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The effect of licorice (Glycyrrhiza glabra) on peptic ulcer in rats

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***Abstract*---**A peptic ulcer is sore on the lining of the stomach or duodenum; the two most common types of peptic ulcer are celled gastric ulcer and duodenum ulcer. Peptic ulcer are found to be due to an imbalance between aggressive factor such as hydrochloric acid (HCL), pepsin and refluxed bile. As the current study aimed to investigate the protective effect of Licorice against peptic ulcer.Thirty male Wistar albino rats were randomly divided into five groups (n = 6) as follow; -ve control group fed basal diet, +ve control group fed basal diet and injected with a single dose of Ranitidine (20mg/kg/day, bw, p.o.) (7 days). Groups 3-5 fed licorice with 1 ml. once a week, 1 ml. twice a week, 1 ml. three times a week respectively. Results revealed that licorice caused a significant decrease in blood cholesterol level, TG, LDL, AST, ALT, urea nitrogen, uric acid, creatinine, uric acid, albumin and VLDL. In addition, licorice caused a significant increase in HDL and PH, especially in group 5 which fed 3 ml. compared to +ve control group. Furthermore, licorice caused marked improvement for damaged histopathological lesions as showed normal histological gastric layers as well as significant improvement in mucosal and submucosal inflammatory cells in which number of cells is decreased. In conclusion, licorice protect rats against peptic ulcer through its active components from isoflavonoids (e.g., isoflavonol, kumatakenin, licoricone, glabrol); chalcones; coumarins (e.g., umbelliferone, herniarin); triterpenoids; and sterols, lignins, amino acids, amines, gums, and volatile oils which demonstrated impressive protection

mechanism against chemically induced ulcer formation in animal studies. So, it may be beneficial to the human beings.

***Keywords*---**peptic ulcer, licorice, rats, PH, helicobacter pylori.

Introduction

Peptic ulcer is an acid-induced lesion of the digestive tract that is usually located in the stomach or proximal duodenum, and is characterized by denuded mucosa with the defect extending into the submucosa or muscularis propria. The estimated prevalence of peptic ulcer disease in the general population is 5–10%, but recent epidemiological studies have shown a decrease in the incidence rates of hospital admissions, and mortality associated with peptic ulcer (Sonnenberg, A. 2013). Risk factors for developing peptic ulcer include H. pylori infection, alcohol and tobacco consumption, non-steroidal anti-inflammatory drugs (NSAIDs) use (Søreide, 2015) and Zollinger–Ellison syndrome. The main risk factors for both gastric and duodenal ulcers are H. pylori infection and NSAID use (Zhang, *et al* 2014).

Some of plants lose their efficiency against H. pylori consequent to the emergence of resistant strains. Consequently, the isolation of various constituents from the most active plant extracts is encouraged. It is important to emphasize that herbal products may contain numerous bioactive constituents with dangerous, but also beneficial effects. The major active component of licorice root is the triterpenoid saponin glycyrrhizin (also known as glycyrrhizic acid or glycyrrhizinic acid), which is usually found in concentrations ranging from 6% to 10%. The intestinal flora is believed to hydrolyze glycyrrhizin, yielding the aglycone molecule (glycyrrhetinic acid) and a sugar moiety, resulting in absorption of both (Hattori, 1983). A processed licorice extract, deglycyrrhizinated licorice (DGL), which is used in the treatment of peptic and aphthous ulcers, is made by removing the glycyrrhizin molecule. The active components of DGL are flavonoids. These compounds demonstrated impressive protection against chemically induced ulcer formation in animal studies (Yamamoto, 1992). Other active constituents of licorice include isoflavonoids (e.g., isoflavonol, kumatakenin, licoricone, glabrol); chalcones; coumarins (e.g., umbelliferone, herniarin); triterpenoids; and sterols, lignins, amino acids, amines, gums, and volatile oils (Chandler, 1985).

Causes of peptic ulcer

It may be varied as Helicobacter pylori, NSAIDs, Stress, Zollinger-ellison syndrome, smoking, caffeine, alcohol or genetic factor. Gastric ulcer is the most common disorder of the upper digestive tract. The prevalence of gastric ulcer is 2.4% in the Western population and annual incidence rates range from 0.10% to 0.19%. In certain regions of Mainland China, the prevalence of gastric ulcer is as high as 6.07% in the general population, and 22.5% of patients with gastrointestinal symptoms have gastric ulcer. Higher incidence usually occurs in people who smoke, use nonsteroidal anti-inflammatory drugs (NSAIDs), or consume alcohol. The recurrence rate is as high as 60%. Gastric ulcer has a significant economic impact. Average annual medical costs are $23819 for gastric

ulcer in the United States. In South Korea, the annual medical costs for gastric ulcer range from $959.6 to $2553.10 (Song, et al., 2013). Although some studies have demonstrated that Helicobacter pylori (H. pylori) eradication therapy is cost-effective, a more systematic study indicated that there was no significant cost difference per subject between eradication therapy and placebo. Although conventional regimens are effective, their side effects are often inevitable and limit clinical utility However, both clinical and experimental studies have demonstrated that herbal medicines exhibit therapeutic benefit for gastric ulcer with fewer side effects. Moreover, the cost of herbal medicine for gastric ulcer is only about one-sixth of that of Western medicine. In this paper, the efficacy, safety and mechanisms of action of herbal medicines in treating gastric ulcer are reviewed (Xiao, *et al.*, 2013).

Studies in humans and animal models suggest that herbal medicines exert their beneficial effects on gastric ulcer via multiple mechanisms, including antioxidant activity, stimulation of mucosal proliferation, inhibition of acid production and secretion, increased mucus production, as well as inhibition of inflammation. The medicinal use of licorice in both Western and Eastern cultures dates back several thousand years. It was used primarily as a demulcent, expectorant, antitussive, and mild laxative. Licorice is one of the most popular components of Chinese medicines. Its traditional uses include treating peptic ulcers, asthma, pharyngitis, malaria, abdominal pain, insomnia, and infections (Chandler, 1985).

The dosage of licorice for most clinical applications is based on the content of glycyrrhetinic acid. The exception is in the treatment of peptic ulcer. In this application, DGL is preferred, as it produces equally effective results compared with glycyrrhetinic acid but is free from any side effects. For most purposes, the goal is to achieve a high level of glycyrrhetinic acid in the blood without producing side effects (discussed later in “Toxicology”). In general, the following doses three times a day are safe and effective in raising glycyrrhetinic acid levels: , Powdered root: 1 to 2 g , Fluid extract (1:1): 2 to 4 mL , Solid (dry powdered) extract (4:1): 250 to 500 mg In the treatment of AIDS, pure glycyrrhetinic acid products or extracts standardized for glycyrrhetinic acid are recommended. Toxicity can become a problem for patients taking licorice for any period longer than 1 month (Stormer, 1993).

Materials and Methods

Materials

Plant Material: Licorice obtained from pharmacy farm, Cairo university, Egypt.
Chemicals: Ranitidine, ethanol and anesthetic ether will be obtained from El-Gomhoriya pharm, Cairo, Egypt.Casein, cellulose, sucrose, choline chloride D-L methionine, vitamins and minerals constituents will be purchased from El-Gomhoriya pharm. Cairo, Egypt.
Experimental animals: Thirty adult male albino rats (Sprague-Dawley strain), weighing about (150 + 10g) obtained from the Farm of Experimental Animals, Helwan, Egypt.

Methods

Preparation of plant Water extract:Dried licorice (Glycyrrhiza glabra leaves ground will be submerged in distilled water and allowed to soak overnight (20g/1litter of water) Induction of gastric ulcers: Ethanol (EtOH)-induced ulcers-The gastric ulcers were induced in rats by administering EtOH (1 ml/ 200 g, 1 hr) (Sairam, *et al,* 2001). Experimental design:Animals will be housed in well conditions in biological studies lab of Faculty of Home Economics. They will be kept in standard cages at room temperature (25±3 °C) with a 12 h dark/light cycle. They had been left for seven days as adaptation period and allowed to fed standard laboratory food and water.The basal diet included protein (14%), fat (5%), mineral mixture (3.5%), vitamin mixture (1%), cellulose (5%), sucrose (10%), choline chloride (0.2%) and the remainder was Corn starch. These constituents had been thoroughly mixed together and formulated according to (Reeves, et al., 1993).

Thirty mice have been divided into 5 groups equally as follows: Group 1: Rats had been only fed on basal diet till the end of the experiment and kept as a negative control group, only given distilled water each day up to 7 days. Group 2: Rats had been only fed on basal diet till the end of the experiment and kept as a Positive control group, given Ranitidine (20mg/kg/day, bw, p.o.) up to 7 days. Group 3: Rats suffered from peptic ulcer only fed on the basal diet till the end of experiment and administrated the aqueous extract of licorice once daily (1mL). Group 4: Rats suffered from peptic ulcer only fed on the basal diet till the end of experiment and administrated the aqueous extract of licorice twice daily (1mL). Group 5: Rats suffered from peptic ulcer only fed on the basal diet till the end of experiment and administrated the aqueous extract of licorice three times daily (1mL).

On the last day of the experimental period (seven days), all rats had fast except for drinking water, and had been sacrificed on the following day. Stomachs ligated around both openings (cardiac and pyloric) and injected by distilled water (2 ml). The gastric juice had been collected in a test tube and its volume measured. Then the stomachs opened longitudinally, washed with saline and examined under dissecting microscope for gastric ulcer. Gastric ulcer index had estimated as the length of gastric ulcer and expressed as (means ± SE) for each group. The curative ratio calculated for each group according to the method described by (Akhatar and Ahmad 1995) using the following equation:

Curative Ratio (CR) = (LC- LT/ LC) x 100

Where: LC = length of gastric ulcer in control positive group.
LT = length of gastric ulcer in treated group.

Measurement of volume of gastric juice: Gastric juices collected in test tubes and centrifuged at 500 rpm for 5 minutes. The volume of gastric juice measured by graduated cylinder.
Determination of total acidity of gastric juice: The total acidity of gastric juice determined by PH meter apparatus.
Biochemical analysis: Serum analyzed to determine the following parameters:
Lipid profile including (cholesterol, triglycerides, HDL-c, LDL-c and VLDL-c).

Kidney function including (Urea, Uric acid and Creatinine). Liver function including (AST, ALT and ALP).

Histopathological examination: The stomachs of the sacrificed rats taken and immersed in 10% formalin solution. The fixed specimens trimmed, washed and dehydrated in ascending grades of alcohol. Specimens then cleared in xylol, embed in paraffin, section at 4-6 microns' thickness and stained with Heamtoxylin and Eosin stain for examination of the stomach according to (Carleton 1979).

Statistical analysis: The obtained data were statistically analyzed according to the SPSS-PC (statistical package software), version, 11.0 (SPSS, 1986). The results were expressed as means ± SE. One-way analysis of variance (ANOVA) was used to test the differences between groups fed different herbs. The differences between means were tested for significance using least significant difference (LSD) test at ($P < 0.05$).

Results and Discussion

Regarding to Table (1): FI in group 5 was higher than all protective and other treatment groups with mean values 18.8g/d, BWG in group 5 fed on 3ml licorice was increased compared with +ve control group with mean values 8.46±0.10 vs 6.07±0.22g, respectively and FE in group 5 of rats was respectively increased compared with +ve control group with mean values 0.12±00.003 vs0.09±00.002. (Shalaby *et al*,. 2004) observed a considerable reduction in food intake and a marked increase in FER in their investigation on the group which impact of ethanol licorice extract against peptic ulcer in rats .

Table (1) - Body Weight Gain (BWG), Feed Intake (FI) and Feed Efficiency Ratio (FER)

Parameters / Groups	FI (g/d/rat)	BWG%	FER
G1: Control (-ve)	16	7.98±0.33 [a]	0.14±0.003 [a]
G2: Control (+ve)	15	6.07±0.22 [b]	0.09±0.002 [d]
G3: 1 ml	16.6	6.28±0.15 [b]	0.09±0.004 [d]
G4: 2 ml	18	7.92±0.26 [a]	0.10±0.003 [c]
G5: 3 ml	18.8	8.46±0.10 [a]	0.12±0.003 [b]

All values represented as mean ±SD.
Means with different superscript are significantly different ($p<0.05$)

Regarding to Table (3): The lowest mean value in total cholesterol was recorded in group 5 compared to the treatment groups 3 and 4, the lowest mean value in triglyceride was recorded in group 5 compared to the treatment groups 3 and 5, the lowest mean value in Low density lipoprotein was recorded in group 5 compared to the treatment groups 3 and 4 and the highest mean value in high density lipoprotein was recorded in group 5 compared to the treatment groups 3 and 4

Table 3 - Effect of licorice on Cholesterol (TC), Triglyceride (TG), High density lipoprotein (HDL), Low density lipoprotein (LDL) and very low density lipoprotein (VLDL) of Rats with ulcer

Parameters / Groups	Total Cholesterol	Triglycerides	HDL-C	LDL-C	VLDL-C
	mg/dl				
G1: Control (-ve)	96.37±1.33 c	79.38±0.66 d	55.90±0.79 a	24.29±0.84 c	15.87±0.13 d
G2:Control (+ve)	120.16±1.19 a	97.55±0.66 a	44.33±0.85 d	56.32±0.69 a	19.51±0.13 a
G3: 1 ml	101.61±1.22 b	92.16±0.75 ab	46.01±0.85 cd	37.18±0.39 b	18.43±0.14 ab
G4: 2 ml	97.96±1.68 bc	90.53±0.89 bc	49.51±0.91 bc	31.06±0.89 bc	18.10±0.55 bc
G5: 3 ml	96.37±1.45 bc	85.42±0.07 c	53.09±0.45 ab	26.21±0.58 c	17.08±0.64 c

All values represented as mean ±SD.
Means with different superscript are significantly different ($p<0.05$)

Regarding to Table (4): Result of kidney functions as evaluated by measuring the concentration of serum urea, creatinine, uric acid and albumin indicated that induced peptic ulcers and administration licorice were not significantly changed. The mean values of Urea concentration were ranged from (30.66±0.66 to 35.83±0.60), while Creatinine concentration means ranged between (0.72±0.07 to 0.84±0.04), Uric Acid concentration means ranged between (3.18±0.47 to 4.20±0.85) and Albumin concentration ranged from (3.30±0.06 to 4.06±0.14).

The effect of aqueous licorice extract (ALE) on antioxidant / oxidant stress balanced glutathione and malondialdehyde (MDA) in induced peptic ulcer (Makky *et al.*, 2012).

Table 4 - Effect of licorice on on serum urea, creatinine, uric acid and albumin of rats

Parameters / Groups	Urea mg/dl	Creatinine mg/dl	Uric Acid mg/dl	Albumin mg/dl
G1: Control (-ve)	30.66±0.66 c	0.72±0.07 b	3.42±0.68 bc	3.30±0.06 b
G2: Control (+ve)	35.83±0.60 a	0.84±0.04 a	4.20±0.85 a	4.06±0.14 a
G3: 1 ml	33.50±0.42 ab	0.83±0.03 a	3.51±0.78 b	3.50±0.11 b
G4: 2 ml	32.55±0.61 bc	0.78±0.02 ab	3.26±0.66 cd	3.49±0.79 b
G5: 3 ml	31.16± 0.53 bc	0.76±0.05 ab	3.18±0.47 d	3.42±0.86 b

All values represented as mean ±SD.
Means with different superscript are significantly different ($p<0.05$)

Regarding to Table (5): pH in (+ve control) was decreased compared with healthy group (-ve control) with mean values 4.00±0.09 vs 5.58±0.07, respectively. PH increased in protective group (G3) compared with (+ve) group with mean values 5.56±0.14 vs 4.00±0.09, respectively. Feed intake in group 4 which fed on diet with (2ml) licorice increased compared to positive control group with mean values 5.53±0.11 vs 4.00±0.09 g\d, respectively. whereas, group 5 was higher than all protective and other treatment groups with mean values 5.63±0.16.

Results of the effect of ALE on gastric juice PH in rats with peptic ulcer results , ulcer induction causes significant increase in the PH of gastric juice .the use of ALE significantly reduced the acidity of gastric juice. The anti-pepsin effect of licorice constituents cause a decrease in gastric juice acidity (Adel *et al.*, 2005).

Table 5 - effect of licorice on pH of gastric juice in rats

Groups	pH
G1: Control (-ve)	5.58±0.07 [a]
G2: Control (+ve)	4.00±0.09 [b]
G3: 1 ml	5.56±0.14 [a]
G4: 2 ml	5.53±0.11 [a]
G5: 3 ml	5.63±0.16 [a]

All values represented as mean ±SD.
Means with different superscript are significantly different ($p<0.05$)

Regarding to Table (6): Mean values of serum alanine amino transferase (ALT) of the +ve control group was significantly increased ($P<0.05$), compared to the negative control group 24.83 ± 0.30 vs 20.16 ± 0.65 respectively. serum alanine amino transferase (ALT) decreased in treatment groups (G3), (G4) and (G5) compared with the (+ve group) with mean values 23.00 ± 0.46, 22.50 ± 0.42 and 21.50 ± 0.43 vs 24.83 ± 0.30 respectively. Mean values of aspartate amino transferase (AST) of the +ve control group was significantly increased ($P<0.05$), compared to the negative control group 48.33 ± 0.55 vs 42.00 ± 0.68 respectively. serum aspartate amino transferase (AST) decreased in treatment groups (G3), (G4) and (G5) compared with the (+ve group) with mean values 44.66 ± 0.88, 43.83 ± 0.65 and 41.84 ± 0.60 vs 48.33 ± 0.55 respectively.

The result could be explained by glycyrrhizin is hepatoprotective propertied (Harwansh *et al.*, 2011). the current findings partially support (shalaby *et al.*, 2004) that oral treatment of licorice roots extract to male rats decrease in level of AST and ALT enzymes in blood serum .

Table 6 - Effect of licorice on liver function by measuring serum alanine amino transferase (ALT) and aspartate amino transferase (AST) of rats

Parameters / Groups	AST	ALT
	(µ /L)	
G1: Control (-ve)	42.00 ± 0.68 [c]	20.16 ± 0.65 [c]
G2: Control (+ve)	48.33 ± 0.55 [a]	24.83 ± 0.30 [a]
G3: 1 ml	44.66 ± 0.88 [b]	23.00 ± 0.46 [ab]
G4: 2 ml	43.83 ± 0.65 [bc]	22.50 ± 0.42 [ab]
G5: 3 ml	41.84 ± 0.60 [c]	21.50 ± 0.43 [bc]

All values represented as mean ±SD.
Means with different superscript are significantly different ($p<0.05$)

Stomach Histopathological

Regarding to Table (7): Microscopical examination of stomach of rat from group 1 revealed no histopathological lesions and normal histological gastric layers (Figs. 1 & 2). On contrary, stomach of rats from group 2 revealed shortening and necrosis of gastric mucosa, congestion of mucosal blood vessel associated with submucosal and inflammatory cells infiltration (Figs. 3, 4 & 5). Meanwhile, some examined sections from group 3 showed no histopathological changes (Figs. 6 & 7), whereas, other sections described mucosal and submucosal inflammatory cells infiltration as well as submucosal edema (Fig. 8). Moreover, some sections from group 4 revealed no histopathological changes (Figs. 9 & 10), whereas, other sections showed mild changes as few mucosal and submucosal inflammatory cells infiltration (Fig. 11). Furthermore, stomach of rats from group 5 exhibited no histopathological alterations (Figs. 12 & 13). According to these results of this experiment, this study recommends that peptic ulcer patients can use Licorice as a safe component for treatment which will be effective with 1ml. three times a day (3ml/ day max.).

Table 7 – Stomach Histopathological

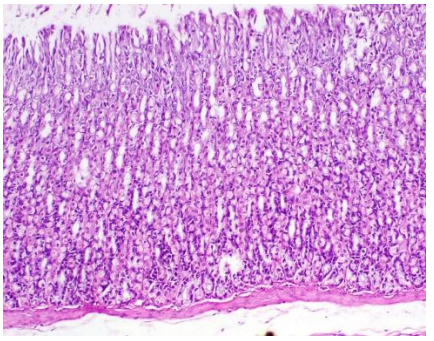

Fig. (1): Stomach of rat from group 1 showing no histopathological lesions; the normal histological gastric layers (H & E X 100).

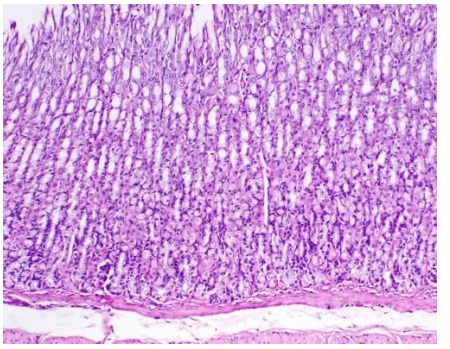

Fig. (2): Stomach of rat from group 1 showing no histopathological lesions; the normal histological gastric layers (H & E X 100).

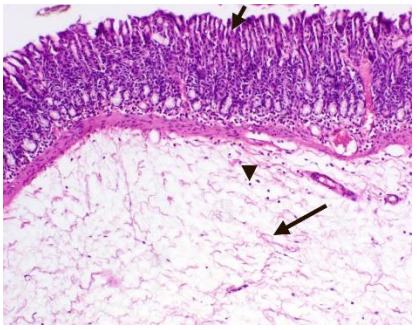

Fig. (3): Stomach of rat from group 2 showing shortening of gastric mucosa, (short arrow) associated with submucosal edema (long arrow) and inflammatory cells infiltration (arrow

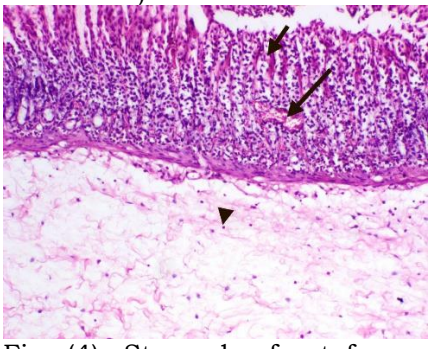

Fig. (4): Stomach of rat from group 2 showing necrosis of gastric mucosa (short arrow) associated with congestion of mucosal blood vessel (long arrow)

head) (H & E X 100).

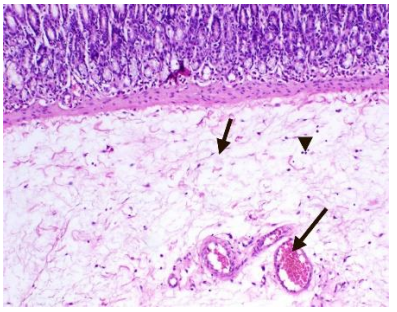

Fig. (5): Stomach of rat from group 2 showing submucosal edema (short arrow), congestion of submucosal blood vessel (long arrow) and inflammatory cells infiltration (arrow head) (H & E X 100).

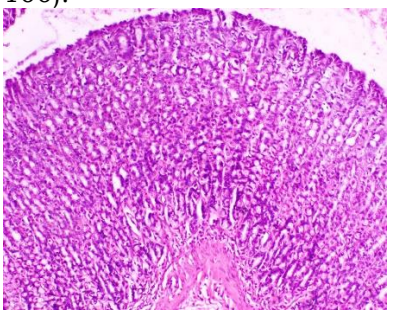

Fig. (7): Stomach of rat from group 3 showing no histopathological changes (H & E X 100).

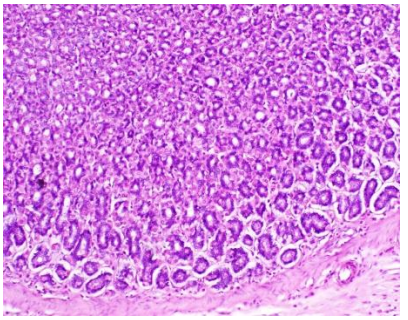

Fig. (9): Stomach of rat from group 4 showing no histopathological changes (H & E X 100).

and submucosal inflammatory cells infiltration (arrow head) (H & E X 100).

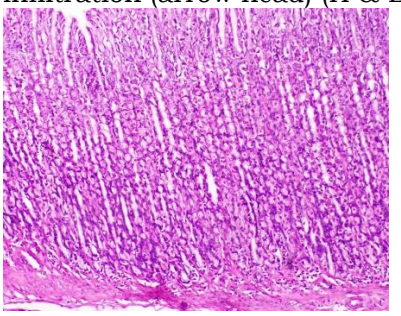

Fig. (6): Stomach of rat from group 3 showing no histopathological changes (H & E X 100).

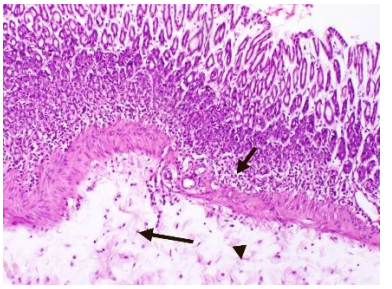

Fig. (8): Stomach of rat from group 3 showing mucosal (short arrow) and submucosal (long arrow) inflammatory cells infiltration as well as submucosal edema (arrow head). (H & E X 100).

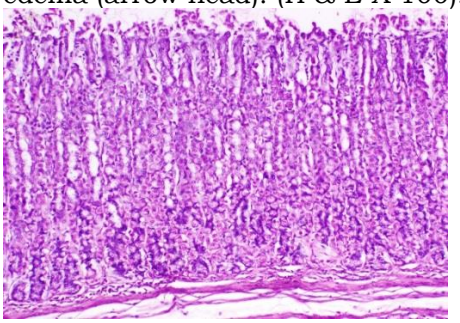

Fig. (10): Stomach of rat from group 4 showing no histopathological changes (H & E X 100).

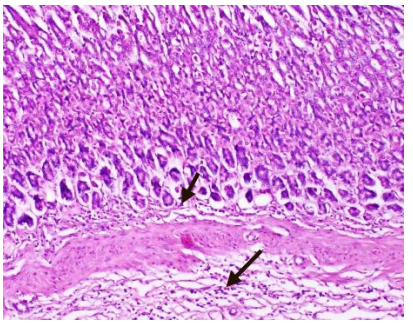

Fig. (11): Stomach of rat from group 4 showing few mucosal (short arrow) and submucosal (long arrow) inflammatory cells infiltration (H & E X 100).

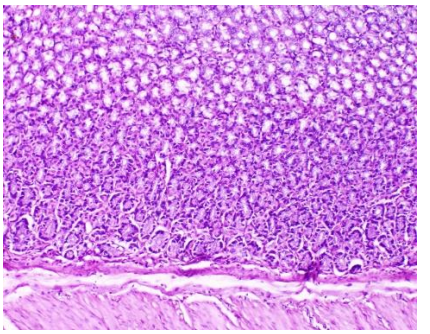

Fig. (12): Stomach of rat from group 5 showing no histopathological alterations (H & E X 100).

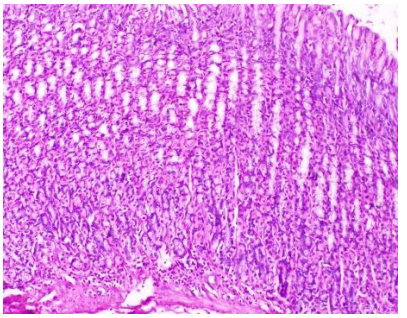

Fig. (13): Stomach of rat from group 5 showing no histopathological alterations (H & E X 100).

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