

Study of the prophylactic activity of *Terminalia chebula* against induced gastric erosion in rabbit model

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Abstract

The study was designed to evaluate the prophylactic activity of Haritaki (*Terminalia chebula*) against induced gastric erosion in rabbit model by using 80% Ethanol for induction. The experiment continued for 16 days, during which 18 rabbits were divided into three groups (6 rabbits/ group) control group, induction group and treatment group, which received normal saline orally daily, 80% ethanol as a single dose or *Terminalia chebula* ethanolic extract (400 mg/kg) orally daily respectively. In the last day of the experiment, a single dose of 80% ethanol was given to the animals in group 3 which received plant prophylactically, 1 hour before animals been scarified to induce gastric erosion in it. Blood samples were collected from animals in the three groups, prior to the end of the experiment, for hematological assessment of blood glucose, blood urea, blood creatinine, alanine aminotransferase test (ALT), and Gamma-Glutamyl Transferase test (GGT) and triglycerides (TG). The results showed that in the group treated with *Terminalia chebula*, a significant reduction in blood glucose, urea, creatinine, ALT and GGT (65.16 ± 0.47 mg/dl, 36.16 ± 2.98 mg/dl, 0.72 ± 0.00 mg/dl, 57.33 ± 0.84 IU/l, 19 ± 3.82 IU/l) respectively was noticed in comparison to the induction group (174 ± 0.36 mg/dl, 46 ± 0.36 mg/dl, 0.83 ± 0.003 mg/dl, 96 ± 0.36 IU/l, 53 ± 0.36 IU/l) and the control group (169.5 ± 11.60 mg/dl, 52.66 ± 5.39 mg/dl, 0.62 ± 0.03 mg/dl, 63.66 ± 3.46 gm/dl, 26.33 ± 5.90 mg/dl) respectively at ($P < 0.05$). TG were not significantly affected in the treatment group comparing to the induction and the control group. The data were analyzed by student's *t*-test using SPSS (Version 10). The results were expressed as mean \pm standard error (mean \pm SE), *P* values < 0.05 were considered statistically significant. The data showed a protective activity produced by *T. chebula* against ethanol induced gastric erosion as showed by the histopathological examination of the harvested stomach from the animals in the three groups, as the distorted superficial gland by the effect of ethanol in the mucosa were regenerated in *T. chebula* treated group. In conclusion, the significant improvement of the blood parameters levels in the treated animals comparing to the induction and the control group, in addition to the protective effect on tissue level suggested the possible prophylactic activity that *T. chebula* have in the studied gastric erosion condition.

Keywords: gastric erosion, *Terminalia chebula*, rabbits

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دراسة الفعالية الوقائية للاهليلج ضد تآكل المعدة المحدث في الارانب

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الخلاصة

صممت هذه الدراسة لتقييم الفعالية الوقائية للاهليلج ضد تآكل المعدة المحدث في الارانب باستخدام الايثانول بتركيز ٨٠%. استمرت التجربة لمدة ١٦ يوم وتم خلالها استخدام ١٨ ارنب، حيث تم تقسيم الارانب الى ثلاثة مجاميع (٦ ارنب/مجموعة) وهي مجموعة السيطرة، مجموعة الاستحداث ومجموعة العلاج، حيث تم تجريب حيوانات المجاميع بالمحلول الملحي فمويا يوميا، ٨٠% ايثانول جرعة واحدة فقط او نبات الاهليلج المستخلص كحوليا بجرعة ٤٠٠ ملغم/كغم فمويا يوميا على التوالي. في اليوم الاخير من التجربة، تم تجريب

جرعة واحدة من الايثانول بتركيز ٨٠% للحيوانات في المجموعة الثالثة التي تتناول الاهليج وقائيا لاستحداث تآكل المعدة، وبعد مرور ساعة واحدة تم التضحية بحيوانات التجربة. عينات الدم تم جمعها من المجاميع الثلاثة قبل نهاية التجربة لغرض التقييم الدموي لمستوى كل من سكر الدم، نسبة اليوريا في الدم، نسبة الكرياتينين في الدم، نسبة الالانين امينوترانسفيريز، نسبة كاما كلوتاميل ترانسفيريز ونسبة الكليسيريدات الثلاثية. حيث اظهرت النتائج ان الحيوانات التي تم تجريعها بنبات الاهليج سجلت انخفاضا معتدا به في نسبة كل من مستوى السكر، اليوريا، الكرياتينين، نسبة الالانين امينو ترانسفيريز ونسبة كاما كلوتاميل ترانسفيريز (0.47 ± 65.16 ملغم/ دسلر، 2.98 ± 36.16 ملغم / دسلر، 0.72 ± 0.00 ملغم / دسلر، 57.33 ± 0.84 وحدة دولية / لتر، 19 ± 3.82 وحدة دولية/لتر) على التوالي مقارنة مع مجموعة الاستحداث (0.36 ± 174 ملغم/ دسلر، 46 ± 0.36 ، 0.03 ± 0.83 ملغم/ دسلر، 96 ± 0.36 وحدة دولية، 53 ± 0.36 وحدة دولية) ومجموعة السيطرة (11.60 ± 169.5 ملغم/ دسلر، 52.66 ± 5.39 ملغم/ دسلر، 0.03 ± 63.66 ملغم/ دسلر، 3.46 ± 26.33 ملغم/ دسلر) على التوالي تحت مستوى احتمالية > 0.05 . بينما لم يحصل هناك تغيير معتد به في مستوى الكليسيريدات الثلاثية. تم تحليل النتائج باستخدام اختبار T الطلبي وباستعمال برنامج التحليل الإحصائي SPSS (النسخة 10) حيث عبر عن النتائج بشكل المتوسط الحسابي \pm الخطأ وتحت مستوى احتمالية > 0.05 . بينت نتائج التقطيع النسيجي لمعدة الحيوانات في التجربة إعادة تشكيل لخلايا الطبقة المخاطية في مجموعة العلاج بالاهليج والتي فقدت شكلها المنتظم في مجموعة الاستحداث بتأثير الايثانول. يستنتج ان التحسن المعتد به في مستوى معايير الدم بين حيوانات مجموعة العلاج مقارنة مع مجموعة الاصابة ومجموعة السيطرة. بالإضافة الى الحماية المستحصلة على المستوى النسيجي، كلها تشير التأثير الوقائي لنبات الأهلج ضد حالة تآكل المعدة المدروسه في البحث.

Introduction

Gastric erosions can be endoscopically described as a recognizable mucosal breaks which do not reach to the muscularis mucosae. It might last for a short-term or can also be, chronic or intermittent. Many factors can play a role in the development of gastric erosions of which Herpes simplex virus (HSV), Helicobacter pylori (H. pylori), hyperacidity, use of alcohol and nonsteroidal anti-inflammatory drugs (NSAIDs), also cigarette smoking (1).

Plants have been used anciently for the treatment of various human diseases, as a potent therapeutic agents, including, cancer, ulcer, inflammations, etc. Large population in the world depend mainly on plants for medication due to the low level of side effect, and the therapeutically effective results they provide (2).

In this modern era also 75-80% of the world populations still use herbal medicine mainly in developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and less side effects. The chemical constituents present in the herbal medicine or plant are a part of the physiological functions of living flora and hence they are believed to have better compatibility with human body (3).

Terminalia chebula is a medium- to large-sized tree that can be found in the tropical and subtropical Asia. It consists of 250 species (4). Antibacterial activity of *Terminalia chebula* extracts against several bacterial strains have been reported (5). *Terminalia chebula* is considered as a traditional medicine that is consistently used to treat diseases such as urinary tract infection, gastrointestinal diseases, skin diseases, fever, diarrhea, and wound infections (4). Extracts from different parts of plant can be used for this applications such as root, flower, leaves and seeds (6).

In *Terminalia chebula*, 33% of the total phytoconstituents are hydrolysable tannins (which may vary from 20-50%) and are responsible for pharmacological activity.

These tannins contain phenolic carboxylic acid like gallic acid, ellagic acid, chebulic acid and gallotannins such as 1,6 di-*O*-galloyl- β -D-glucose, 3,4,6 tri-*O*-galloyl- β -D-glucose, 2,3,4,6 tetra-*O*-galloyl- β -D-glucose, 1,2,3,4,6 penta-*O*galloyl- β -D-glucose. Ellagitannin such as punacalagin, casuarinin, corilagin and terchebulin and others such as chebulanin, neochebulinic acid, chebulagic acid and chebulinic acid reported in literature (7,8). The tannin content varies with the geological variation. Flavonol glycosides, triterpenoids, coumarin conjugated with gallic acid called chebulin, as well as phenolic compounds were also isolated (9).

The effect of concentrated ethanol in the induction of gastric lesion was described previously(10). 40% ethanol produce both focal mucosal hyperemia and widespread exfoliation of the surface epithelium. Massive release of mucus accompanied both events (11).

The *T. chebula* extract increased mucus production in aspirin and ethanol-induced ulcer models and showed antisecretory activity in pylorus ligated model leading to a reduction in the gastric juice volume, free acidity, total acidity, and significantly increased gastric pH (12).

This study aimed to discover the prophylactic effect of *Terminalia chebula* in induced gastric erosion in rabbits and to find it is effect on different parameters including the histopathological examination of the stomach of the treated animals in the end of the experiment and some other blood sample tests.

Materials and methods

Medicinal plants

The fruits of *Terminalia chebula* (Haritaki) was purchased from local market, identified by the national Iraqi institute for herbs, the fruits of the plant were subjected to aerial drying for two weeks, after drying were grinded very well until it became as a fine powder using electric grinder (Alaraby, Egypt).

Animals

Eighteen healthy, local, domestic rabbits weighing (1750-2000) gm of both sexes were used in this study. They were supplied by the local animal market at Al-Diwaniya city. Rabbits were housed two per cage, and were fed standard oxid pellets, also given water *ad libitum*.

Experimental design

Eighteen rabbits were randomly divided into three groups (6 rabbits/ group). The first group (control group) given normal saline daily for 15 days, while each animal in the second group (induction group) received one dose of 1 ml/kg of 80% ethanol to induced gastric erosion only in day 16 of the experiment 1 hour before the animals been sacrificed. Animals of the third group (treatment group) received (400 mg/kg B.W./day) of ethanol extract of *T.chibula* orally daily for 15 days using gavages needle (13).

Preparation of ethanol extract

Ethanolic extract of *T.chibula* was prepared according to the method of Le Grand (14).

Gastric erosion induction in rabbits

One ml of 80% ethanol was used orally to induce gastric erosion (15). Animals were fasted for 24 hour following the last dose of *T.chibula* extract on day 15 of the experiment. For the induction and treatment group animals, 1 ml/kg of 80% ethanol was administered orally, and one hour after the ethanol administration, animals in the three groups were sacrificed under chloroform anesthesia, and the abdomen was opened.

The stomach was removed and placed on Petri dish, then injected via any of gastric orifices with 10 ml of formalin 10% for 10 minutes to preserve the liner layer of the stomach. After that, the stomach was incised along the greater curvature and washed gently in running tap water. Finally, it was immersed in formalin 10% to be ready afterward for sectioning.

Blood samples

At the end of experiment, after induction of gastric erosion, blood samples were taken at 9 am on the last day

of the experiment, at most care by heart puncture. 5 ml of blood could be aspirated and collected in the Ethylene diamine tetra acetic acid anticoagulant coating tube (EDTA tubes), shaking gently to be used then for haematological assessment of blood glucose, blood urea, blood creatinine, ALT, GGT, and Triglycerides by using of Reflotron[®] Strips.

Histopathological examination

The tissue samples were fixed in 10% buffered formalin and processed with paraffin wax. For histopathological examination, 5 μ m sections were stained with hematoxylin and eosin. Histopathological examination was done by pathologist assistant lecturer Khalil Gizar in the Department of Pathology, Veterinary Medicine College, Al Qadissiyah University.

Data analysis

The data were analyzed by student's *t*-test using SPSS (Version 10). The results were expressed as mean \pm standard error (mean \pm SE), P values < 0.05 were considered statistically significant.

Results and discussion

Terminalia chebula have been claimed to be useful in various complaints. *Terminalia chebula* (family Combretaceae) is distributed throughout the sub-himalayala tracks and all deciduous forest of India. The plant has been studied for its antibacterial, antiviral, antifungal, antimutagenetic activity, antioxidant activity, hypolipidemic, adaptogenic and antianaphylitic activity, gastrointestinal motility improving and anti-ulcerogenic activity, radioprotective, antidiabetic, antispasmodic, wound healing, purgative, immunomodulatory and chemopreventive activity (15). Fruit of *Terminalia Chebula* is composed chemically of the myrobalan fruit has tannin (24-32%), the chief constituents of this tannin is Chebulagic acid, Chebulinic acid, Corilagin and gallic acid. It has 18 amino acids, sugar, phosphoric acid, succinic acid and some other acids in minute quantities. The concentration of tannin decreases in fruit as it matures and the acidity increases. Resin and purgative principle of anthraquinone and sennoside nature is also present. The seed pulp has a yellow colored oil. Ethanol serves as a most common ulcerogenic agent and when given intragastrically it produces severe gastric hemorrhagic erosions (16). The genesis of ethanol-induced gastric lesions is multifactorial with the depletion of gastric wall mucus content as one of the involved factors (17). This damage induced by ethanol may be due to mucosal leukotriene release (18). Mucosal blood flow has also been attributed to be an important factor in the damage caused by alcohol and is modulated by prostaglandin (19) Submucosal venular constriction by

ethanol and eventual injury is caused due to perturbations of superficial mucosal cells (19) notably the mucosal mast cells leading to release of vasoactive mediators including histamine, that cause damage to gastric mucosa (20). Ethanol-induced damage to the gastric mucosa is associated with a significant production of free radicals leading to an increased lipid peroxidation and damage to the cell and cell membranes. Accumulation of activated neutrophils in the gastric mucosa may be a source of free radicals (21).

One of the most sensitive and dramatic indicators of hepatocyte injury is the release of intracellular enzymes such as ALT and AST in the circulation. During hepatic damage, these transaminases present in the liver cells leak in to the serum, resulting in increased concentrations. The elevated activities of these enzymes are indicative of cellular leakage and loss of the functional integrity of the cell membranes in liver (21). The measurement of ALT is a sensitive and valuable indicator of hepatic injury since the enzyme activity is confined to the cytoplasm of liver (22).

The effect of *T.chebula* on the level of blood ALT enzyme and GGT was indicate a significant reduction of it is level (57.33±0.84 IU/l, 19±3.82 IU/l) which was agree with the result of (20) who also found that In *Terminalia chebula* treated group, liver enzyme level showed a significant decrease.

T. arjuna which is a species of *Terminalia* genus acts as an gastroprotective agent probably due to its free radical scavenging activity and cytoprotective nature (23).

The effect of *T.chebula* in lowering blood glucose level in this study (65.16±0.47 mg/dl) is also agree with the result of (24) who indicated a significant antidiabetic and renoprotective effects with the chloroform extract of *T. chebula* which is probably mediated through enhanced secretion of insulin from the β-cells of Langerhans or through extra pancreatic mechanism (24). Our result of blood glucose is also agree with the result of (25) who also used the extract of *T.chebula* and find that it cause a decrease in blood glucose level, serum creatinine level was

also reduced which was agree with our results, while he also mentioned that blood urea level was decreased by the effect of *T.chebula* which disagree with our results, also it had been found (15), that treatment with *T.chebula* lead to prevent the elevation of serum levels of creatinine, uric acid and blood urea, which is agree with our result for blood urea while disagree for the result of serum creatinine. Another group (26) used *T.chebula* in induced case of hyperlipidemia. They found that the rats receiving treatment with Haritaki (*T.chebula*) showed significant reduction in total cholesterol, triglycerides, total protein and elevation of high density lipoprotein cholesterol. Haritaki was found to possess significant hypolipidemic activity, while our results of TG level was none significant at (P<0.05) while, the result of our study showed that pretreatment with *T. chebula* extract showed a significant reduction in blood glucose, urea, creatinine, ALT, and GGT (65.16±0.47 mg/dl, 36.16±2.98 mg/dl, 0.72±0.00 mg/dl, 57.33±0.84 IU/l, 19±3.82 IU/l) respectively in comparison with the induction group (174±0.36 mg/dl, 0.83±0.003 mg/dl, 96±0.36 IU/l, 53±0.36 IU/l) respectively at (P < 0.05), whereas TG were not significantly affected (Table 1; Figure 1).

The histopathological examination of the stomach sections of the animals in the three tested groups showed a normal, mucosa layer and submucosa also with collagen fibers (Figure 2), while for the induction group an erosion in the superficial part of mucosa, produced by necrosis and destruction of the superficial glandular tissue was noticed (Figure 3), in the treatment group, the distorted superficial gland in the mucosa were regenerated, while some glands still necrotic (Figure 4), which might be due to the long duration of exposure to ethanol, or probably an after induction treatment with *T.chebula* is required to give a boost for the stomach mucosa recovery, which might require an addition of a fourth group of animals where the animals receive an a pre and post induction treatment with *T. chebula* for a few days then sacrificed and examined.

Table 1: Effect of *T. chebula* fruits ethanol extract on blood glucose, blood urea, blood creatinine, ALT, GGT, and triglycerides in 80% ethanol-induced gastric ulcer model (Mean±SE, n=6 animals).

Parameters Group	B.Glucose mg/dl	Urea mg/dl	Creatinine mg/dl	ALT IU/l	GGT IU/l	T.G mg/dl
Control group (normal saline)	169.5±11.60	36.16±2.98	0.62±0.03	63.66±3.46	26.33±5.90	128.5±16.05
Induction group (Ethanol)	^a 174±0.36	^a 46±0.36	^a 0.83±0.003	^a 96±0.36	^a 53±0.36	128±0.36
Treatment group (<i>T. chebula</i>)	^a 65.16*±0.47	^a 52.66*±5.39	^a 0.72*±0.004	^a 57.33*±0.84	^a 19*±3.82	122±23.19

*Significant lowering effect comparing to the induction group at P< 0.05,

^a Significant lowering effect comparing to the control group at P< 0.05

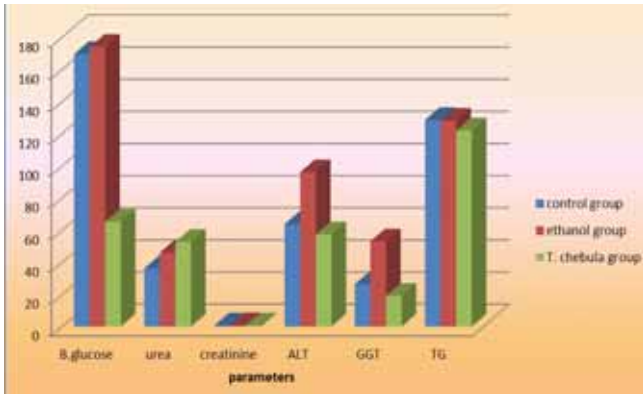


Figure 1: Effect of *T. chebula* fruits ethanol extract on blood glucose, blood urea, blood creatinine, ALT, GGT, and triglycerides in 80% ethanol-induced gastric ulcer model.

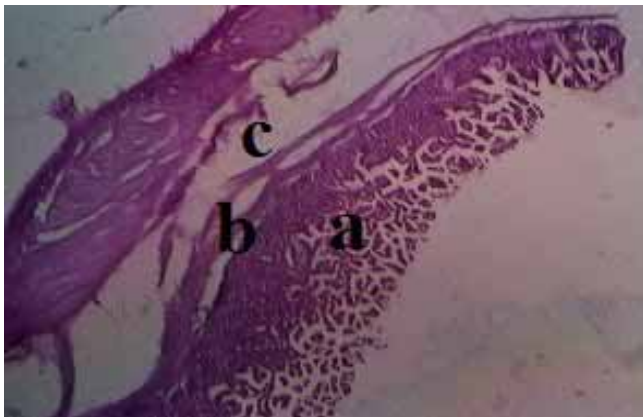


Figure 2: Control group- Normal, mucosa layer (a), submucosa with sparsely distributed collagen fibers (b) and muscularis layer (c). H&E, 40X.

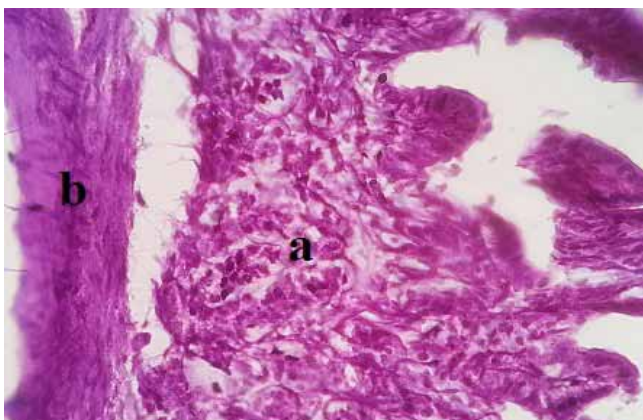


Figure 3: Control group -Normal, mucosa layer, submucosa with collagen fibers. H&E, 400X.

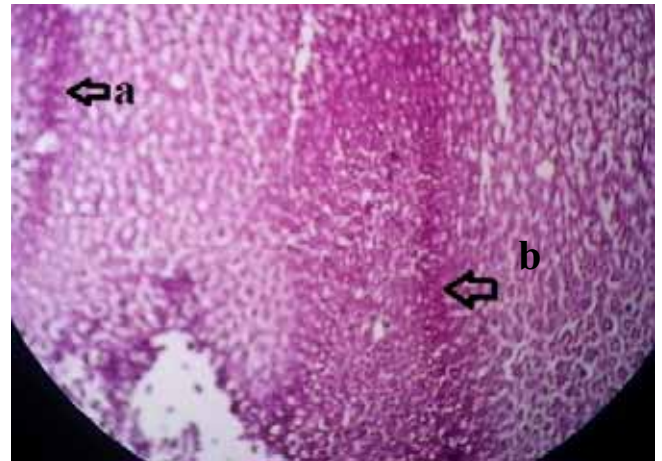


Figure 4: Induction group-There is saucer-shape erosion (a) and Wedge-shape erosion (black arrow) in the superficial part of mucosa, produced by necrosis and destruction of the superficial glandular tissue. H&E, 100X.

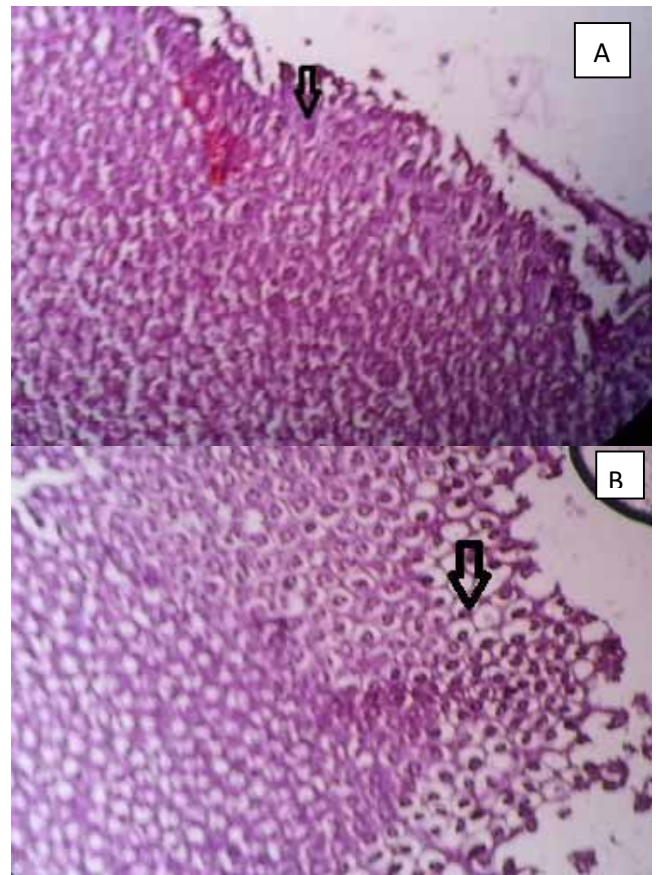


Figure 5: Induction group- (A&B) The superficial gland in the mucosa are distorted and necrotic (black arrow). H&E, 100X.

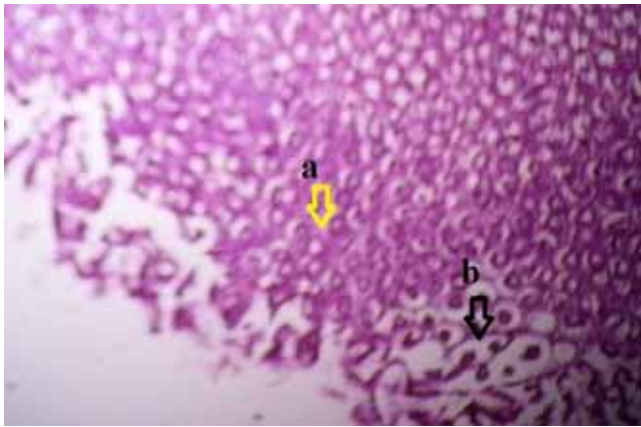


Figure 6: Treated group-Regenerated gastric erosion, (a) the distorted superficial gland in the mucosa are regenerated (yellow arrow), (b) while some glands still necrotic (black arrow). H&E, 100X.

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