Histological Evaluation of the Protective Potential of Pioglitazone and Omega 3 on Dextran Sodium Sulphate Induced Colitis in Rats

Original Article

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ABSTRACT

Introduction: The management of ulcerative colitis (UC) depends on establishing novel alternate approaches that might minimize intestinal inflammation. Omega 3 and Pioglitazone has been found to suppress pro-inflammatory pathways via activating peroxisome proliferator activated receptor-γ (PPARγ).

Aim of the Work: The research effort attempted to assess the impact of omega 3 and pioglitazone on acute colitis which is experimentally triggered by dextran sodium sulphate (DSS) in rats.

Material and Methods: In the current work four distinct groups of 42 adult healthy male albino rats were established in the following order:

Group I (normal control group). Group II (DSS group): got 5% DSS via oral gavage daily for the first seven days, then followed by 3% DSS daily for the subsequent seven days. Group III (DSS+ PIO group): Rats recieved pioglitazone at daily dose of 10 mg/kg. Pioglitazone was dissolved in 0.9% NaCl via oral gavage for a total of 14 days consecutively commenced with the first day of DSS administration and proceeded until the completion of the study. Group IV (DSS+OMEGA3 group): Rats got omega 3 daily at a dose of 300 mg/kg via intragastric intubation for 14 days commenced with the first day of DSS administration and ending at the completion of the trial. Two weeks since the start of the study, rats were sacrificed then colon specimens were obtained, processed and evaluated using histological and immunohistochemical techniques.

Results: The DSS-induced colitis group displayed colonic epithelial erosions, inflammatory infiltration of the lamina propria, dilated and destructed intestinal crypts, mucin depletion, and goblet cell structural distortion. Group III exhibited improvement of these changes, whereas Group IV showed amelioration of the majority of these changes.

Conclusion: Omega 3 and pioglitazone mitigated most pathological alterations in DSS induced colitis.

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Key Words: Dextran sodium sulphate, omega 3, pioglitazone, ulcerative colitis.

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INTRODUCTION

Ulcerative colitis (UC) along with Crohn's disease is regarded as inflammatory bowel disorders, which are complex inflammatory diseases. Considering the etiology of UC is multifaceted, pharmacological treatment has not been refined, and the global incidence of UC is growing. All of these issues make UC a significant burden for both patients and society[1,2].

Because of the significant morbidity and treatment costs associated with UC, it is critical to establish experimental animal models that mirror the pathological process exhibited in humans, ultimately leading to novel efficient therapy alternatives. Colitis triggered by DSS is one of the most prevalent UC models mainly because of its rapidity, brevity, reliability, and controllability. Dextran sodium sulphate is a poly-anionic sulfated polysaccharide. It is solvable in water. Dextran sodium sulphate is of various sizes; nevertheless, DSS in the 40-50 kDa spectrum is typically utilized in model studies[3,4].

Pioglitazone is a highly selective agonist of PPARγ. Activation of these receptors inhibits multiple proinflammatory pathways that activate macrophages[5,6,7,8]. Pioglitazone is used to relieve metabolic abnormalities in type II diabetes[9,10,11]. Pioglitazone was proven to attenuate renal oxidative stress induced by gentamicin[12] and enhanced colonic barrier in animal model of irritable bowel syndrome[13]. Pioglitazone attenuated oxidative and endoplasmic reticulum stress in hypertensive rats[14].

Recently, a greater focus is paid to promising anti-inflammatory nutritional therapies, notably omega-3[15]. Omega-3 is a natural PPAR-γ agonist[16]. Omega-3 and its metabolites, possess multiple adventageous biological effects, comprising, anti-inflammatory, antiapoptotic, immunoregulatory, antioxidant and anticancer properties. Plants and marine animals are the main suppliers of omega-3. Omega-3-rich plant seeds include chia seed, flaxseed, and perilla seed.fat-laden fish as salmon and mackerel, as well as the liver of white lean fish like cod, are regarded excellent sources of omega-3 fatty acids[17].

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MATERIAL AND METHODS

Chemicals

- Dextran sodium sulphate (DSS) (MW, 40 kDa -whitish odorless powder) was gotten from Sigma Company, Cairo, Egypt.
- Pioglitazone tablets was purchased from (Actos® - Takeda Pharmaceuticals America, Inc.)
- Pure fish oil (100% concentration of Omega-3 fatty acids) was gotten from Sigma Company, Cairo, Egypt.

Animals and Ethical approval

Faculty of Veterinary Medicine, Benha University ethical committee validated the study's animal care and experimental protocols. Ethics committee approval (No: RC 20-2-2024).

A total of 42 adult healthy male albino rats aged two months, ranging between 180 and 200 grams were taken from the animal house at Faculty of Veterinary Medicine, Benha University. Rats were imposed five for each cage. All rats got free use of regular chow food and sterile water. Rats were kept under pathogen-free environment and under a controlled setting of humidity and temperature throughout the experiment.

Colitis induction and study plan

Animals were randomly assigned into four groups. Treatments were administered in accordance with the following daily pattern for 14 consecutive days:

Group I (control group; 12 rats): animals were evenly distributed to three subgroups:

- Subgroup Ia: Rats weren't offered any medications.
- Subgroup Ib: Rats were administered distilled water only by oral gavage (equivalent volume of distilled water to that of the model group, 0.5ml/rat/day) For a total of 14 days
- Subgroup Ic: Rats were given 0.9% NaCl saline (0.5 ml/rat/day) by oral gavage for 14 days (vehicle for pioglitazone).

Group II (DSS group; 10 rats): Rats were administered 5% (w/v) DSS by oral gavage daily for the first seven days to induce colitis, followed by 3% (w/v) DSS for the next seven days to prevent self-cure[18].

Group III (DSS + PIO group; 10 rats): Rats were given pioglitazone (10 mg/kg/d) dissolved in 0.9% NaCl to a volume of 0.5 ml/rat and supplied via oral gavage[8].

Pioglitazone was given simultaneously with DSS for 14 days.

Group IV (DSS + OMEGA3 group; 10 rats): Omega-3 was supplied to rats through oral gavage at a daily dose of 300mg/kg[19]. Omega-3 was given simultaneously with DSS for 14 days.

Sample collection

Rats were put under anesthesia with ether and sacrificed via dislocation of the cervical spine. All rats were sacrificed 14 days after the start of DSS consumption. Once sacrificed, the whole colon was collected. Digesta was carefully eliminated from the colon by washing with phosphate buffered saline (PBS), through a gavage needle. Tissue sections were prepared from distal colon tissues in the same horizontal segment.

Fresh colonic tissue was promptly immersed in the fixative, either 10% neutral buffered formalin (NBF) solution or 2.5% gluteraldehyde, for further histological analysis using light or electron microscopy respectively. Rats were eliminated through incineration.

Light microscopy

Haematoxylin and eosin staining (H&E):

A small segment of fresh colonic tissue was fixed in 10% NBF overnight before being serially dehydrated in ethanol (25%, 50%, 70%, 90%, 100%, 2 hours each) and then treated with xylene (2 hours twice). After embedding and forming paraffin blocks, sections of 5µm thickness were obtained. Then, colonic sections were deparaffinized with xylene (2-5 min, twice) and serially rehydrated in ethanol (100% to 25%, 2min each) before being washed with water. Colon sections were immersed for 10 minutes in Hematoxylin, washed, counterstained for five minutes with 1% eosin before being washed under running water. Sections were serially dehydrated, xylene-treated, and DPX-mounted. Stained slides were subsequently examined under the same lighting conditions, and photos were captured at various magnifications[20].

Alcian blue/ PAS stained- colonic sections (AB/PAS):

Combined AB/PAS staining, it is a comprehensive and a valuable technique as a means of detecting mucin. Alcian blue stains acid mucins blue but does not stain neutral mucins. The neutral mucins will be stained deep purple once the PAS technique has been applied. Sections were deparaffinized and hydrated. Then, Slides were immersed in 3% acetic acid before being immersed for 15 minutes in 1% alcian blue (pH 2.5). Colon sections were washed, then dipped for five minutes in periodic acid (0.5%). Colon sections were washed, then placed in Schiff Reagent, McManus. After washing, the slides were dipped in Hematoxylin Stain, Mayer Modified, for one minute. The slides were then dehydrated, cleared, and finally mounted[21].

Immunohistochemistry (IHC) to measure interleukin 17A (IL-17A):

Five µm – distal colon sections were deparaffinized by xylene, then subjected to serial rehydration in ethanol (100%, 90%, 80%, and 70%).The slides were then microwaved at 100°C for five minutes to retrieve antigens. Following washing in PBS, the slides were submerged

for five minutes in a 3% hydrogen peroxide solution. To reduce nonspecific background staining, 3-5 drops of blocking solution were added to each slide for 15 minutes. Slides were treated overnight at 4°C with Anti-IL-17A antibody (Cat. No. ab79056 at 2 µg/mL; Abcam, Cambridg, UK). Then, per the manufacturer's directions, a biotin conjugated secondary antibody was added to the slides, followed by streptavidin –HRP conjugate. The slides were treated with DAB chromogen (3,3′-diamino benzidine tetrahydrochloride) to detect peroxidase binding sites. Slides were placed in hematoxylin for counterstaining, dehydrated, cleaned with xylene, and finally mounted with DPX[22].

IL17A positive immunostaining is detected as brown cytoplasmic reaction in IL17A positive cells, and secreted in extracellular matrix(ECM). Both positive and negative controls were examined for specific immunohistochemical reactivity. Negative control slides conducted exactly the same immunostaining protocols, except that PBS was applied in place of the primary antibody. Positive control slides were human tonsil tissue, based on information supplied by the antibody manufacturer.

Transmission Electron Microscopy (TEM):

Specimens of distal colon were prefixed in glutaraldehyde (2.5% - 120 min) before being post-fixed in osmium tetraoxide (1% - 120 min). Following dehydration, specimens were dehydrated and placed into epoxy resin to form resin blocks. The semithin and ultrathin sections were obtained. Toluidine blue was utilized to stain the semithin (0.5µm thick) slices. To color ultrathin sections, the sections were cut at 80-90 nm thickness, mounted on copper grids, and for staining the ultrathin section, a two-step staining method was utilized, sections were placed for 15 minutes in 5% uranyl acetate and then placed in lead citrate for eight minutes. Ultrathin sections were examined and microphotographs were obtained by a transmission electron microscope (JEOL TEM; 100 CX; Japan) at EM unit of Faculty of Science, Alexandria University, Egypt[23].

Morphometric study

Sections were captured with Olympus® digital camera mounted on Olympus® microscope with a 0.5 X picture adaptor, a 40X objective, and saved as TIFF. The photos were processed on an Intel® Core I7® computer running VideoTest Morphology® software (Russia). Mean area % of goblet cells stained with alcian blue/PAS stain and mean area % of IL17A immunoreaction was measured. The results were put into an Excel sheet and displayed as percentage area of positive stain in relation to the overall field area. Two slides from each rat were used, and random five fields from each slide were analyzed.

Statistical analysis

Statistics measurements collected from the research were evaluated, and expressed as mean±SD of the individual groups with Statistical Package for Social Science software computer database variety 23 (SPSS, Inc., Chicago, IL, USA). In order to analyze variances between groups one-way analysis of variance (ANOVA) was used followed by Tukey's multiple comparisons test. Values of p less than 0.05 were set to be the minimum criterion for statistical significance.

RESULTS

Light Microscopic Results

In this study, no mortality between rats was recorded. Outcomes of all control subgroups showed similar histological findings; so, they are represented as one group.

H & E stain (Figures 1,2)

Group I (control group): Colonic histology displayed; mucosa, submucosa, musculosa and serosa. Colonic mucosa showed the surface epithelium that exhibited columnar absorptive cells with oval basal nuclei, abundant goblet cells with vacuolated cytoplasm and oval nuclei, lamina propria , occupied with long straight crypts reaching the prominent muscularis mucosa (Figures 1,2 (A,B)).

Group II (DSS group) showed surface epithelium with focal erosions, separation of surface epithelium, and cytoplasmic vacoulation of surface epithelium. Few goblet cells, abnormal crypts, diffuse inflammatory infiltration of lamina propria. Columnar absorptive cells exhibited pyknotic nuclei and lymphocytes infiltrating the crypts were frequently noticed. (Figures 2 C,D).

Group III (DSS+ PIO group) showed Lamina propria with leukocytic infiltration. Apparently normal surface epithelium with some intra epithelial lymphocytes. Numerous goblet cells were observed. Lamina propria with congested blood vessels and some peri-vascular inflammatory cells (Figures 2 E,F).

Group IV (DSS+ OMEGA 3 group) showed many colonic crypts with numerous goblet cells, lamina propria showed few inflammatory cells. Preservation of surface epithelium nearly normal columnar absorptive cells and abundant goblet cells were seen (Figures 2G,H).

Alcian blue/PAS stain: (Figure 3)

Group I colonic mucosa exhibited numerous crypts. Goblet cells lining the colonic crypts were numerous and goblet cells that dispersed among the columnar absorptive cells lining the colonic surface were frequently noticed (Figure 3A).

Group II showed deformed crypts lined with apparently fewer goblet cells. No goblet cells were observed between the surface epithelial cells (Figure 3B).

Group III showed mucosal crypts lined with numerous goblet cells with large thecae. Goblet cells were seen among the surface epithelium (Figure 3C).

Group IV showed numerous apparently normal crypts lined with abundant goblet with large thecae and goblet cells between surface epithelium were also noticed (Figure 3D).

IL17 immunohistochemical staining results: (Figure 4)

Positive immune reaction was indicated as brown cytoplasmic reaction in IL17A positive cells and secreted in ECM in lamina propria of colonic tissue.

Group I showed slight IL17 immune positive reaction (Figure 4A).

Group II showed strong positive immune reactivity (Figure 4B).

Group III displayed moderate positive immunostaining (Figure 4C).

Group IV displayed mild IL17 positive immunostaining (Figure 4D).

Transmission Electron microscopic results: (Figures 5,6,7,8)

Control group (Figure 5): ultrathin section showed columnar absorptive cells with normal well developed cell junctions of lateral borders composed of zonula occludens, zonula adherence and desmosomes , apical border with closely packed regular microvilli and basal euchromatic nuclei. Many mitochondria were noticed in the cytoplasm. Goblet cells showed normal polarization contained basal nuclei, abundant supranuclear cisternae of rER and distended apical thecae containing numerous mucin granules. Thin regular basal lamina was noticed. Lamina propria displayed well-organized collagen fibers, fibroblasts and blood vessels (Figure5 a,b,c).

DSS group (Figure 6): ultrathin section showed some columnar absorptive cells with disrupted apical microvilli some are lost. Abnormal cell junction with noticed wide separation between the cells, cell extrusion. Apoptotic cells separated from epithelial layer, appear shrunken and rounded up, surrounded by intact cell membrane were noticed, some cells appear electron dense with heterochromatic nuclei. Abnormal goblet cells some with few disarranged mucin granules and cytoplasmic vacuoles, other goblet cells with mucin granules of variable electron density. We also noticed degenerated goblet cells with abnormal dark condensation of mucin. Lamina propria revealed congested blood vessels, inflammatory cell infiltration with mast cells, plasma cells and lymphocytes. The basal lamina was thickened and interrupted. (Figure 6 d,e,f).

DSS+ PIO group (Figure 7): Showed columnar absorptive cells with partial preservation of microvilli structure. Focal loss of microvilli and cytoplasmic vacuoles are noticed. Cell junctions were preserved with desmosomes delineating the cell junction with preserved inter cellular space. Some desmosomes appeared disarranged with wider intercellular space. Partial preservation of goblet cells structure with basal nuclei and apical mucous granules. Partially thickened and interrupted basal lamina. Lamina propria exhibited some inflammatory cells like lymphocytes and eosinophils. (Figures g,h,i).

DSS+ OMEGA 3 group (Figure 8): ultrathin section showed columnar absorptive cells with euchromatic oval basal nuclei, abundant mitochondria, preserved closely packed apical microvilli and well-organized cell junctions with desmosomes delineating preserved intercellular spaces. Some columnar absorptive cells with small nuclei with nuclear chromatin condensation and swollen mitochondria were noticed.

Nearly normal goblet cells with basal nuclei, apical mucin granules (mu) and normal cytoplasmic electron denisity. Lamina propria showed more organized collagen fibers, fibroblast with elongated nucleus, some inflammatory cells like lymphocytes and eosinophils (Figures j,k,l).

Morphometric and statistical results

Descriptive statistics of mean area % of goblet cells stained with alcian blue/PAS stain (±SD) in in colonic sections of all the studied groups was done (Figure 3 Histogram E, Table 1)

The mean value reported for group I (control group) was (19.14±2.27). The mean value in group II (DSS group) was significantly reduced ($p<0.05$) to reach (7.89±0.94) in comparison with group I, group III (DSS+PIO group) (10.66±1.50), and Group IV (DSS+ OMEGA3) (14.11±1.54). The mean value reported for group III was reduced significantly ($p<0.05$), in comparison with group I and group IV. The mean value reported for group IV was significantly elevated ($p<0.05$) in coparison with group II and group III. However, it displayed a statistically significant decrease ($p<0.05$), as compared with group I.

Descriptive statistics of mean area % of IL17 immunoreaction (±SD) in colonic sections of all the studied groups was done (Figure 4 Histogram E, Table 2)

The mean value reported for group I (control group) was (2.02±0.37). There was a significant increase ($p<0.05$) in the mean value in group II (DSS group) to reach (32.43±4.14) in comparison with group I, group III (DSS+PIO group) (27.72±3.14), and Group IV (DSS+ OMEGA3) (17.28±2.53). The mean value reported for group III was statistically significantly elevated ($p<0.05$), when compared to group I and group IV. The mean value reported for group IV was statistically significantly decreased ($p<0.05$), in comparison with group II and group III. However, it displayed a significant decrease ($p<0.05$), as compared to group I.

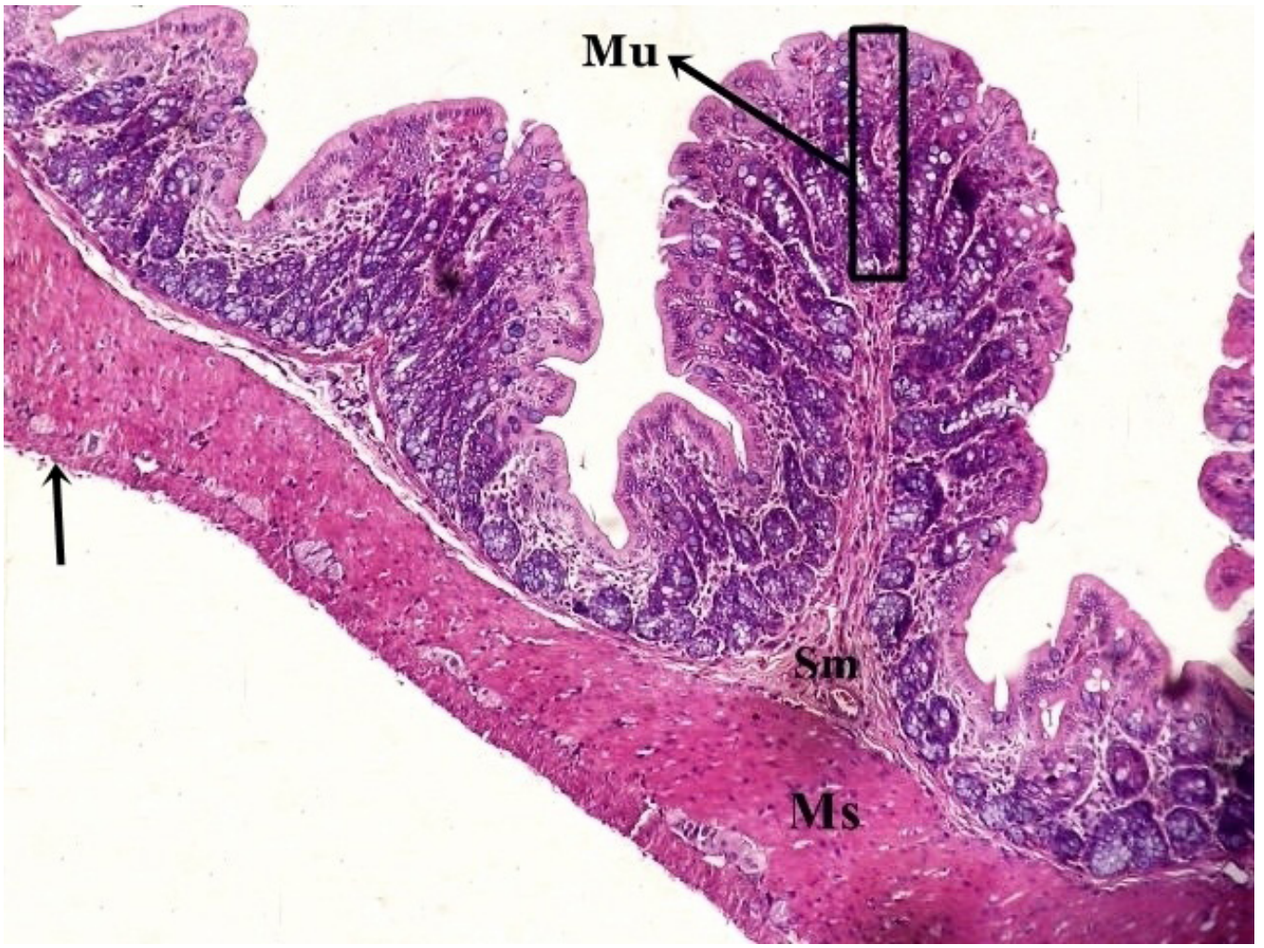

Fig. 1: Panoramic view of distal colon of adult male albino rat from control group Showing normal configuration of the wall layers; mucosa (Mu), submucosa (Sm) , musculosa (MS) and serosa (arrow). (H&E: X100).

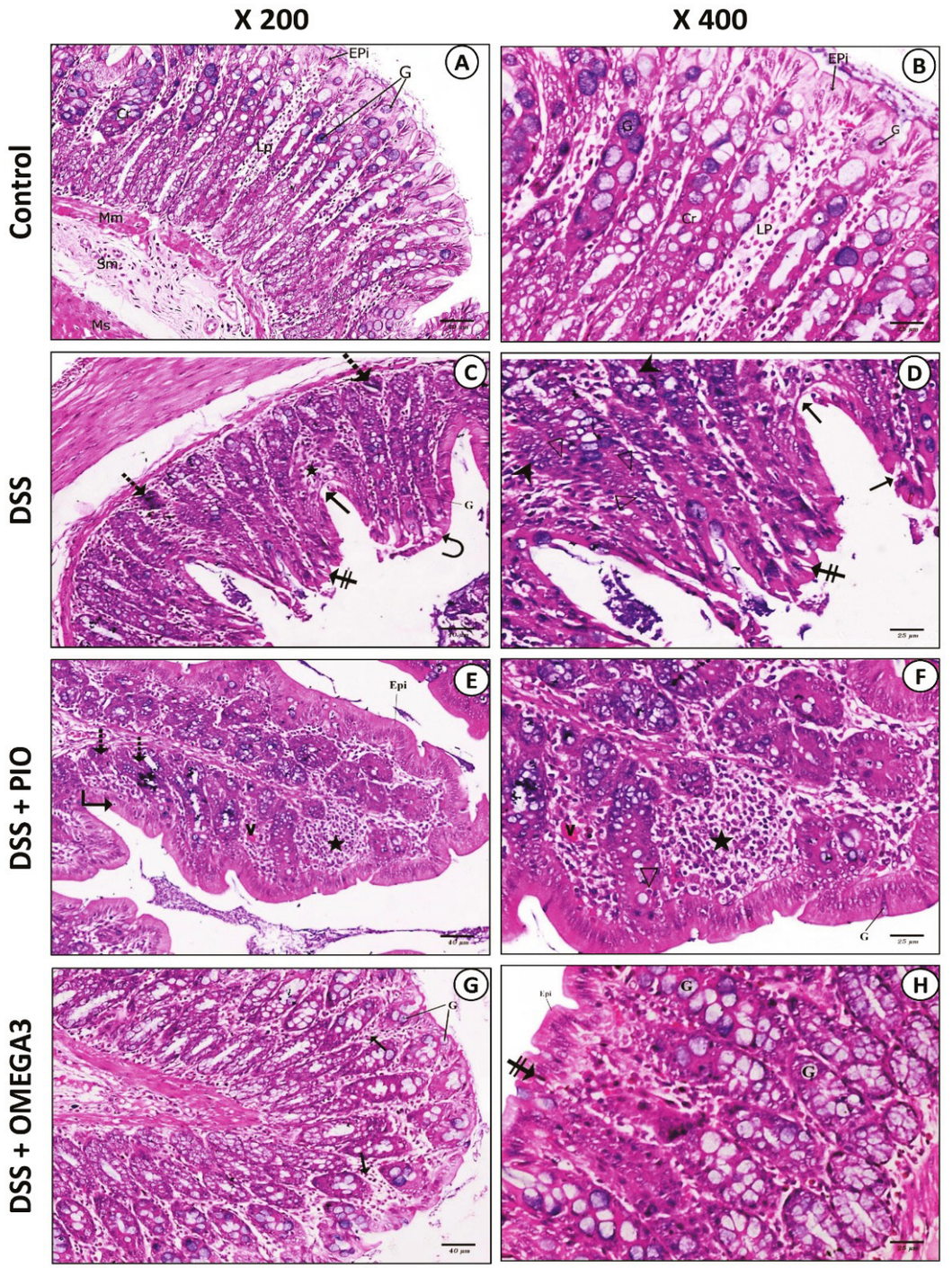

Fig. 2: (A&B: control group): (A) Mucosa is formed of surface epithelium (EPi), lamina propria (LP) , muscularis mucosa (Mm) , submucosa (Sm) and musculosa (Ms).G refers to goblet cells (B) Columnar absorptive cells (Epi) with basally located oval nuclei, abundant goblet cells (G) with vacuolated cytoplasm and oval nuclei, lamina propria (LP), occupied with long straight crypts (Cr). (C&D: DSS group): (C) Showing surface epithelium with focal erosions (arrow), separation of surface epithelium (curved arrow), cytoplasmic vacculation of surface epithelium (crossed arrow) , few goblet cells (G), abnormal shape of crypts (dashed arrows), diffuse inflammatory infiltrate of lamina propria (star). (D) Columnar absorptive cells with pyknotic nuclei and vaculated cytoplasm (crossed arrow), focal erosions(arrows), abnormal crypts (arrow heads) and lymphocytes infiltrating the crypts (hollow arrow heads). (E&F=DSS+ PIO group); (E) Lamina propria with leukocytic infiltration (star). Abnormal shape of crypts (dashed arrow). Apparently normal surface epithelium (Epi) with some intra epithelial lymphocytes (angled arrow), Letter V refers to blood vessel. (F) Lamina propria with blood vessel (V) and some perivascucular inflammatory cells. Arrow head refers to some lymphocytes infiltrating the crypt. G refers to goblet cells. (G&H=DSS+ OMEGA3 group): (G) Many crypts with numerous goblet cells (G) are noticed in the section, few inflammatory cells in lamina propria (arrows). (H) Preservation of columnar absorptive cells (Epi). Crossed arrow refers to a cell with pyknotic nucleus. Numerous goblet cells (G) were seen.

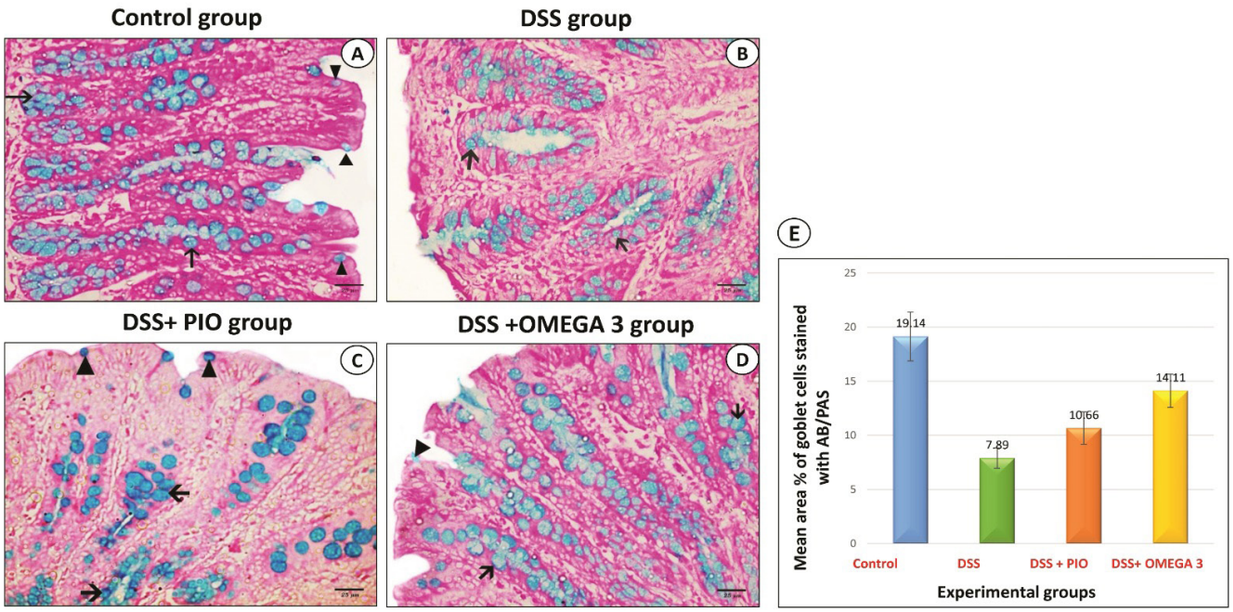

Fig. 3: Alcian blue/ PAS stained- colonic sections of adult male albino rats. (A) Control group: Representative of normal control group showing numerous crypts with numerous goblet cells (arrows) and numerous goblet cells on the surface (arrow heads). (B) DSS group: Showing deformed crypts lined with apparently fewer goblet cells(arrows) and no goblet cells noticed on the surface. (C) DSS + PIO group: Mucosal crypts lined with numerous goblet cells with large thecae(arrows). Goblet cells are seen between surface epithelium (arrow heads) (D) DSS + OMEGA 3 group: Numerous apparently normal crypts lined with abundant goblet with large thecae (arrows) and goblet cells between surface epithelium are also noticed (arrow head). (E) Statistical analysis Statistical analysis of % area of goblet cells stained with Alcian blue/PAS. Expressed as Mean ± SD between experimental groups (Alcian blue/PAS stain; X400).

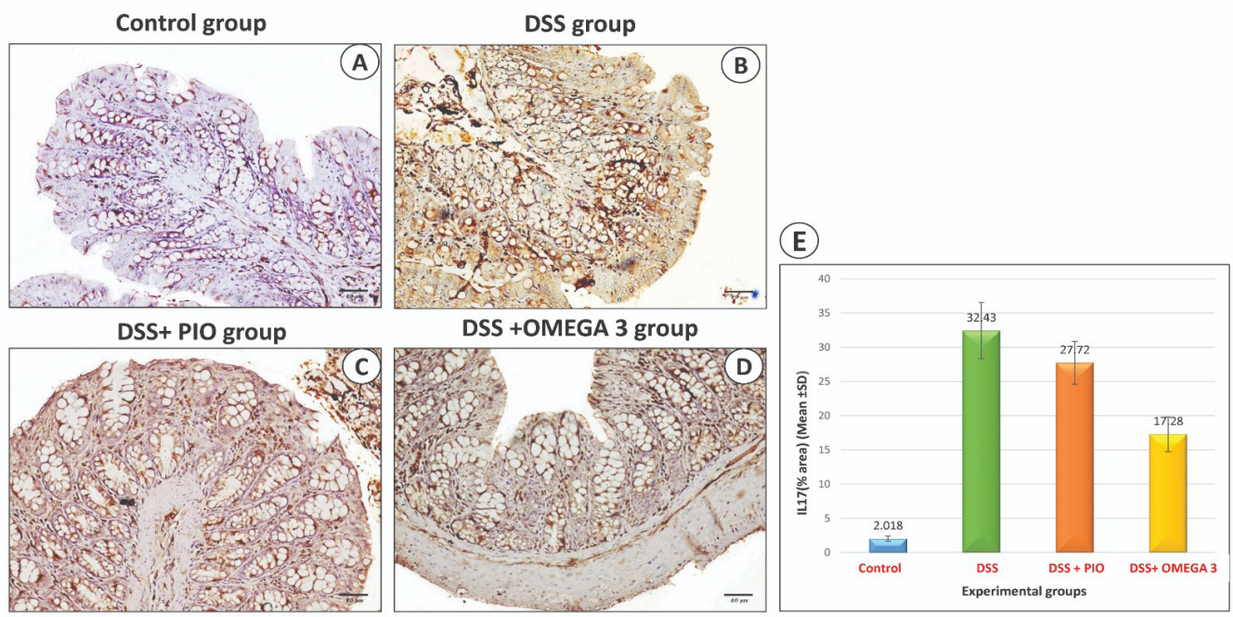

Fig. 4: Expression of IL17 in colon tissues of adult male albino rats, brown color indicates positive staining. (A) Control group: showing slight IL17 immune positive staining. (B) DSS group: strong immune positive reaction is noticed; (C) DSS + PIO group: Showing moderate positive reaction. (D) DSS + OMEGA 3 group: mild IL17 positive immunostaining is observed. (E) Statistical analysis of % area of IL17 positive immunoreaction. Expressed as Mean ± SD between experimental groups. (Anti-IL 17 stain; X400).

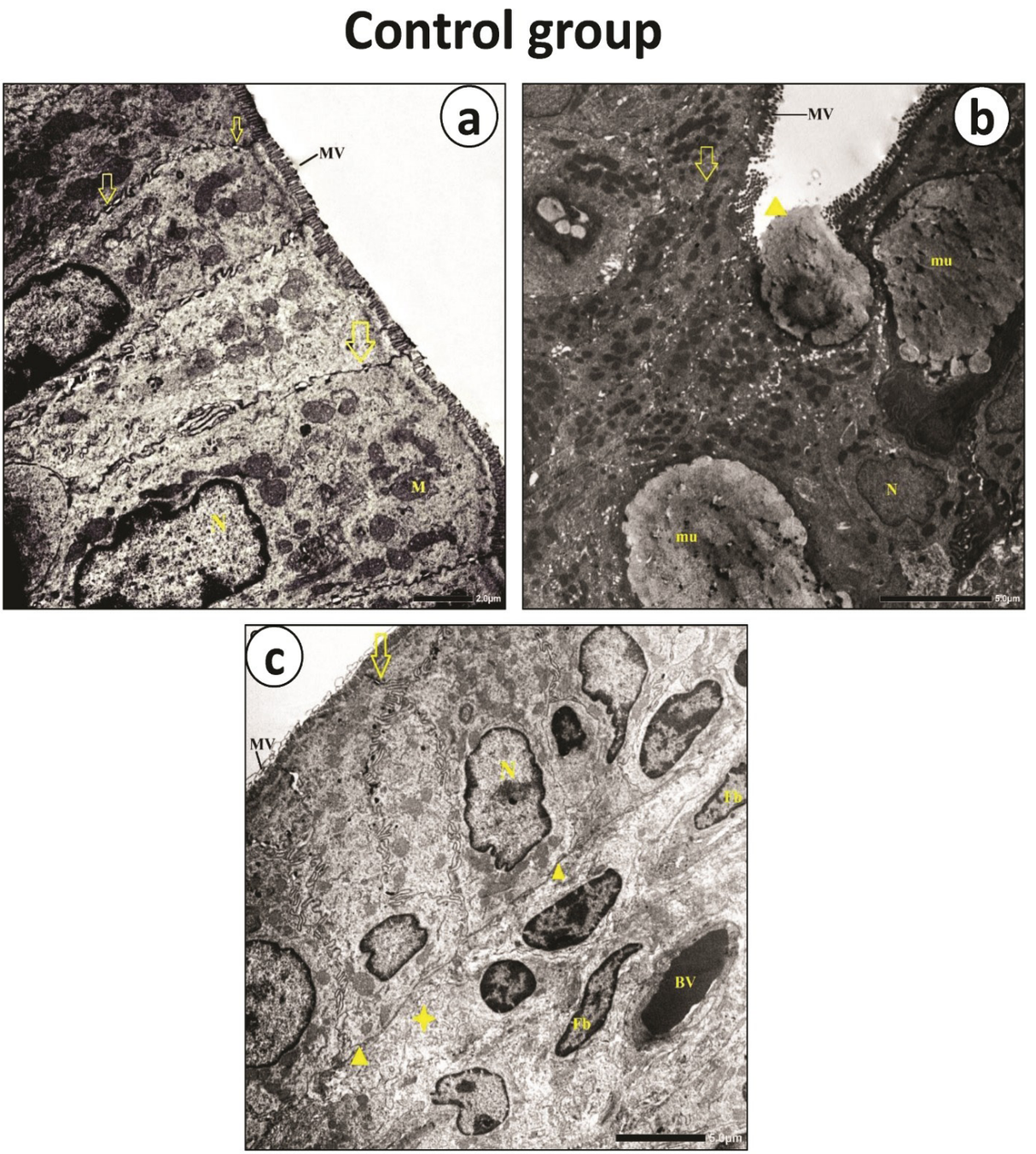

Fig 5: Photomicrographs of distal colon of adult male albino rats by transmission electron microscope (a, b & c= Control group); a) Showing columnar absorptive cells with normal well developed cell junctions of lateral borders composed of zonula occludens, zonula adherence followed by desmosomes (arrow), apical border with closely packed regular microvilli(MV), basal euchromatic nuclei (N) and normal mitochondria (M). b) Showing normal polarized goblet cells contained basal nuclei (N) and distended apical thecae containing numerous mucin granules (mu). Arrow head refers to goblet cell expelling its mucous onto the surface. Columnar absorptive cells also noticed containing regularly arranged closely packed microvilli (MV) and normal lateral borders (arrow). c) Showing columnar cells with apical microvilli (MV) and well developed lateral cell junctions (arrow) and thin regular basal lamina (arrow heads). Lamina propria (asterisk) was also seen with fibroblasts containing elongated nuclei (Fb) and blood vessel (BV) (a, b: Scale bar 2.0µm, c: Scale bar: bar 5.0µm).

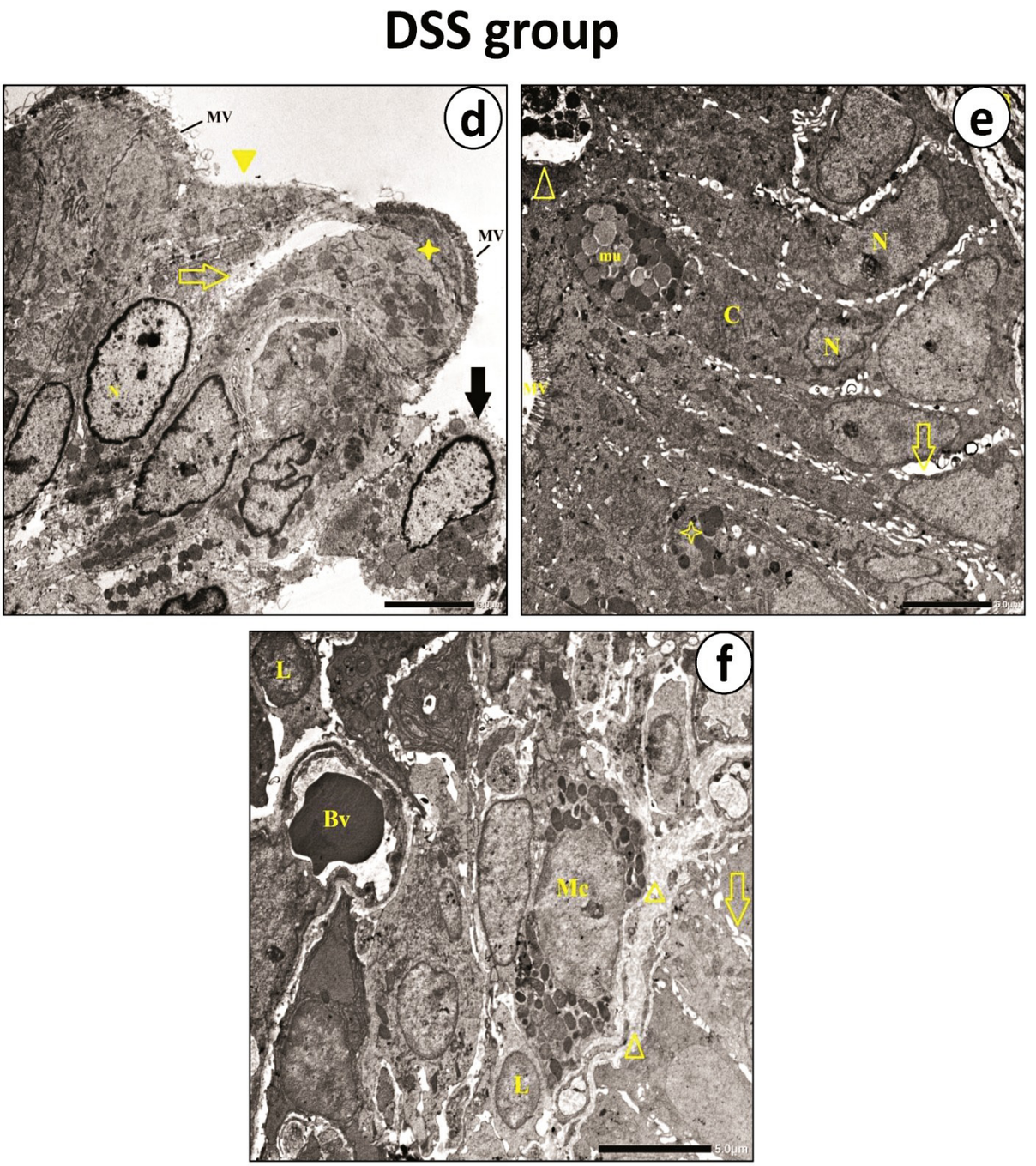

Fig 6: Photomicrographs of distal colon of adult male albino rats by transmission electron microscope (d,e,f= DSS group) ; d) Some columnar absorptive cells exhibited disrupted apical microvilli (MV) some are lost (arrow head), abnormal cell junction with noticed, wide separation between the cells (hollow arrow),cell extrusion(asterisk). Black arrow refers to an apoptotic cell separated from epithelial layer, which appears shrunken and rounded up , surrounded by intact cell membrane. N refers to the nucleus e) Abnormal goblet cells some with few disarranged mucin granules(asterisk) and cytoplasmic vacuoles, other goblet with mucin granules of variable electron density(mu). Arrowhead refers to degenerated goblet cell with abnormal dark condensation of mucin. Abnormal cell junctions and enhanced inter cellular spaces between columnar absorptive cells could be observed (hollow arrow).MV refers to apical microvilli. Notice the electron dense cytoplasm (C) and heterochromatic nuclei (N) f) Lamina propria revealing congested blood vessel (BV), inflammatory cell infiltration with mast cell (Mc) with plentiful electron dense granules and lymphocytes (L) arrow heads refers to thickened interrupted basal lamina. Separations between the cell were noticed (hollow arrow) (d, e, f: Scale bar: bar 5.0µm).

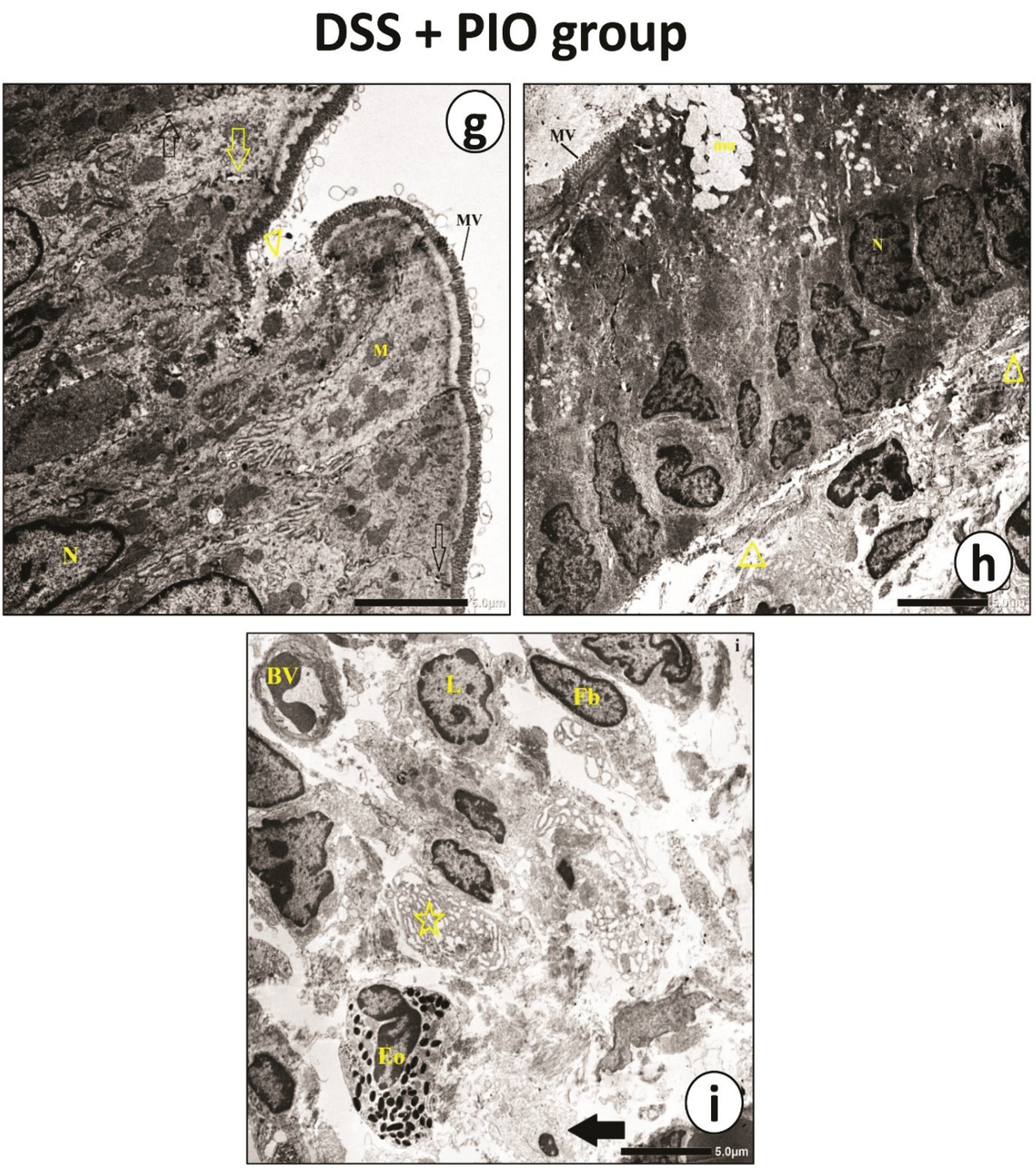

Fig. 7: Photomicrographs of distal colon of adult male albino rats by transmission electron microscope (g, h, i= DSS+PIO group). g) Columnar absorptive cells showed partial preservation of microvilli structure (MV). Focal loss of microvilli and rupture of cell membrane (arrow head). Cell junctions are preserved with desmosomes delineating the cell junction with preserved inter cellular space (black arrow) some desmosomes appeared disarranged with wider intercellular space (yellow arrow). Numerous mitochondria (M). Parts of nuclei (N) could be noticed h) Goblet cell with basal nucleus and apical mucous granules (mu) that coalesced and was discharging mucous onto the surface. Also, columnar absorptive cells are seen with basal nuclei (N), cytoplasmic vacuoles and some apical microvilli (MV) with partial loss of microvilli.Partially thickened and interrupted basal lamina (arrow heads). i) Lamina propria (star) with fibroblasts with elongated nuclei (Fb), blood vessel (BV), some inflammatory cells like lymphocytes (L) and eosinophils (Eo) with abundant elliptical dense core granules could be noticed. A cell with cytoplasmic rarefaction and condensed nuclear chromatin were indicated by an arrow. (g, h, i: Scale bar: bar 5.0µm).

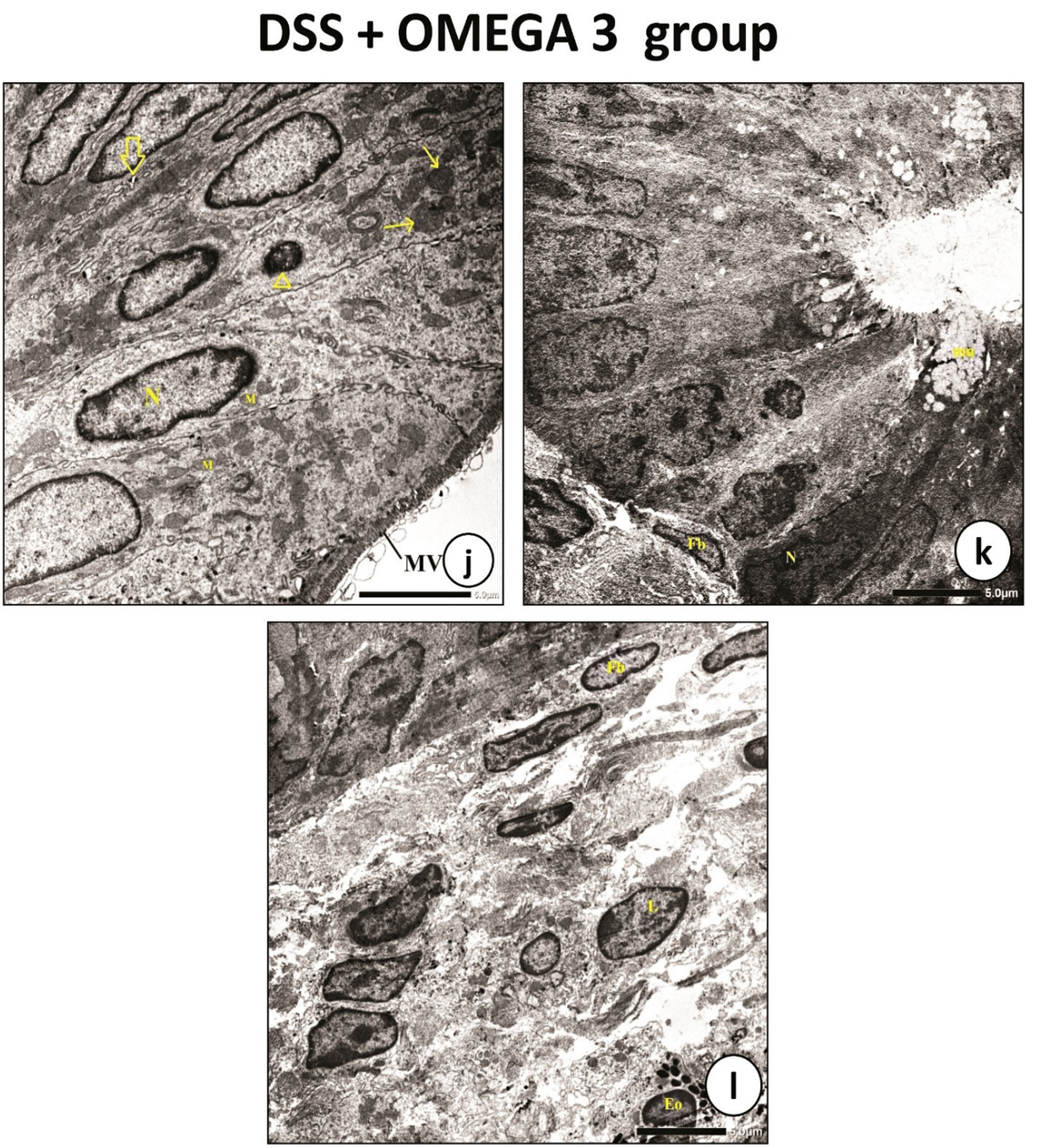

Fig. 8: Photomicrographs of distal colon of adult male albino rats by transmission electron microscope (j,k,l= DSS+ OMEGA3 group); j) Columnar absorptive cells with oval basal euchromatic nuclei (N), abundant mitochondria (M), microvilli (MV) were preserved and packed closely and well organized cell junctions with desmosomes delineating preserved intercellular spaces (hollow arrows). A cell with small pyknotic nucleus with nuclear chromatin condensation (arrow head) contained some swollen mitochondria (thin arrows) could be noticed. .k) Goblet cell with basal nucleus (N), apical mucin granules(mu) was expelling mucous onto the surface. Fb. refers to fibroblast in lamina propria. l) Lamina propria shows fibroblast with elongated nucleus (Fb), some inflammatory cells like lymphocytes (L) and eosinophils (Eo) which contained less numerous elliptical dense-core granules. (j, k, l: Scale bar: bar 5.0µm).

Table 1: Comparison of (% area) of goblet cells stained with alcian blue / PAS between experimental groups.

	Groups				*P*
	Control	DSS	SS +PIO	DSS + OMEGA 3	
Alcain blue /PAS(% area)	19.14±2.27^{A}	7.89±0.94^{D}	10.66±1.50^{C}	14.11±1.54^{B}	<0.001*

Table 2: Comparison of % area of IL17 positive immunoreaction between experimental groups.

	Groups				*P*
	Control	DSS	SS +PIO	DSS + OMEGA 3	
IL17 (% area)	2.02±0.37^{D}	32.43±4.14^{A}	27.72±3.14^{B}	17.28±2.53^{C}	<0.001*

Data presented as mean& SD
P: Probability *: significance ≤0.05
Employed test: One way ANOVA followed by post-hoc tukey's
Different superscript large alphabetical letters demonstrate the significance between different groups in the same raw

DISCUSSION

Precise pathogenesis of ulcerative colitis (UC) has not been fully identified, nevertheless colonic inflammation and aberrant mucosal immunity have been identified as significant pathways implicated in UC pathophysiology[24]. The aberrant immune system and inflammatory response is mainly represented by a rise of proinflammatory cytokines and increased reactive nitrogen and oxygen species production[25].

Rat model of colitis that triggered by DSS represents one of the most commonly utilized models of bowel inflammation[26,27]. Manifestations of DSS-colitis are remarkably comparable with those of ulcerative colitis including superficial mucosal ulceration, and mucosal destruction[28-30].

In the present research, DSS treatment effectively produced acute colitis. Model rats showed typical colitis-related abnormalities such as damaged colonic crypts, as well as focal erosions of the colon's surface epithelium, a reduction in goblet cells, and lamina propria infiltration by inflammatory cells this is in consensus with[31]. Meanwhile, in Pioglitazone group, DSS induced colitis was less prevalent, in agreement with[5]. Omega 3 reduced DSS acute colitis and helped to the preservation of colonic crypt structure in comparison with the model group, this finding is in accordance with[32].

Mucins are highly glycosylated O-glycoproteins. They form a protective layer, which acts as a barrier against pathogens, toxic substances, and colorectal diseases. Mucins are additionally crucial in the prevention of UC. Colitis is caused by disruption of the intestinal mucus layer, which is followed by inflammation; hence, restoring the colonic mucosal layer improves colitis[33]. A crucial approach to UC treatment is to inhibit inflammation and restore the intestinal mucosa. In line with UC management recommendations, the objective of the treatment of UC has switched from immunological dysfunction to mucosal repair[34].

In the current study, DSS promoted intestinal crypt damage, which caused a reduction in goblet cells. We demonstrated that pioglitazone enhanced goblet cells and promoted mucus production in the colon. Additionally, Omega 3 statistically increased goblet cells area % and mucus formation in our DSS-colitis model. Nevertheless, the protective effect of omega 3 was superior to pioglitazone. Reduction of goblet cells and diminished mucus layer are frequent in both UC patients as well as animal models of colitis. A potential clinical treatment for UC is to protect goblet cells and restore the mucosal barrier[35].

T helper cell 17 (Th17) is a recently identified type of T cells that secrete interluekin-17 (IL-17). Interleukin 17 has recently implicated in UC pathogenesis. Under normal settings, mucosal Th17 cells regulate the integrity of colonic epithelial physical barriers via neutrophil and macrophage chemotaxis and encourage epithelial cells to release antimicrobial peptides. Th17 cells constitute an essential player in the development of autoimmune illnesses, such as inflammatory bowel disease, has recently been elucidated. Their role is dependent on the release of their downstream effector cytokines. Interleukin 17 is thought to be a fundamental cytokine that causes inflammation and autoimmune response[36].

In the current work, DSS group exhibited strong positive IL17 immunoexpression. The pioglitazone group demonstrated less significant IL17 immunoreactivity. In the omega-3 group, IL17 expression was minimal in accordance with[37] who proved that DSS-induced colitis was IL-17 dependent. Moreover a recent research concluded that IL-17 expression was marked in the serum and mucosal biopsies of patients with active UC[38].

Our electron microscopy images clearly demonstrated that DSS caused loss and disruption of apical microvilli of columnar absorptive cells along with abnormal chromatin condensation and apparently abnormal cell junction and cell separation. Apoptotic cells are also shown. Goblet cell showed few disorganized mucin granules and cytoplasmic vacoulation. Some goblet cells were degenerated. Pioglitazone group showed partial preservation of the structure of columnar absorptive cells as well as goblet cells with partial preservation of cellular junctions. Our results were parallel to[5,39]. Omega 3 groups showed

apparently normal columnar absorptive cells with normal microvilli structure, normal nuclear and cytoplasmic structure with well-organized cell junctions with preserved goblet cell structure with numerous mucin granules. Our findings are consistent with those of[40], who concluded that supplementing with omega-3-rich algal oil minimized intestinal inflammation and increased tight junction proteins generation in mice with colitis. Moreover, a recent review emphasized that dietary omega-3 fatty acids mitigated inflammation at the intestinal mucosa by enhancing epithelial proliferation, increased mucous production, immunomodulation, as well as preventing inflammatory cell infiltration. Furthermore, omega 3 has shown high bio-accessibility and bioavailability throughout the intestinal epithelium[41].

The current work demonstrated that both pioglitazone and omega 3 repaired goblet cells and increased mucus production in the colon. They likewise motivated epithelial repair and crypt structural restoration and reduced inflammatory cell infiltration of the lamina propria. We attributed this to their PPARγ agonistic action. Hence, activation of PPARγ induces inactivation of Nuclear Factor Kappa B (NF-κB) during inflammation. Activation of NF-κB promotes inflammation. Additionally, PPARγ promotes antioxidant enzyme production thereby decreasing the level of reactive oxygen radicals, which considered secondary mediators of inflammation. Consequently PPARγ agonism has anti-inflammatory and antioxidant action. Also, PPARγ regulates cell proliferation in the colon[42]. Both humans and rats show high levels of PPAR γ receptors in colon. Moreover, PPAR γ expression is higher in the distal colon as compared to the proximal colon[6].

It has been reported that pioglitazone showed anti-inflammatory action and boosted production of proteins of tight junction in colonic epithelium in mice with induced colitis[5].

Moreover, the PPAR γ agonistic action of omega 3, the anti-inflammatory role of omega 3 has many prospectives, this will be explained as follows, Omega-3 poly unsaturated fatty acids (PUFAs) are stored in cell membrane phospholipids.They maintain the cell membrane fluidity, structure, and signaling[43,44]. Omega 3 PUFAs incorporate into membrane phospholipids and displace arachidonic acid from inflammatory cell membranes, lowering the release of arachidonic acid-derived mediators of inflammation such as pro-inflammatory cytokines, thromboxanes, prostaglandins, and leukotrienes[45]. Furthermore, the generation of specific omega-3-derived metabolites, such as Eresolvins, D-resolvins and protectins, which all function as potent anti-inflammatory agents and help restore immune homeostasis[15,46,47,48].

CONCLUSION

Both pioglitazone and omega 3 restored goblet cells and increased mucus production. They enhanced epithelial repair and restored the crypt architecture in colonic mucosa. Furthermore, both attenuated IL17 immunexpression and reduced inflammatory cell infiltration of colonic mucosa of DSS colitis in rats. Nevertheless, the protective impact of omega 3 was statistically superior to that pioglitazone.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

التقييم الهستولوجى للدور الوقائى المحتمل للبيوجليتازون وأوميجا ٣ على التهاب القولون المستحدث بدكستران كبريتات الصوديوم فى الجرذان

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المقدمة: يعتمد علاج مرض تقرحات القولون على إنشاء أساليب جديدة تقلل من الالتهابات المعوية.وقد وجد أن الاوميجا ٣ والبيوجليتازون يثبطان المسار المسبب للالتهابات.

هدف البحث: الهدف من هذه الدراسة هوالتقييم الهستولوجى لتأثير الاوميجا ٣ والبيوجليتازون على التهاب القولون الحاد المستحدث تجريبيا بواسطة ديكستران كبريتات الصوديوم فى الجرذان.

المواد والطرق المستخدمة: تم توزيع ٤٢ جرذا أبيضًا بالغًا على اربعة مجموعات. مجموعة (التحكم) لم تتلقى أي علاج، المجموعة الثانية (مجموعة التهاب القولون الحاد بديكستران كبريتات الصوديوم): حصلت الجرذان على محلول ديكستران كبريتات الصوديوم بتركيز ٥٪ بواسطة انبوب عن طريق الفم يوميا لمدة السبعة ايام الاولى ثم حصلت على نفس المحلول لكن بتركيز ٣٪ فى السبعة ايام التالية ، المجموعة الثالثة (ديكستران كبريتات الصوديوم +بيوجليتازون) حصلت الجرذان على ديكستران كبريتات الصوديوم مثل المجموعة الثانية وحصلت على البيوجليتازون (١٠ مج / كج) يوميا بواسطة انبوب عن طريق الفم من اول يوم للتجربة ولمدة ١٤ يوم ، المجموعة الرابعة (ديكستران كبريتات الصوديوم + اوميجا ٣) عولجت مثل المجموعة الثانية، وحصلت على الاوميجا ٣ (٣٠٠مج /كج) يوميا بواسطة انبوب عن طريق الفم من اول يوم للتجربة ولمدة ١٤ يوم.. تم ذبح الجرذان وجمع عينات من أنسجة القولون ومعالجتها وفحصها نسيجيا تحت الميكرسكوب الضوئى و الإلكتروني.

النتائج: أظهرت مجموعة ديكستران كبريتات الصوديوم تشوهًا نسيجيًا ملحوظًا، وتقرحات فى النسيج الطلائى للقولون، وارتشاح التهابى فى النسيج الضام وانخفاض عدد الخلايا الكأسية ونقص فى افرازاتها المخاطية، ، وزياده في المؤشرات المناعية لبروتينات ضد IL١٧. وأظهرت مجموعة ديكستران كبريتات الصوديوم+ البيوجليتازون تحسنًا نسجيًا بسيطا،وزيادة الخلايا الكأسية وانخفاض بسيط في المؤشرات المناعية ضدIL١٧. أظهرت مجموعة ديكستران كبريتات الصوديوم + الاوميجا ٣ تحسنًا نسيجيًا معتدلًاوزيادة فى اعداد الخلايا الكأسية و انخفاض معتدل للمؤشرات المناعية ضد IL١٧.

الاستنتاج: اظهرالبيوجليتازون والاوميجا ٣ تحسنا نسيجيا فى التهاب القولون الحاد المستحدث فى الجرذان بمادة ديكستران كبريتات الصوديوم وكانت مؤشرات التحسن اعلى فى مجموعة الاوميجا ٣.