm) is formed of loose areolar connective tissue. The double arrows point at the lymphocytic infiltration normally present in the mucosa and submucosa. Blood vessels (v) are also seen . Hx. & E.; X400

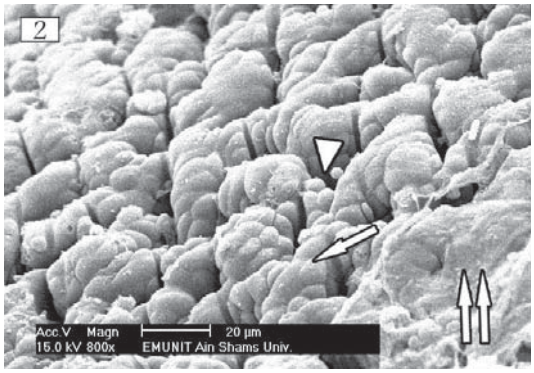


Fig. 2: A scanning electron-micrograph of control male rat gastric mucosa, showing the surface epithelial lining; the cells appear dome shaped with well defined boundaries and studded with microvilli (arrow). Notice the opening of the gastric pits (arrowhead) and the mucus covering (double arrows). X800

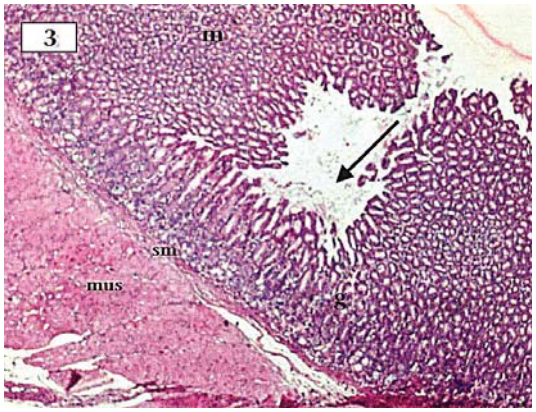


Fig. 3: A photomicrograph of the gastric mucosa of a male rat from the indomethacin treated group showing an ulcer destructing the mucosa (m) and its gastric glands (g). Cellular debris is seen inside the ulcer cavity (arrow). Notice the submucosa (sm) and the musculosa (mus). Hx. & E.; X100

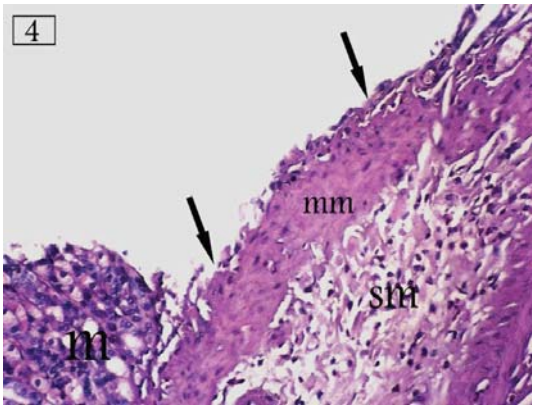


Fig. 4: A photomicrograph of a male rat gastric mucosa treated with indomethacin showing an ulcer (arrow) completely destructing the mucosa (m). The muscularis mucosa (mm) is exposed to the surface with underlying submucosa (sm). Hx. & E.; X400

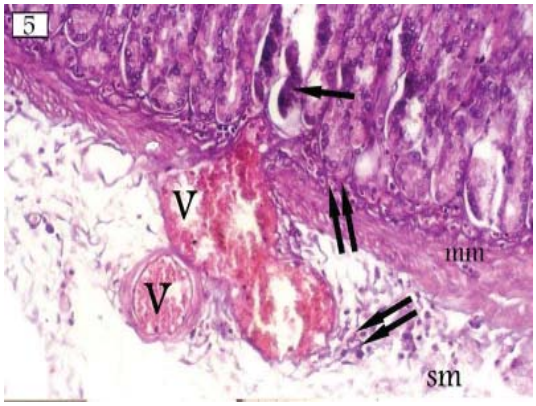


Fig. 5: A photomicrograph of a male rat gastric mucosa treated with indomethacin showing marked congestion (V) in the submucosa (sm) which also invades the muscularis mucosa (mm). Notice the destructed gastric gland (arrow) and the lymphocytic infiltration (double arrows). Hx. & E.; X400

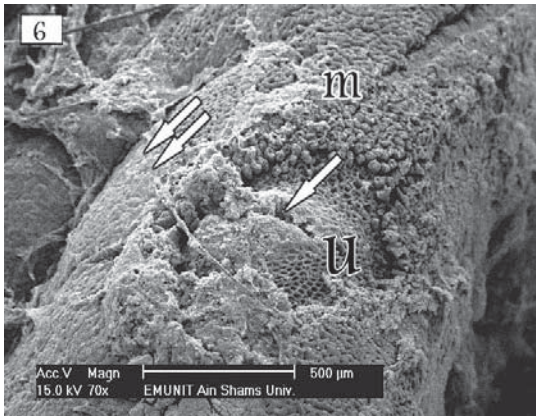


Fig. 6: A scanning electron-micrograph of a male rat gastric mucosa treated with indomethacin showing a deep ulcer (u) with sharp edges. A deep crack (arrow) can be identified in the mucosa (m). Some mucus remnants (double arrow) are detected in the section. X70

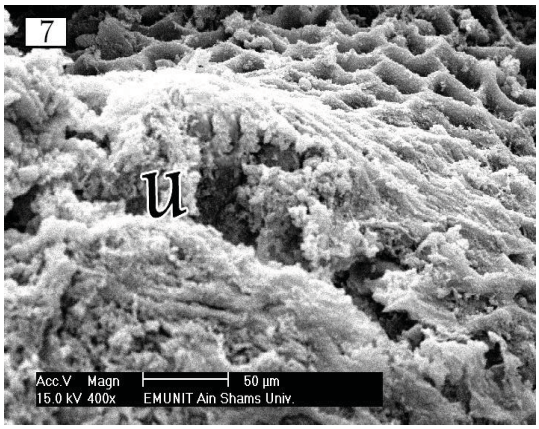


Fig. 7: A higher magnification of the previous fig. showing marked destruction of the mucosa with complete loss of its cellular architecture. Notice the deep ulceration (u). X400

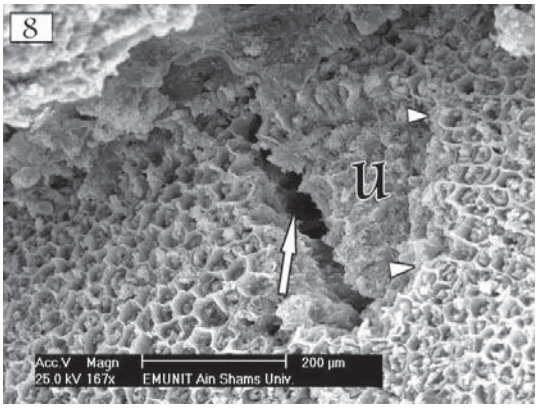


Fig. 8: A scanning electron-micrograph of the gastric mucosa of a male rat treated with indomethacin showing the ulcer (u) with sharply destructed edge (arrowhead). Notice the mucosal destruction and the deep crack (arrow). X167

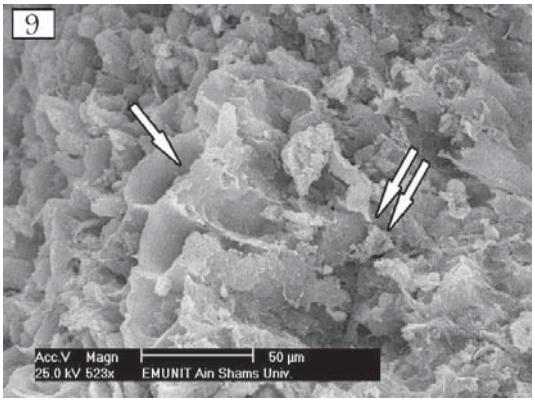


Fig. 9: A scanning electron-micrograph of a male rat gastric mucosa treated with indomethacin showing the destructed gastric glands (arrow). Notice the distorted mucosal cellular architecture (double arrows). X523

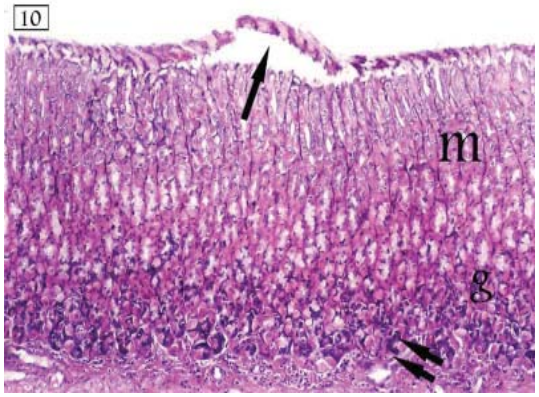


Fig. 10: A photomicrograph of a male rat gastric mucosa treated with indomethacin following curcumin protection showing the mucosa (m) with its lining epithelium and a mild grade of ulcer in which only the superficial epithelium is detached (arrow). Gastric glands (g) at the base of the mucosa are preserved. The double arrows point at the lymphocytic infiltration. Hx. & E.; X200

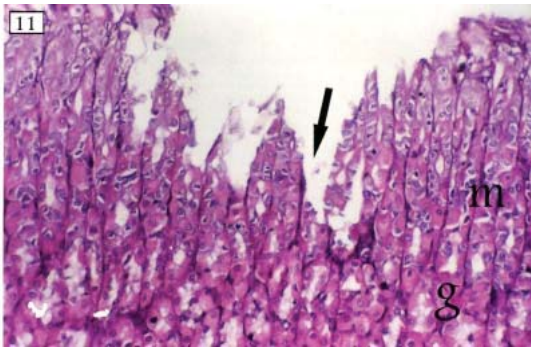


Fig. 11: A photomicrograph of a male rat gastric mucosa treated with indomethacin following curcumin protection showing the mucosa (m) with an area of mucosal ulceration (arrow). Gastric glands (g) at the base of the mucosa are preserved. Hx. & E.; X400

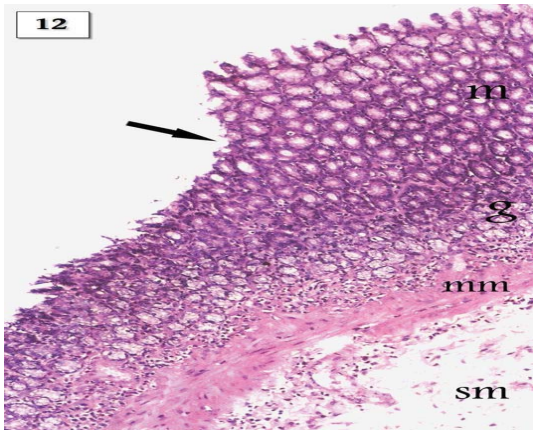


Fig. 12: A photomicrograph of a male rat gastric mucosa treated with indomethacin following curcumin protection showing an area of mucosal ulceration (arrow) in the mucosa (m). Gastric glands (g), muscularis mucosa (mm), submucosa (sm) are seen. Lymphocytic infiltration without congestion is detected in these layers. Hx. & E.; X100

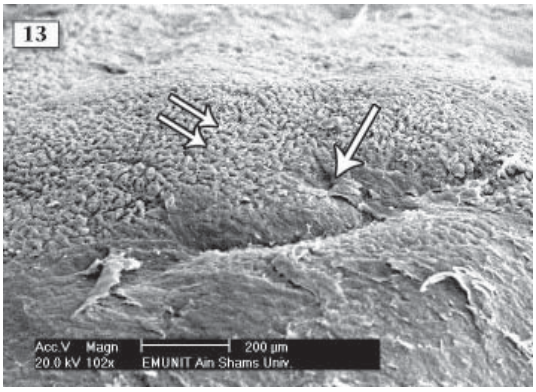


Fig. 13: A scanning electron-micrograph of a male rat gastric mucosa treated with indomethacin following curcumin protection showing an area of surface mucosal erosion (arrow) in addition to detached mucus in some areas (double arrows). X102

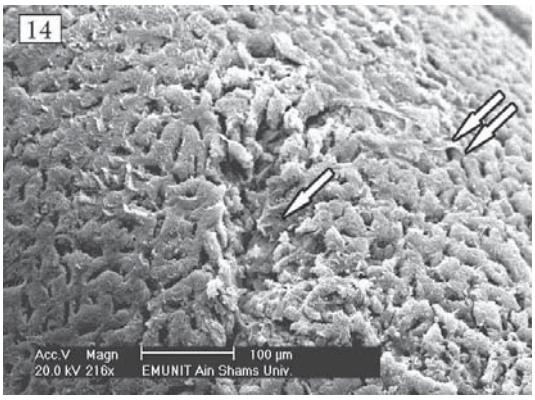


Fig. 14: A scanning electron-micrograph of a male rat gastric mucosa treated with indomethacin following curcumin protection showing an area of ulceration (arrow) as well as mucus (double arrows) covering the surface epithelium. X216

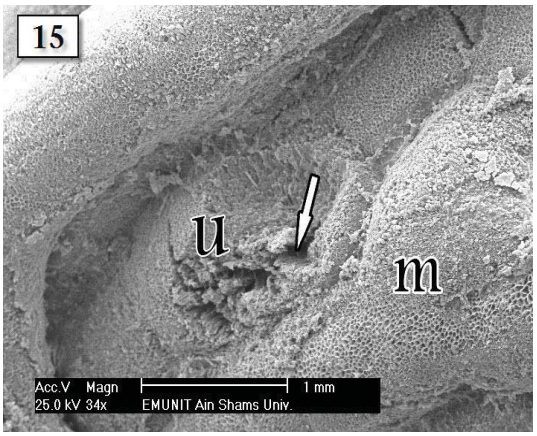


Fig. 15: A scanning electron-micrograph of a male rat gastric mucosa treated with indomethacin following curcumin protection showing an area of ulceration (u) and a crack (arrow) in the mucosa (m). X34

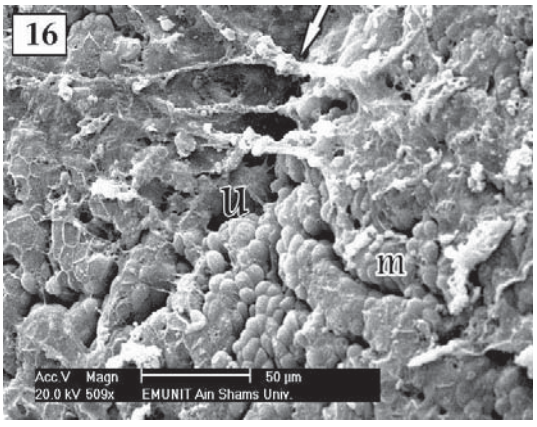


Fig. 16: A scanning electron-micrograph of a male rat gastric mucosa treated with indomethacin following curcumin protection showing an area of ulceration (u).Note that the mucosa (m) still preserves its normal dome-shaped lining cells with mucus covering it (arrow). X509

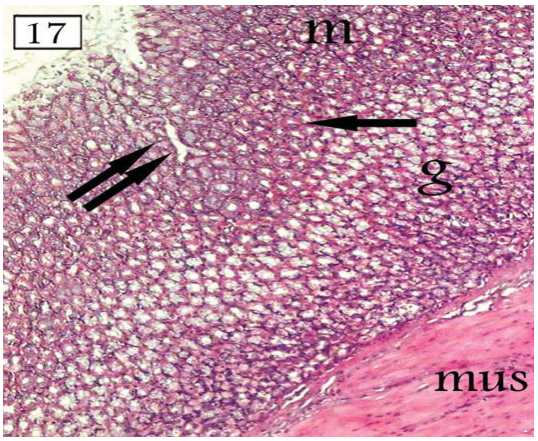


Fig. 17: A photomicrograph of a male rat gastric mucosa in the auto-healing group, showing the healed mucosa (m) in an unorganized architecture (arrow) with remnant of ulceration (double arrows). Note the gastric glands (g) and the musculosa (mus). Hx. & E.; X100

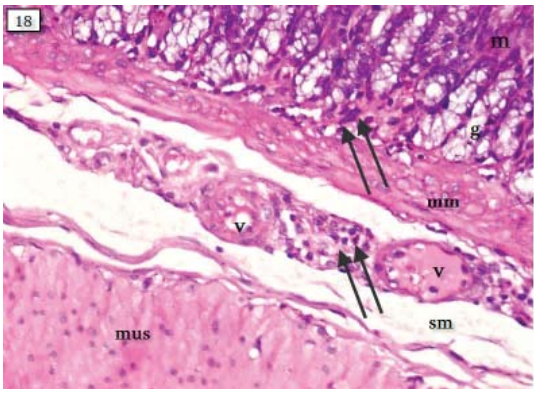


Fig. 18: A photomicrograph of a male rat gastric mucosa in the auto-healing group showing the healed mucosa (m) with congestion and exudation in the blood vessels (V) of the submucosa (sm). Lymphocytic infiltration (double arrows) is obvious. Notice the gastric glands(g), muscularis mucosa (mm) and musculosa (mus). Hx. & E.; X400

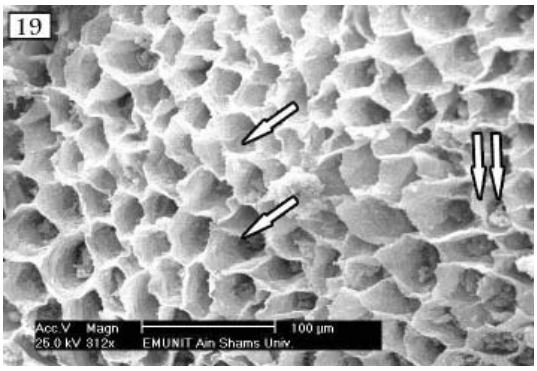


Fig. 19: A scanning electron-micrograph of a male rat gastric mucosa in the auto-healing group showing the sprouting of the regenerating cells (double arrows) from the base of the gastric mucosal glands (arrow). X312

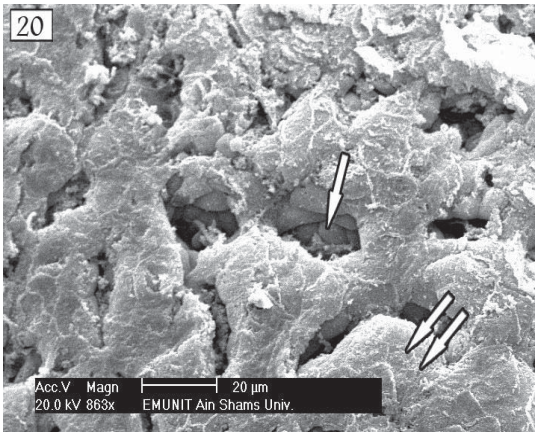


Fig. 20: A scanning electron-micrograph of a male rat gastric mucosa in the auto-healing group showing swollen mucosa (double arrows) in addition to the regenerated mucosal cells arising from the neck of the gastric glands (arrow). X863

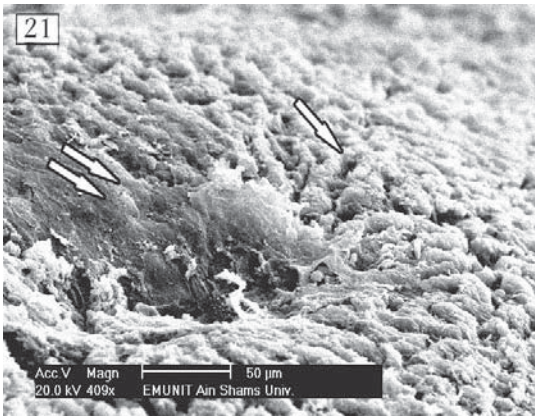


Fig. 21: A scanning electron-micrograph of a male rat gastric mucosa in the auto-healing group, showing the healing mucosa (arrow) accompanied with reappearance of the mucus covering (double arrows). X409

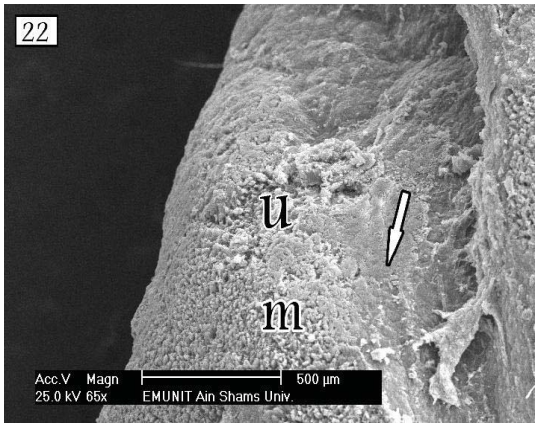


Fig. 22: A scanning electron-micrograph of a male rat gastric mucosa in the auto-healing group showing the surface mucosa (m) and the remnant of an ulcer (u). Note the presence of mucus (arrow). X65

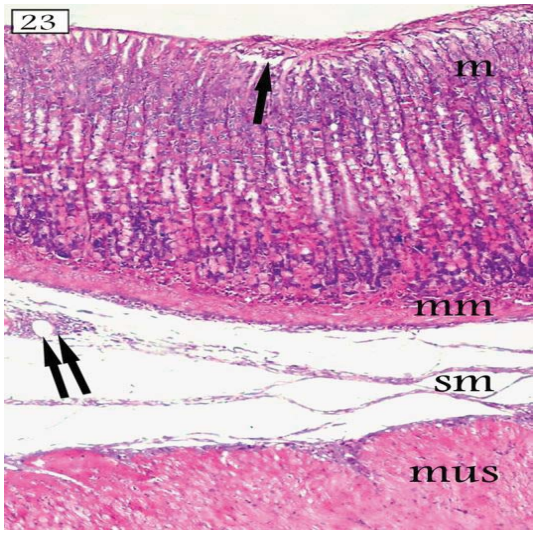


Fig. 23: A photomicrograph of a male rat gastric mucosa in the healing group using curcumin showing the healing mucosa (m) and the formation of a membrane covering the ulcer area (arrow). No congestion (double arrows) is seen in the submucosa (sm).Note the muscularis mucosa(mm) and the musculosa (mus). Hx. & E.; X40

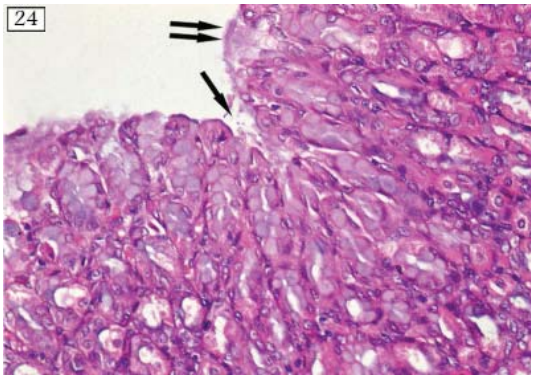


Fig. 24: A photomicrograph of a male rat gastric mucosa in the healing group using curcumin, showing the healing mucosa with a membrane (double arrows) that covers the ulcer region (arrow). Hx. & E.; X400

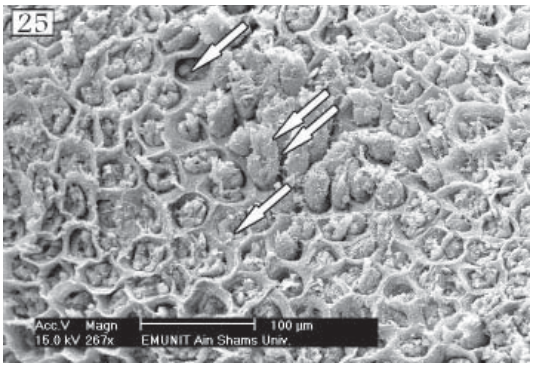


Fig. 25: A scanning electron-micrograph of a male rat gastric mucosa in the healing group using curcumin showing marked filling and sprouting of the regenerated cells (double arrows) from the base of the gastric glands (arrow). X267

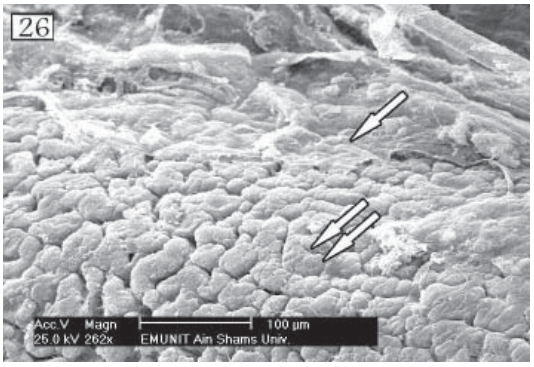


Fig. 26: A scanning electron-micrograph of a male rat gastric mucosa in the healing group using curcumin, showing regaining of the normal architecture of the healed mucosa (double arrows) and reappearance of the covering mucus (arrow). X262

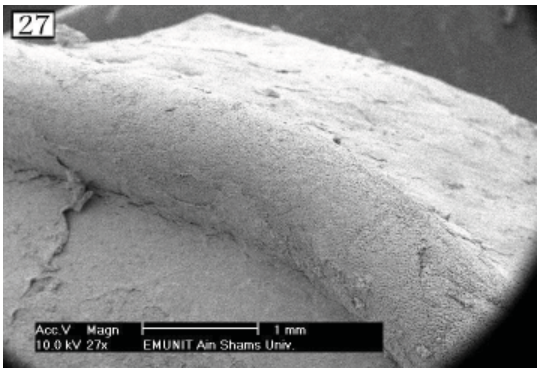


Fig. 27: A scanning electron-micrograph of a male rat gastric mucosa in the healing group using curcumin showing normal surface mucosal lining. No signs of scarring could be detected. X27

DISCUSSION

Several mucosal defense mechanisms protect the stomach against hydrochloric acid and noxious agents. The pre-epithelial protection is made up of mucus-bicarbonate barrier that creates a near neutral pH. Surfactants in apical cell membranes prevent water-soluble agents, in the gastric lumen from reaching and damaging the epithelium. Rapid cell turn-over and the process of restitution contribute to an intact epithelial lining. In subepithelial protection, the mucosal blood flow is essential for supplying the epithelium with nutrients and oxygen and for disposal of hydrogen ions and noxious agents permeating the mucosa *(Forssell, 1988)*.

The period of ten- days- protection and treatment was chosen in the present study after the work of *Baumgartner et al. (1986)*. The mucosal

morphology and the balance between cell loss and cell renewal were analyzed during treatment with a non-ulcerative dose of Indomethacin. The authors found that cell shredding began on day seven and ended on day fourteen of Indomethacin administration.

During the current work, the group protected with Curcumin showed less severe forms of gastric ulceration as compared to the non- protected group. These findings were analyzed statistically and proved to be significant ($p<0.01$). Curcumin protects rats' gastric mucosa from ulcerations possibly through its anti-oxidant action against oxidative stress induced by Indomethacin *(Morsy et al., 2009)*. In the present research, the mucosal cell architecture was still preserved. Moreover, mucus covering, which was still detected, was thicker than that of the non- protected group. *Meyer-Hoffert et al. (2008)* postulated that mucus plays important role in the prevention of bacterial colonization and translocation and in prevention of mechanical injury to the epithelium through providing a microenvironment over which rapid repair can occur.

It has long been assumed that the mucosa in areas of grossly healed gastric or duodenal ulcers returns to normal, either spontaneously or after treatment. This assumption was based almost entirely upon visual, superficial examination by endoscopy. Few, if any, histological and ultrastructural studies examined the deeper mucosa in the areas of these healed ulcers *(Tarnawski et al., 1991)*. Ulcer healing is an active and complicated process of filling the mucosal defect with proliferating and migrating epithelial cells and connective tissue components to reconstruct the mucosal architecture *(Chow et al., 1998)*. Moreover, healing of ulcers encompasses a complex series of cell/matrix interaction involving cellular proliferation, migration, and differentiation *(Tomita et al., 2009)*.

In group (III-b), the healing was organized and started from the deeper layers. The gastric glands showed sprouting of new cell population. This growth was much evident in the Curcumin healing group as compared to the auto-healing one. *Jones et al. (1999)* stated that repair of ulcer requires the complete re-establishment of a connective tissue foundation, the re-formation of glandular architecture, and the growth of new blood vessels. Infiltration of the ulcer bed by granulocytes is important for minimizing the translocation of bacteria from the lumen.

In the present study, lymphocytic infiltration was observed in both healing groups. *Granger and Kubes (1994)* found that when the superficial levels of mucosal defense fail, the next level of mucosal defense is the acute inflammatory response. Neutrophils are recruited from the circulation to the sites of injury to facilitate repair and to reduce the entry of microbes into the systemic circulation. In addition to removing damaged cells, foreign matter and microbes, neutrophils also participate in the formation of granulation tissue.

De Paulis et al. (2009) mentioned that cell migration and proliferation, as well as the expression of vascular endothelial growth factor, promoted gastric mucosal healing. Healthy vascular supply is essential for this migration to occur. The current work revealed that in the healing group using Curcumin, no signs of congestion or inflammatory exudation in the submucosal blood vessels were found as compared to the auto-healing group. Moreover, *Voravuthikunchai and Mitchell (2008)* noted that medicinal plants extracts like turmeric and its derivatives have inhibitory and killing activities against multiple antibiotic resistant Helicobacter Pylori that cause mucosal infection, inflammation or even predispose to gastric carcinomas.

Tarnawski et al. (1991) as well as *Gisbert and Pajares (2005)* postulated that the quality of mucosal structural restoration rather than the speed of ulcer healing is the most important factor in determining risk of ulcer recurrence. The authors described two patterns of scarring in the auto -healing ulcers; either the mucosa in the area of healed ulcer was thinner with increased connective tissue and poor differentiation, or marked dilation of gastric glands with poor differentiation of the glandular cells and a reduction in the supportive microvascular network. These abnormalities could interfere with oxygenation, nutrient supply, mucosal resistance and defense and could be the basis for ulcer recurrence. The current study revealed a statistically significant more organized healing in the Curcumin group than in the auto-healing group ($p<0.05$). A well -formed membrane was seen on the surface epithelium and gastric cells regained their normal architecture. *Mahattanadul et al. (2006)* and

Itokawa et al. (2008) suggested that the preventive and curative effects of Curcumin might be due to an increase in the mucosal defensive mechanism through its antioxidant property and inhibition of Nitric oxide or cytokine-mediated inflammation. An important finding in the current work was the absence of scarring on the surface epithelium by scanning electron microscopy in some animals. This could give a hope for decrease in the incidence of ulcer recurrence.

Lee et al. (2010) postulated that the quality of ulcer healing remains crucial for preventing recurrence. Unfortunately, the rate of ulcer recurrence with the use of common anti-ulcer drugs available in the market is still high. A search for an alternative nontoxic anti-ulcer compound is always welcomed. Since pro-inflammatory and pro-oxidant states are closely linked to ulcer development, a polyphenolic compound like Curcumin having potent anti-inflammatory and antioxidant activities is anticipated to exert an anti-ulcer effect.

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دراسة تركيبية لدور الكركم فى وقاية وعلاج قرحة المعدة المحدثة بعقار الإندوميثاسين فى ذكر الجرذ الأبيض البالغ باستخدام المجهرين الضوئي والماسح الإلكترونى

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ملخص البحث

إن استخدام النباتات الطبية أو مكوناتها النشطة لعلاج الأمراض المختلفة بما في ذلك قرح الجهاز الهضمي أصبح نهجا جذابا فى زيادة مضطردة، ويعتبر الكركم واحدا من هذه المشتقات الطبيعية التى أثبتت الدراسات أن لديه خاصية مضادة للالتهابات وللأكسدة. ولما كان استخدام الكركم لعلاج القرح الحادة والمزمنة لا يزال بحاجة إلى مزيد من البحث، لذا كان الهدف من هذه الدراسة توضيح دور الكركم في الوقاية وعلاج قرحة المعدة التي يسببها عقارالإندوميثاسين في ذكور الجرذان البيضاء البالغة، وذلك بدراسة تأثيره على التركيب الهستولوجى للمعدة باستخدام المجهرين الضوئي والماسح الإلكترونى.

وقد استخدم في هذه الدراسة ثلاثون جرذ ذكر أبيض بالغ، تم تقسيمهم إلى خمس مجموعات: مجموعة ضابطة، ومجموعة تم احداث قرحة بمعدتها باستخدام عقارالإندوميثاسين، ومجموعة تم أيضا استخدام نفس العقار ولكن بعد فترة وقاية بالكركم لمدة عشرة أيام. وأخيرا مجموعتان للشفاء، واحدة منهما شفاء تلقائى والأخرى باستخدام الكركم لمدة عشرة أيام.

وقد أوضحت النتائج أن استخدام الإندوميثاسين بدون وقاية أدى الى إحداث أشكال حادة من تقرحات المعدة، وتدمير الغشاء المبطن لها وفقدان البنية الخلوية بها. أما في المجموعة التى تلقت الحماية باستخدام الكركم فقد ظهرت تقرحات المعدة بصورة أقل ضراوة سواء في الحجم أو المدى مع انخفاض كبير في احتقان الغشاء المبطن للمعدة. وقد تم تحليل هذه النتائج وأثبتت أنها ذات دلالة إحصائية. وفى مجموعة الشفاء التلقائى ظهرت القرح بصورة شفاء غير منتظم، أما المجموعة التى تلقت الكركم فالشفاء كان أكثر انتظاما، وظهرالغشاء المعدى بشكل طبيعى. وكان هذا العلاج المنتظم ذو دلالة إحصائية.وبذلك يتضح أن الكركم يلعب دورا هاما في كل من الوقاية وعلاج قرحة المعدة وذلك بفضل خصائصه المضادة للاكسدة والألتهابات.