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RESEARCH ARTICLE

Potential Curative Effect of Curcumin on Gastric Ulcer Induced by Piroxicam in Male Albino Rats

Hosny A. E. Ibrahim[1], El–Sayed K. Metwaly[2], Azza A. A. Galal[1] and Sarah A. Sherif [3*]
[1]Pharmacology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Zagazig, Egypt
[2]Pharmacology Department, Faculty of Medicine 44519, Zagazig University, Egypt
[3]Health Institution, Ministry of Health 11516, Cairo, Egypt

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Abstract

This study intended to investigate the curative effect of curcumin on piroxicam-induced gastric ulcer in rats. Twenty-seven male albino rats were allocated into three similar groups (9 of each). The first group (G1) was the control, G2 received piroxicam (30 mg⁄ kg BW.) to induce gastric ulcer and G3 received piroxicam (30 mg⁄ kg BW.) and on the third day it received curcumin (200 mg ⁄ kg BW.) orally for 21 day. At the end of the experiment, the rats were humanly euthazied and blood and serum samples were taken for haematological and biochemical analysis, respectively. Subsequently, the stomachs were opened along their curvature for evaluation of ulceration, gastric juice was measured and gastric samples were preserved in 10% neutral buffered formalin for histopathological examination. Piroxicam administration induced gastric ulceration (100%), non-significant changes in the gastric juice volume and a remarkable decrease in the number of red blood cells, hemoglobin concentration and packed cell volume with a significant increase in platelets count, white blood cells, neutrophils, eosinophils and monocytes. Furthermore, it displayed a significant reduction of glutathione peroxidase, superoxide dismutase and catalase activities with a significant increase in malondialdehyde and tumor necrosis factor alpha concentrations. Histopathological results revealed focal mucosal erosive and ulcerative changes with sever hyperemia of stomach in piroxicam treated group (G2). Oral administration of curcumin treated the piroxicam induced gastric ulceration and improved the altered hematological parameters, oxidant ⁄ antioxidant status and histological pictures of rats in G3. Therefore, curcumin may offer an attractive strategy for treatment of gastric ulcer.

Keywords: *Curcumin, Peptic ulcer, Piroxicam, Albino rats, tumor necrosis factor-alpha, oxidant ⁄ antioxidant status.*

Introduction

Peptic ulcer is a disease that affects a significant number of individuals around the world as a result of an imbalance on the luminal surface of the epithelial cells between the "aggressive" and "protective" factors. Non-steroidal anti-inflammatory drugs (NSAIDs), *Helicobacter pylori*, Hydrochloric acid (HCl), pepsins, bile acids, hypoxia, ischemia, smoking, and alcohol are the main aggressive factors. While mucus layer, bicarbonate, mucosal blood flow, growth factors, and prostaglandin are the defensive factors [1]. Piroxicam is a potent non selective Cyclooxygenase enzyme (COX) inhibitor which inhibits conversion of arachidonic acid into prostaglandin resulting in an oxidative stress in the gastric mucosa [2].

Many researches were conducted to find out alternative treatments of peptic ulcer from natural sources to substitute the currently used medications of dubious efficacy and safety [3]. Medicinal plants and crude substances are regarded as an important source for the control of many diseases, including gastric ulcer and ulcerative colitis [3]. Curcumin is the most important natural polyphenol in the rhizome of *Curcuma longa* [4]. It is a lipophilic

***Corresponding author e-mail: (ota_sarah2008@yahoo.com), Health Institution, Ministry of Health 11516, Egypt.**

polyphenol that is almost insoluble in water but stable in the stomach's acidic pH [5]. Because of its pharmacological activities, curcumin is commonly used in herbal medicine [6]. It also has a significant anti-inflammatory, antioxidant, antimicrobial and anticarcinogenic effects as a monotherapy [7]. Besides, it displays an antiulcer activity by inhibition of the multiple ulcerative effectors, including hyper secretion of gastric acid, myeloperoxidase activity, apoptotic incidence, peroxides, and interleukin-6 (IL-6), along with its inhibitory activity to pepsin [8]. Several properties help to recognize its effect against *H. pylori*, including pro-apoptotic effect, inhibition of angiogenesis, proliferation and metastasis [9]. Accordingly, this research intended to investigate the therapeutic benefit of curcumin in treatment of piroxicam induced peptic ulcer in male albino rats.

Materials and Methods

Drug and Curcumin

Piroxicam (Felden®) 20 mg capsules DB00554 (APRD01187) obtained from Pfizer chemical company, Egypt. Curcumin (458-37-7) was bought from Sigma Chemicals Company, Egypt.

Experimental animals

This study was conducted on twenty-seven male albino rats weighing 180-200 g, purchased from the laboratory animal house, Faculty of Veterinary Medicine, Zagazig University, Egypt. Rats were housed in cages and kept at room temperature and humidity (65-70%) with 12 h light and dark cycle before starting the experiment. Rats were fed on standard diet with water *ad libitum* [10]. The experiment was conducted in line with rules set by the Animal Welfare and Research Ethics Committee, Faculty of Veterinary Medicine, Zagazig University, Egypt.

Experimental design

Following acclimatization for 14 day, the 27 rats were classified into three equal groups each of 9 rats. The 1st group (G1) was kept as control and received distilled water. The second group (G2) received piroxicam (30 mg⁄kg BW.) [11] as a single oral dose after fasting 24 h, this dose was a very high dose, to induce peptic ulcer in rats. The third group (G3) was given piroxicam the same single oral dose then on the third day; it received curcumin (200 mg⁄kg BW.) as a single oral dose daily for 21 day [12].

Sampling

At the end of the experiment, the rats were humanly euthazied under light anaesthia via intramuscular injection of Ketamine hydrochloride 1867-66-9 (50 mg⁄kg Bw) and xylazine 23076-35-9 (5 mg⁄kg BW) mixture obtained from Sigma Chemicals Company, Egypt and then two blood samples were taken (18 from each group). The first one was on EDTA for haematological examination, while the second blood sample was without anticoagulant, and centrifuged for 10 min at 3000 rpm. Serum samples were collected and kept at -20°C for biochemical analysis. Thereafter, the stomach was immediately removed and its content was collected then gastric tissue samples were preserved in 10% neutral buffered formalin for histopathological examination.

Measurement of gastric juice volume

The euthanized animal stomach was immediately dissected and the gastric content was gathered and centrifuged for 10 min at 3000 rpm to isolate the aqueous phase. The volume of centrifuged gastric juice was measured by a graduated cylinder and expressed as ml [13].

Recording of ulcer score

The stomachs were opened along their curvature and evaluated for ulceration. The number and intensity of the glandular mucosa's discrete damage areas were scored and the ulcer score was determined using the scoring scheme 1 to 5 outlined by Wilhlmi and Menasse-Gdynia [14].

Stomach ulceration was expressed by ulcer index (U.I)

Ulcer index =Mean ulcer score of animals group treated similarly x % of ulcerated animals of this group [15].

Estimation of hematological parameters

Erythrogram as well as leukogram including the total and differential leukocytic counts were estimated by using an automatic cell counter (Countess II FL Automated Cell Counter, Catalog number: AMQAF1000, Thermo Fisher Scientific company, USA.) [16].

Determination of oxidant /antioxidant status and tumor necrosis factor-alpha concentration

Superoxide dismutase (SOD) [17], catalase (CAT) enzyme [18], glutathione peroxidase (GPx) [19], Tumor necrosis factor-alpha (TNF-α) [20] and malondialdehyde (MDA) concentrations [21] were determined in serum samples.

Histopathological examination

The preserved gastric specimens in 10% neutral buffered formalin solution were dehydrated in gradual ethanol (70-100%) cleared in xylene, then embedded in paraffain. Sections (5µm thickness) were prepared, stained with Hematoxylin and Eosin (H&E) and then examined under light microscope [22].

Statistical analysis

The data were displayed as mean ± SE and assessed using SPSS software (2006), one-way analysis of variance (ANOVA). Significant difference between means was estimated at $p < 0.05$ [23].

Results

Effect of oral administration of curcumin on gastric ulceration induction, mean ulcer score, ulcer index and curative index of piroxicam treated rats

Administration of piroxicam orally in male rats induced gastric ulceration in all rats in G2 (100%) and a significant ($p<0.05$) increase in mean ulcer score (2.75±0.25) and high ulcer index (275) in comparison with the control group (G1). Administration of curcumin resulted in a remarkable curative effect on gastric ulcers in curcumin treated group (G3) compared with G2 (piroxicam treated group). Furthermore, the curative ratio of curcumin treated group was (100%) compared with piroxicam group (Table 1).

Table 1: Induction of gastric ulcer, mean ulcer score, ulcer index and curative ratio among the different albino rats group

Groups	G1	G2	G3
Induction of gastric ulceration	0	100%	**0**
Mean ulcer score	0	2.75 ± 0.25^{a}	**0**
Ulcer Index	0	275	**0**
Curative Index	0	0	**100%**

G1: Control, G2: Piroxicam treated group (30 mg⁄kg BW.) and G3: curcumin treated group (200 mg⁄kg BW.) Means ± SE within the same column carrying different superscripts are significant different at ($p<0.05$).

Effect of oral administration of curcumin on hematological parameters of piroxicam treated rats.

Rats in G2 showed a significant ($p<0.05$) decrease in RBCs count, Hb concentration and PCV % with a significant increase in platelets, WBCs, neutrophils, eosinophils and monocytes counts compared with control group. Oral administration of curcumin to rats in G3 significantly increase RBCs count, Hb concentration and PCV value and significantly ($p<0.05$) decrease platelets, WBCs, neutrophils, eosinophils, monocytes counts in comparison with piroxicam treated group (G2) (Table 2).

Table 2: Effect of oral administration of curcumin on the haematological parameters of piroxicam-treated rats

Groups	G1	G2	G3
RBCs($\times10^6$/µl)	6.81± 0.16[a]	4.38± 0.05[d]	6.03± 0.10[b]
HB (g/dl)	15.70± 0.26[a]	10.43 ± 0.13[d]	13.10± 0.31[c]
PCV (%)	46.25± 1.11[a]	29.50± 0.65[c]	41.50± 0.65[b]
Platlets ($\times10^3$/µl)	246.75± 4.11[c]	348.50± 1.55[a]	273.00± 1.22[b]
WBCs($\times10^3$/µl)	9.24 ± 0.08[d]	14.97 ± 0.31[a]	10.68± 0.17[b]
Neutrophil ($\times10^3$/µl)	2.68± 0.08[b]	6.90± 0.34[a]	3.33± 0.10[b]
Lymphocyte ($\times10^3$/µl)	5.61± 0.09[a]	5.53 ± 0.09[a]	5.71± 0.14[a]
Eosinophil ($\times10^3$/µl)	0.67 ± 0.03[d]	1.70± 0.02[a]	1.19 ± 0.03[b]
Monocyte ($\times10^3$/µl)	0.29 ± 0.02[c]	0.85± 0.02[a]	0.45± 0.02[b]

G1: Control, G2: Piroxicam treated group (30 mg⁄kg BW.) and G3: curcumin treated group (200 mg⁄kg BW.). Means ± SE within the same column carrying different superscripts are significant different at (p<0.05). RBCs: red blood cells, HB: Hemoglobin, PCV: packed cell volume, WBCs: White Blood Cells.

Effect of oral treatment with curcumin on oxidant /antioxidant status and tumer necrosis factor- alpha concentration of piroxicamtreated rats

The present work disclosed that oral administration of piroxicam in male rats elicited a significant reduction (p<0.05) in GPX, SOD and CAT activities with a significant (p<0.05) increase in MDA concentration and TNF-α concentration. Administration of curcuminto piroxicam-treated rats significantly increase the SOD, CAT and GPX activities with a significant decrease in MDA concentration and TNF-α values compared with piroxicam treated rats (Table 3).

Table 3: Effect of oral administration of curcumin on the antioxidant enzymes activities, malondialdehyde and Tumor necrosis factor-alpha concentration in piroxicam-treated rats

Groups	G1	G2	G3
CAT (U/L)	236.75± 3.45[a]	135.25± 1.89[d]	199.00± 2.35[c]
SOD (U/ml)	2.72± 0.28[a]	0.75± 0.04[d]	1.70± 0.03[c]
GPX (U/L)	60.63± 0.78[a]	26.70± 1.32[d]	44.98± 1.86[c]
MDA(nmol/ml)	4.80 ± 0.22[d]	27.03± 1.66[a]	10.49± 0.35[b]
TNF-alpha(pg/ ml)	25.28 ± 0.58[d]	91.05± 0.58[a]	47.88± 2.49[b]

G1: Control group, G2: Piroxicam treated group (30 mg⁄kg BW.) and G3: curcumin treated group (200 mg⁄kg BW.)
Means ± SE within the same column carrying different superscripts are significant different at (p<0.05).
CAT: catalase enzyme, SOD: superoxide dismutase, GPx: glutathione peroxidase, MDA malondialdehyde and TNF-α : Tumor necrosis factor-alpha

Effect of oral treatment with curcumin on histopathological structures in piroxicam treated rats

Control group had normal different layers of the stomach including the mucosa, sub mucosa and the muscular coat (Figure 1 A, B), while, Piroxicam administration in rats (G2) induced multiple ulcerative lesions with mild to intense inflammatory cells and mild inflammatory reactions in the mucosa and submucosa (Figure 1 C, D) and this evidence of ulcer was abolished in curcumin treated rats. Few sections showed focal epithelial degeneration with mild hyperemia (Figure 1 G, H).

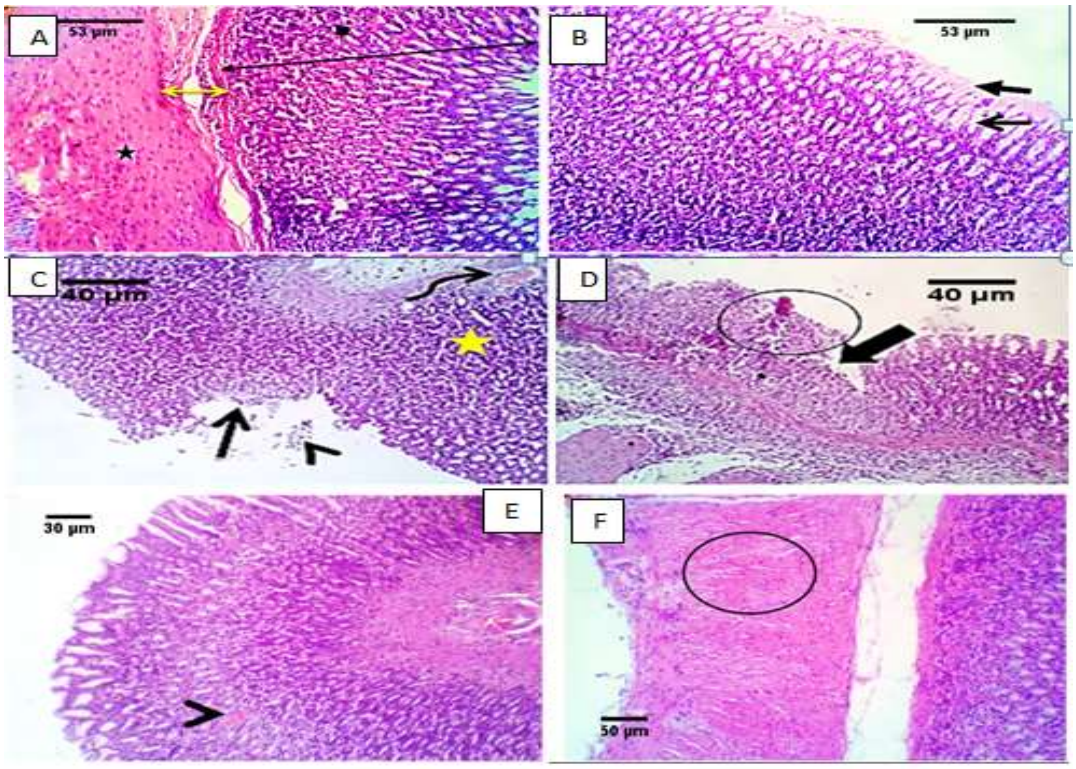

Figure 1: tissue section of rat's stomach under different treatments :(A Control group (G1) showing normal different layers of the stomach including the mucosa (black double headed arrow), sub mucosa (yellow double headed arrow) and the muscular coat (star) .(B)The control animal mucosa comprises the lining mucosal columnar cells with some goblet cells (open arrow) and film of mucus materials covering it (closed arrow) Scale bars (53µm). (C)Section of rat's stomach of piroxicam (G2) showing erosive changes which represented by superficial necrosis (open arrow) of the first layer of the mucosa with presence of desquamated cells (arrow head) in the gastric lumen, mild inflammatory reactions in the mucosa and submucosa (yellow stars) beside congested mucosal blood vessels (curved arrow), (D) the ulcerative lesion (thick arrows) ,in second group, scale bars (40 µm). (E)Section of rat's stomach of piroxicam -curcumin group and (F) normal gastric layers with focal mild capillary hyperemia beside focal epithelial regeneration (openwere shown in G# arrow) , H&E X 100. scale bars E (30µm) and F (50µm).

Discussion

Gastric ulcer is mainly induced in 80 % of instances due to the use of non-steroidal anti-inflammatory drugs (NSAIDs), 10% by *H. Pylori* and around 8-10% using very spicy and fast food [24]. Despite a variety of antiulcer medications, such as H_2 receptor antagonists, cytoprotectants, andproton pump inhibitors, are available; all these medications have side effects and constraints [25]. An extensive investigation for identification of new antiulcer medications from synthetic and natural resources has been initiated in the last years. Therefore, the current study is carried out to investigate the curative effect of curcumin against gastric ulcer induced by piroxicam. Our results revealed a high incidence of gastric ulceration, high ulcer index and ulcer score in piroxicam group (G2). The erosive effect of piroxicam is mainly due to its ability to reduce the cyclic guanosine monophosphate (cGMP). This nucleotide is responsible for decreasing acid secretion, pepsinogenesis and elevation of bicarbonate (HCO_3) secretion [26].

The recorded results were supported by Scarpignato [27], who mentioned that absorption of piroxicam is raised and the mucosa enters in a cycle of degeneration which exposes the gastric mucosal defense mechanism to the harmful effect of HCL.

The obtained results revealed that curcumin has a high incidence of curative index (100%). Curcumin antiulcer effect is due to its antioxidant activity and inhibition of the multiple ulcerative effectors, including hyper

secretion of gastric acid, peroxides, myeloperoxidase activity, apoptotic incidence and IL-6, along with pepsin inhibitory activity [8]. The antioxidant ability of curcumin originates from the phenolic OH group which is the major functional group in curcumin [8, 28, 29]. Curcumin has been verified to be able to block ethanol, indomethacin, and stress-induced gastric ulcer and to stop pylorus-based acid secretion [30].

In this study, there was a significant decrease in RBCs count, hemoglobin, PCV% in piroxicam treated group (G2). These results may be due to congestion of blood vessels and extravasation of RBCs [31-33]. Moreover, piroxicam induced a significant increase in total and differential leukocytic counts especially neutrophils and lymphocytes. This result agreed with Blandizzi *et al*. [33], who stated that piroxicam induced neutrophils activation which led to leukotrienes release. The current data revealed an elevation in platelets count of piroxicam treated group. Hirata *et al.* [34] reported that NSAIDS acts by suppression of cyclooxygenase enzyme which responsible for formation of prostaglandins and thromboxane A2 which involved in platelets activation and aggregation mechanism.

The current results elicited a significant elevation in RBCs count, hemoglobin concentration and PCV% in curcumin treated group (G3). Curcumin protects hemoglobin against oxidation and enables oxygen transportation efficiently in the tissues. A significant amelioration of the erythrocytic count results from the stabilized effect of curcumin on the RBCs cell membrane and restoration of multiple blood variables; also, it protects against H_2O_2-induced hemolysis of RBCs [35]. Our resultswere supportedby the results recorded by Sharma *et al.* [36] who proved that curcumin administration improved the erythrocytic count, Hb and blood indices by its immune-stimulating effect.

The current data indicated that curcumin administration in piroxicam treated rats resulted in a significant decrease in the number of total WBCs, monocytes, lymphocytes, eosinophils, andneutrophils. These results were in accordance with those obtained by Kamarudin *et al*. [37] who recorded a decrease in WBCs and lymphocyte counts after curcumin administration due to its anti-inflammatory effect. Curcumin reduced the neutrophil infiltration in inflammatory conditions [38, 39]. The anti-inflammatory effects of curcumin are due to its ability to inhibit the cyclooxygenase and decrease the level of histamine. Also, it increases production of cortisone by the adrenal glands [40].

The result of the present study revealed that piroxicam induced a significant increase in MDA concentration with a significant decrease in the activities of SOD, CAT and GPX enzymes. These results were in agreement with Basu *et al*. [11] who stated that piroxicam decreases gastric glutathione peroxidase level through generation of oxygen and hydroxyl free radical. So, an imbalance arises between reactive oxygen species (ROS) and antioxidant defense mechanism**.**

Piroxicam administration in male rats resulted ina significant increase in serum TNF-α. This results in agreement with the findings of Rosenstein *et al*.[41], Sugimoto *et al*. [42] who recorded that overproduction of TNF-α increases the risk of gastric ulcer and tumor by enhancement of neutrophil derived-superoxide generation and stimulation of 1L-1 production resulting in neutrophil aggregation and subsequently over production of TNF-α.

curcumin markedly increased SOD, CAT and GPX activities in G3 and decreased MDA concentration in G2. Curcumin's antioxidant mechanism is ascribed to its distinctive conjugated structure, which involves two methoxylated phenols and an enol form of b-diketone; this structure demonstrates a typical radical capability as an antioxidant that breaks the chain [43]. The effect of curcumin as a superoxide scavenger was studied and it was found to be a potent superoxide radical scavenger [44].

It was observed that curcumin prevents the oxidative damage not only by preventing gastric peroxidase inactivation, but also by direct H_2O_2 and •OH scavenging. Since ROS have been implicated in different pathological

circumstances development, curcumin can combat these disorders through its powerful antioxidant activity [45].

The present study revealed that curcumin induced a significant decrease in TNF-α concentration in piroxicam treated rats. This result go hand in hand with Chan [46] and Kondo *et al.* [47] who stated that curcumin inhibits pro-inflammatory cytokines (IL and TNF-α).

Conclusion

Curcumin was an effective treatment of piroxicam induced gastric ulcer by inhibiting lipid peroxidation and TNF-α alongside with activating of antioxidant enzymes like SOD, CAT, and GPX. Thus, it is a potent anti- ulcer and it can give an appealing approach for treatment of gastric lesions in human.

Conflict of interest

The authors have no conflict of interest to declare.

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الملخص العربي

التأثير العلاجي المحتمل للكركم على قرح المعدة المحدثة بالبيروكسيكام في ذكور الجرذان البيضاء

حسنى عبد الفضيل ابراهيم[١]، السيد كامل متولى [٢] ، عزة أحمد جلال[١] و سارة أحمد عطية[٣*]
[١]قسم الباثولوجيا الإكلينيكية - كلية الطب البيطري - جامعة الزقازيق ٤٤٥١١ - الزقازيق- محافظة الشرقية- مصر
[٢]قسم الباثولوجيا الإكلينيكية - كلية الطب - جامعة الزقازيق ٤٤٥١٩ - الزقازيق- محافظة الشرقية- مصر
[٣] معهد الصحة بالزقازيق ، وزارة الصحة ١١٥١٦ ، مصر

تهدف هذه الدراسة إلى تقييم التأثير العلاجي للكركم على قرح المعدة المحدثة بالبيروكسيكام والتي أجريت على سبعة وعشرين ذكر من الجرذان البيضاء، حيث قُسمت إلى ثلاث مجموعات متساوية في كل مجموعة تسعة جرذان. المجموعة الأولى هي المجموعة الضابطة بينما تم تجريع الجرذان في المجموعة الثانية بعقار البيروكسيكام (٣٠مجم/ كجم من وزن الجسم) عن طريق الفم لإحداث قرح المعدة و جرُعت الجرذان في المجموعة الثالثة بعقار البيروكسيكام (٣٠ مجم/ كجم من وزن الجسم) لإحداث قرحة المعدة وفى اليوم الثالث جرُعت بالكركم بجرعة (٢٠٠ مجم / كجم من وزن الجسم) لمدة ٢١ يوم متتالية . وفي نهاية التجربة تم ذبح الجرزان وأخذ عينة من الدم لفحصها، كما تم فتح المعدة وتنظيف محتواها لتقيم حدوث القرح بها وأيضاً حجم عصارة المعدة كما تم أخذ عينات من المعدة وحفظها في الفورمالين لفحصها باثولوجياً. أظهرت النتائج أن إعطاء البيروكسيكيام أدى إلى حدوث التقرح (100%) بالإضافةإلى أنه قد تسبب في إحداث نقص معنوي في عدد كرات الدم الحمراء والهيموجلوبين وحجم معبأة الخلية عند مقارنتها بالمجموعة الضابطة. أوضحت هذه الدراسة أن إعطاء البيروكسيكيام في ذكور الجرذان أدي إلي زيادة في عدد الصفائح الدموية وزيادة معنوية في العدد الكلى لكرات الدم البيضاء وأنواعها المختلفة مقارنة بالمجموعة الضابطة بالإضافة إلي نقص في نشاط الجلوتاثيون بيروكسيديز والسوبر اوكسيد ديسميوتيز والكاتليز مقارنة بالمجموعة الضابطة، مع زيادة معنوية في تركيز المالون داى ألدهايدوعامل نخز الورم- ألفا مقارنة بالمجموعة الضابطة .وأوضحت النتائج أن تجريع البيروكسيكام أدى إلى وجود تغيرات تأكلية وتقرحية في أشكال مختلفة بالغشاء المخاطي.علي الجانب الاخرأظهرت النتائج أن العلاج بالكركم أدي إلي تحسن معنوي في قرح المعدة فى المجموعة ٣ مقارنة بمجموعة البيروكسيكام (مجموعة٢) حيث نتج عن إستخدامه خفض معدل التقرح وتحسين جميع التغيرات التي أحدثها عقار البيروكسيكام. نخلُص من هذه الدراسة أن الكركم له تأثير فعال في علاج قرحة المعدة.