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TAURINE AMELIORATED THE COLONIC INFLAMMATORY SIDE EFFECTS OF INDOMETHACIN-TREATED RATS

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Abstract

Indometacin®, also known as indomethacin, is a nonsteroidal anti-inflammatory drug (NSAID) commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling from inflammations. Common side effects are headache, nausea, upset stomach and dizziness; others were diarrhea, constipation, sleepiness, stomach pain & ear ringing (tinnitus). Also, with indomethacin the gastrointestinal tract's mucosa is adversely affected. Taurine is the most abundant semi-essential β-amino acid in mammals with a broad anti-inflammatory and antioxidant activity, approved by FDA with its relatively high daily safe dose as an on-shell supplement and in various clinical cases.

The present study evaluated the effect of taurine on colonic inflammation and disrupted colonic architecture resulted as side effect in rats treated with indomethacin®.

A total of seventy female Sprague-Dawley (SD) rats were divided into four groups: Control (W), Water and taurine (W+T), indomethacin-treated (INDO) and taurine-treated (T). In indomethacin-treated group, rats received 1.5mg /1ml of water/rat for five consecutive days via intra-gastric gavage. In taurine-treated group, rats received taurine (0.05g/kg/day) in drinking water for one month after indomethacin treatment. Colonic inflammation, edema, macroscopic and microscopic damage were evaluated.

The results showed that indomethacin drug given for five consecutive days caused severe colitis with high levels of occult blood and loose stool consistency. Severe colonic shrinkage and colonic edema were also observed. Histological examination revealed disrupted histological architecture with presence of cryptic distortion and abscesses. Ulceration was also observed with disruption of epithelial surface. After taurine treatment, the average rate of water consumption was increased. Stool consistency, occult blood and body weight change significantly improved. The rate of colon shrinkage and colonic edema were also reduced. Also, taurine treatment restored almost normal histological structure.

Key words: Indomethacin, Taurine, colonic inflammation, colitis.

Introduction

The group of non-steroidal anti-inflammatory drugs (NSAIDs) is one of the most utilized groups of medications (Conaghan, 2012). They were approved FDA for use as antipyretic, anti-inflammatory and analgesic agents. These effects make NSAIDs useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout and migraines. Unfortunately, these treatments are usually associated with negative side effects, the most common of which are those affecting the gastrointestinal (GI) tract (Castellsague *et al,* 2012; Bjarnason *et al,* 2018). In addition to the upper GI tract, NSAIDs can also induce distal intestinal damages ranging from trivial small intestinal to colonic lesions (McEvoy *et al,* 2021). Few studies estimated mortality resulting from GI complications by NSAIDs (Lee and Katz, 2021).

Indomethacin (INDO) is one of the most common NSAIDs. It has negative effects on the mucosa of the gastrointestinal tract. Extra-intestinal lesions, inflammatory responses and inhibition of mucosal cell renewal are all caused by indomethacin therapy (Maity *et al,* 2009). The effect of indomethacin occurs by inhibiting the synthesis of prostaglandins that are produced primarily by cyclooxygenase (COX) enzymes (Gliszczyńska and Nowaczyk, 2021). Prostaglandins are essential for maintaining a healthy GIT, renal function and platelet function as well as being important mediators of pain, inflammation and fever. Indomethacin is considered as a prototype for a non-selective drug because it inhibits equally both COX-1 & COX-2 (Papich, 2020). Inhibition of COX enzymes by NSAIDs may explain some of

the drugs side effects (Moreira and Castells, 2011). Thus, finding ways to avoid gastrointestinal mucosal injury and inflammation efficiently and safely is a top goal.

Taurine is 2-aminoethane sulfonic acid derived from methionine and cysteine metabolism. It is one of the most prevalent free amino acids present in various mammalian tissues (Marcinkiewicz and Kontny, 2014). It plays a critical role in a number of vital biological processes including osmoregulation and membrane stabilization, maintenance of calcium homeostasis and bile acid conjugation (Ripps and Shen, 2012). Clinically, taurine has been used to treat various conditions including cardiovascular diseases, hypercholesterolemia, epilepsy and other seizure disorders, macular degeneration, Alzheimer's disease, hepatic disorders, alcoholism, and cystic fibrosis (Baliou *et al,* 2021). The preventive of taurine in treatment of several immune diseases particular certain intestinal disorders via reduction of inflammatory response were reported (Zhao *et al,* 2008).

The present study aimed to evaluate the effect of taurine supplementation on the colonic inflammation resulting as a side effect after treatment with indomethacin drug.

Materials and Methods

Animals: A total of seventy Sprague-Dawley (SD) female rats (n=70) were supplied by the experimental animal section of National Research Center (NRC, Cairo, Egypt). They were 7-9 weeks old and weighed 150-200g. Animals were randomly divided and housed 5 per cage. All animals had free access to food and water and maintained on a 12 h light: 12 h dark cycle, in a 21-23˚C room with 55-65% relative humidity. They were acclimatized for 7 days before being allocated to the main experimental groups. The animals were maintained, and the experimental procedures carried out in accordance with the Institutional Animal Care and Use Committee of Cairo University, Faculty of Science, Giza, Egypt (CU/1/S/27/16).

Experimental design: Seventy Sprague-Dawley (SD) female rats 70 were divided randomly into four groups: G1: 12 controls received water only without any treatments. G2: 12 didn't receive supplemented water for 5 consecutive days then received taurine (0.05g/kg/day) in drinking water for a month. G3: 23 received (1.5mg/ml/day) indomethacin (EIPICO-USP24) suspension via intra-gastric gavage for 5 consecutive days. G4: 23 received indomethacin via intra-gastric gavage for 5 consecutive days then taurine (0.05g/kg/day) was added to drinking water for one month. The given taurine concentration was a pharmacological dose and similar doses were used by as given (Erman *et al,* 2004).

Water consumption: Water consumed by each group was measured in ml, and the average consumption per each group was calculated.

Changes in body weight: Changes in body weight were measured in grams for all groups. The percentage of weight change was calculated compared to baseline weight using the following formula: (%) Body weight= [(final weight- initial weight)/ initial)]*100

Stool consistency and fecal blood: Stool consistency and fecal gross blood were monitored. If no blood was visible in the fecal material, hem-occult test was done using a calorimetric Kit (Testing Feces for Occult Blood, Bio-diagnostic, Dokki, Egypt) to evaluate fecal occult blood.

Collection of tissue samples: On days 6 & 30, 4 rats from each group were sacrificed using overdose of pentobarbital (50mg/kg, I.P). Colon was transected from the distal rectum and just distal to the cecum.

Colonic shrinkage: Colon was quickly flushed using cold phosphate-buffered saline (PBS) to remove feces and blood then its length was measured. Colon shrinkage rate was calculated as the following equation: (%) colonic shrinkage= [(Initial length (from control)- final length) /Initial length]*100

Wet: dry ratio: After flushing, parts of colon were gently dried and weighed. They were allowed to dry until the dry weight was

constant. Tissue water content was calculated from the following equation: Wet to dry ratio= (wet weight-dry weight)/ dry weight.

Microscopic examination: After flushing, colon was opened longitudinally and examined by a stereomicroscope; visible damage was scored on a 0-5 scale (Chen *et al,* 2007).

Histological examination: Different colon portions were fixed in 10% neutral buffered formalin. After routine processing for embedding in paraffin, the tissue blocks were prepared by histological techniques and cut at 5-6µm using Rotary Microtome (Levitz). Sections were stained with hematoxylin and eosin (Bancroft and Gamble, 2008). Stained tissue sections were examined using light microscope (CX41RF, Olympus light microscope; Olympus Corporation, Tokyo, Japan) and photographed using Olympus soft imaging camera (model SC100, Germany).

Statistical analysis: Data were completed using SPSS statistical software (SPSS for Windows, version 23.0). All values were expressed as mean± standard deviation. Statistical significance between different groups was determined using one-way analysis of variance (ANOVA) and Tukey's post-test. A value of $P<0.05$ was considered statistically significant.

Results

Water consumption: In G3, average water consumption rate significantly decreased (19.63±8.99ml) compared to G1 & G2. Taurine treatment caused significant water consumption increase compared to G3, & equal to average rates of G1 & G2 (23.80±5.61ml & 24.45±7.05ml) respectively.

Changes in weight: Significant decrease in body weight was in G3 (-13.48±5.16%) compared to other controls. Taurine treatment caused significant increase in body weight (16.09±5.88%) compared to G3.

Stool consistency and fecal blood: Stool was oval-shaped pellet with medium brown color in G1without consistency. In G3, stool became very soft to loose with a significant increase with average score of consistency (1.94±1.32). Post taurine treatment stool was mild soft to well-formed compared to others, with average consistency (0.41±1.18) decreased significantly compared to G3. In G3, average score of occult blood (2.20±1.40) increased significantly comparable to G1 & G2. Post taurine treatment, average score decreased significantly (0.28± 0.46) compared to G3, close to G1 & G2.

Examination of colon: Significant decrease in colon length (36.63±23.16 %) was in G3 compared to G1 & G2. Taurine treatment caused significant increase in colon length compared to G3. After taurine treatment length exceeded initial length in controls.

Wet: Dry ratio: There was a significant increase in wet/dry ratio (4.85±2.69) in G3 comparable to G1 & G2. Post taurine treatment (3.81±0.60) decreased significantly compared to G3, but with slightly edematous compared to controls.

Macroscopic score along colon: Extensive macroscopic damage along colon was in G3 as compared to G1 & G2. Serious colonic hemorrhagic ulceration, erosion and even perforation in some colon parts were seen as an obvious thinning in the colon middle part wall. Taurine treatment ameliorated macroscopic damage along colon and cured edema and hemorrhage, no erosion in colon and thickness returned to normal compared to G3. There was a significant increase in macroscopic scoring in G3 (4.40±2.355) compared to controls with significant decrease (0.33± 0.58) after taurine treatment.

Histological examination: Colon sections of G1 & G2 showed normal histological structure, with intact epithelial layer and numerous goblet cells surrounding crypts. Colons from G3 showed wide areas of mucosal necrosis, edema, desquamated areas and loss of epithelium. Diffused polymorphonuclear leucocytic infiltration in lamina propria and muscularis mucosa were clearly seen. Crypts were reduced in number with loss of goblet cells and even completely lost in some foci. Damage in structure of crypts and abscesses were noticed. After taurine treatment, inflammation and ulceration greatly reduced,

with a marked improvement and recovery of epithelial layer architecture, glandular structure and majority of crypts distribution be came almost normal.

Details were shown in table (1) and figures (1, 2, 3, 4, 3, 5, 6, 7, 8 & 9).

Table 1: Criteria for scoring of gross morphologic damage of colon

Score	Gross Morphology
0	No damage
1	Localized hyperemia, but no ulcers or erosions
2	Ulcers or erosions without significant inflammation
3	Ulcers or erosions with inflammation at one site
4	Two or more sites of ulceration and/or inflammation
5	Two or more major sites of inflammation and ulceration or one major site of inflammation and ulceration extending > 1 cm along colon length.

Discussion

In the present study, oral administration of indomethacin (1.5mg/ml/day) for 5 consecutive days caused severe colitis in rats caused 100% mortality. The rate of water consumption and body weight severely decreased. The score of stool consistency significantly decreased with high ratio of occult blood. Colon showed severe shrinkage with serious hemorrhagic ulcers, erosion and even ceacal perforation. The wall of the colon middle part was extremely thin. Severe edema in colonic tissue was also observed.

In the present study, the colon showed diffused inflammatory lesions and ulceration. Severe leucocyte infiltration in the mucosa with submucosa reached muscularis. There was focal erosion in the muscularis mucosa in some foci. There was also erosion of the epithelial surface with loss of goblet cells. Crypts were reduced in number and even lost in some loci. Damage in the structure of crypts as well as crypt abscesses were noticed. This agreed with Noori *et al*. (2020) who dealt with rodents. Besides, Nabarawi (2013) reported that mice received oral indomethacin (1mg/mouse) daily for five days showed severe gastro-enteropathy on the sixth day, with ulcer formation at many sites of digestive tract, especially in colon with increased granulocytes in intra-epithelium and lamina propria. Despite of the widespread usage of non-steroidal anti-inflammatory drugs (NSAIDs) in treatment of various inflammatory conditions, others showed that NSAIDS induced GI complications (Bonner, 2001; Takeuchi *et al,* 2006). Also, Oren and Ligumsky (1994) reported bleeding ulceration of the ascending colon associated with short-term indomethacin intake. Sigthorsson *et al.* (1998) found that NSAIDs-induced gastrointestinal injury due to a multistage process Tanaka *et al.* (1999) reported that NSAIDs increased intestinal expression of nitric oxide synthase and activity, leading to increased levels of NO and promoting increased intestinal permeability. NSAIDs can also impair the mitochondrial energy production necessary for tight junction (TJ) complex integrity, leading to increased intestinal inflammation and permeability (Somasundaram *et al,* 2000). Besides, Goldstein *et al.* (2005); Graham *et al,* (2005) reported that use of NSAIDs seriously affected the lower gastrointestinal tract and led to ulceration and perforation as well as extra-intestinal lesions, inflammatory responses, and the inhibition of mucosal cell renewal.

In the present study, colitis treated with taurine showed an obvious curative effect. Physiologically, taurine reverted bloody loose stool into normal with increase in water consumption and body weight. It also ameliorated macroscopic colonic shrinkage, lesions and colonic edema. This agreed with Shimizu *et al.* (2009) who in C57BL/6 mice reported that taurine supplementation significantly alleviated diarrhea severity, body weight decrease and colon shorten in dextran sulfate sodium (DSS)-induced colitis.
Taurine resulted as well in improved histological architecture. Restored crypts, goblet cells and decreased inflammatory cells infiltration occurred (Sukhotnik *et al,* 2016). The present results may be attributed to the char-

acteristics of taurine that were reported in previous studies. Taurine was found to be a protective agent against oxidative stress-induced pathologies such as gastrointestinal damage (Baliou *et al,* 2021). Its protection action against oxidative injury may take place through several mechanisms. Taurine was reported to act as membrane stabilizer against oxidative stress and inflammation by inhibiting chemokine secretion from intestinal cells (Shimizu *et al,* 2009; Sukhotnik *et al,* 2016; Schaffer and Kim, 2018). It was also reported to scavenge oxygen free radicals by up-regulating the anti-oxidant defenses, forming chloramines with HOCl, or binding free metal ions by its sulphonic acid group (Hagar, 2004; Çetiner *et al,* 2005).

In addition, taurine was also reported to inhibit oxidative stress-induced apoptosis in several cells including epithelial cells (Li *et al,* 2016). Several studies have shown that treatment with taurine has a protective effect on intestinal injuries owing to ischemia–reperfusion and lipopolysaccharides, which is supported by the significant decrease in histological scores and apoptosis indices after ischemia-reperfusion in rats (Xiao *et al,* 2018). In a model of potassium bromate-induced intestinal oxidative injury, taurine exerts an ameliorative effect by improving antioxidant defense and duodenum tissue integrity (Ahmad *et al,* 2015). The taurine treatment was found to ameliorate trinitrobenzene sulfonic acid (TNBS) - induced colitis by reducing pro-apoptotic pathway activation and preventing the loss of the anti-apoptotic pathway through inhibition of oxidative stress.

Such anti-inflammatory effects of taurine have been reported to occur locally in the inflamed tissues (Zhao *et al,* 2008) and the oral route is the best route of administration (Aïnad-Tabet *et al,* 2019). So, both *in vitro* & *in vivo* studies as well as clinical trials considered taurine and taurine derivatives as potential drugs in human medicine, including infectious and chronic inflammatory disease (Marcinkiewicz and Kontny, 2014).

Conclusion

The results proved positive impact of taurine supplementation on the side effects of post-indomethacin treatment. The beneficial anti-colitis effect of taurine was due to its ability to restore structure and function of colonic mucosa. Taurine® restored integrity of the colonic mucosal barrier was associated with its anti-oxidant and anti-inflammatory properties. So, the study recommended the taurine in patients treated with indomethacin either for short or long time.

Authors' declaration: They neither have conflict of interest nor received fund

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Explanation of figures

Fig. 1: Mean rate of water consumption by rats in all groups. Taurine significantly increased rate of water consumption compared to indomethacin ($P < 0.05$) a & b: different small letters indicate statistical significance.

Fig-2: Mean % changes of body weight in all groups (n=12/group), Taurine significantly increased % body weight changes compared to Indomethacin ($P < 0.05$).

Fig. 3: Stool consistency in groups. A significant decrease in consistency in taurine compared to INDO with significant difference ($P < 0.05$).

Fig. 4: Mean score of occult blood in groups, INDO recorded highest score of occult blood, but taurine showed significant decrease ($P < 0.05$).

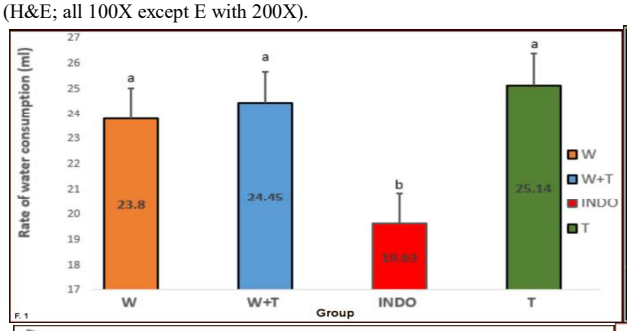
Fig. 5: Colonic shrinkage % in all groups, INDO showed significant colonic shrinkage compared to G1 & G2 Taurine caused significant recovery ($P < 0.05$).

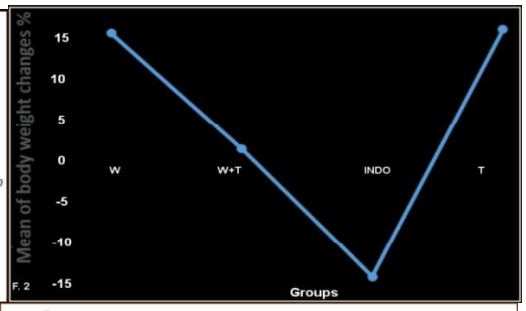
Fig. 6: Mean wet/dry ratio in all groups, Taurine showed significant reduction in wet/dry ratio comparable to indomethacin ($P < 0.05$).

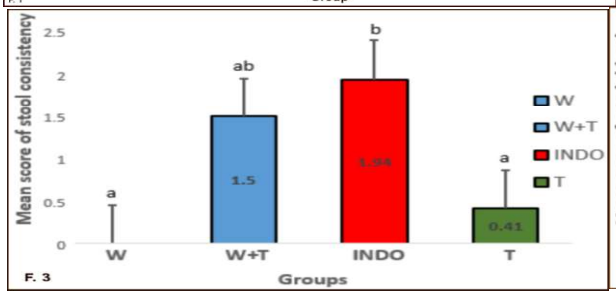
Fig. 7: Colon examination. (A) & (B): Of G1 & G2 showed no plaque lesions or ulceration. (C): Of INDO showed high level of hemorrhage, erosion and even perforation (black, blue and yellow arrows respectively). (D): Of INDO showed obvious lesions and thinning in middle wall (red arrows). (E): Of taurine-treated showed great amelioration in colonic damage and restored normal architecture.

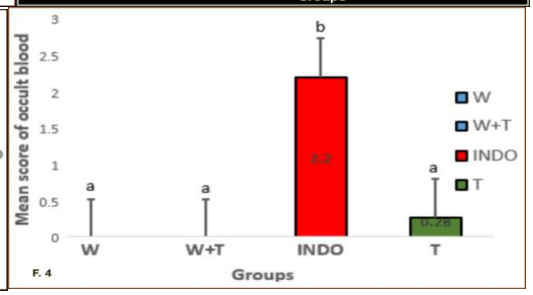
Fig. 8: Indomethacin caused a significant increase of colonic damage than control, taurine caused significant decrease ($P < 0.05$).

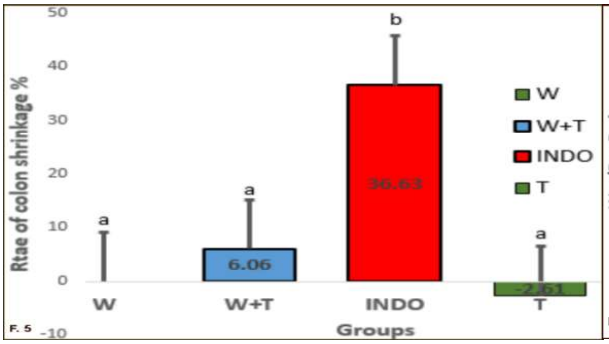
Fig. 9: Colon sections. A: control, showed neither histological changes nor tissue composition with normal epithelial layer (arrow). B: control G2, without histological changes in architecture or composition. C: indomethacin showed loss of crypts, ulceration and strong mucosa and submucosa inflammation down to muscularis (red arrow). D: diffused lesions of inflammation and ulceration (Green arrow). E: zonal erosion reached muscularis (Blue arrow). F & G: taurine caused improvement of epithelial layer compared to INDO with minor damaged foci (H&E; all 100X except E with 200X).

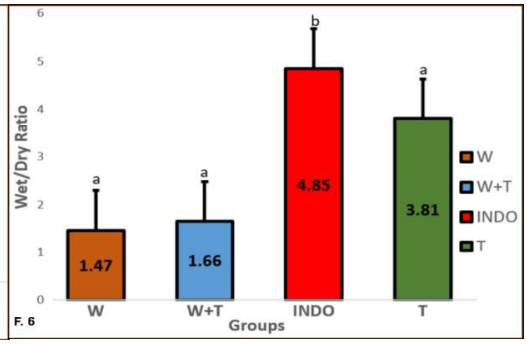


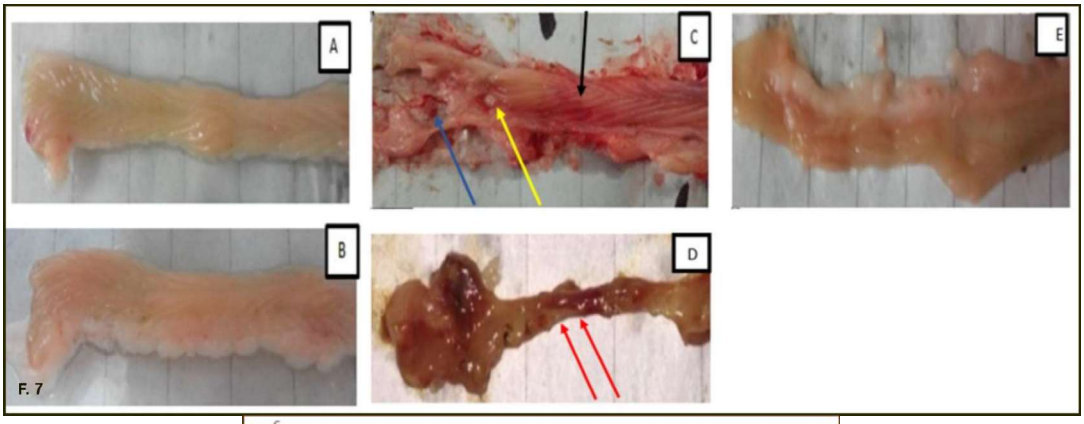








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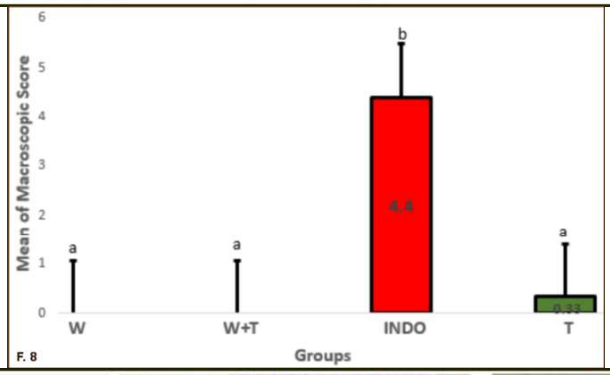
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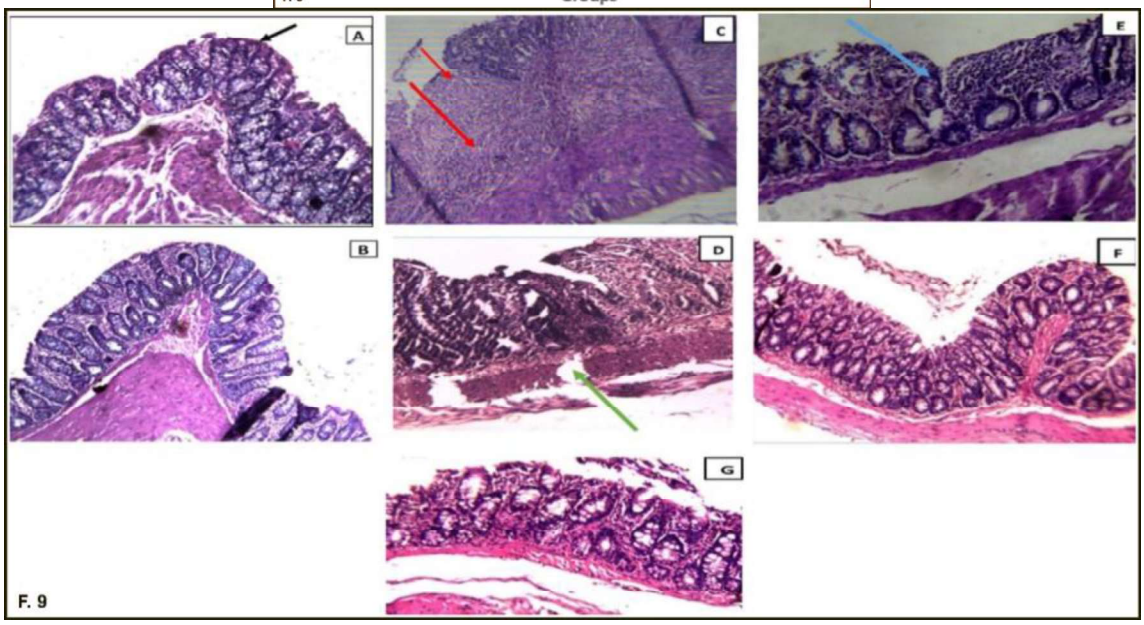
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