Original Article

The Possible Therapeutic Effect of Platelet Rich Plasma Versus Platelet Rich Plasma Derived Exosomes on Experimentally Induced Ulcerative Colitis in Adult Male Albino Rats : A Histological Study

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ABSTRACT

Introduction: Ulcerative colitis is a chronic inflammatory bowel disease, that causes organ damage. There is currently no effective clinical treatment. Platelet rich plasma (PRP) and PRP- derived exosomes are a challenging therapeutic measure. measure for treatment.

Aim of the Work: Evaluate the possible therapeutic role of PRP versus PRP- derived exosomes in healing of experimentally induced ulcerative colitis in rats.

Material and Methods: Four groups of forty mature male albino rats were created: group I (control group); subgroup IIa (ulcerative colitis), given single transrectal injection of 2ml of 4% acetic acid, were sacrificed after 24 hours; subgroup IIb (recovery group) were left for spontaneous healing after induction of colitis then were sacrificed on day 16; group III (PRP treated), given 0.5 ml/day of PRP intraperitoneally for 7 days, 24 hours after induction of colitis then rats were left for further 1 week, and group IV (PRP derived exosomes) given 0.5 ml/day of PRP derived exosomes intraperitoneally for 7 days, 24 hours after induction of colitis then rats were left for further 1 week. Samples from the colon were prepared for histological and immunohistochemical study.

Results: Acetic acid injection significantly induced colonic damage. Loss of mucosal architecture, extensive granulation tissue containing mononuclear cellular infiltration and absence of goblet cells were detected. Treatment with PRP derived exosomes and PRP showed apparent histological improvement. A significant reduction in both area percentage of PCNA and TNF-α in these groups compared to the ulcerative colitis subgroup. However, rats treated by PRP derived exosomes showed better improvement.

Conclusion: PRP derived exosomes showed better therapeutic effect than PRP in an ulcerative colitis model.

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Key Words: Exosomes, PCNA, PRP, TNF-α, ulcerative colitis.

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INTRODUCTION

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, nonspecific inflammatory condition that poses a major danger to human health[1]. The gut's epithelial lining is destroyed by IBD, which significantly lowers the quality of life for the majority of patients. Numerous factors, including genetic, environmental, and inflammatory ones, may contribute to pathogenesis of IBD. Among these factors, epithelial dysfunction and crypt destruction play a defining role in the process of IBD[2]. Ulcerative colitis (UC), a chronic and relapsing-remitting inflammatory bowel disease (IBD), causes persistent mucosal inflammation in the colon, resulting in organ damage and reduced quality of life[3]. Hospitalisation may be necessary for patients who frequently come with symptoms like weight loss, diarrhea, and rectal bleeding[4]. Despite recent advancements in IBD research, an effective clinical treatment strategy for the disease remains elusive. Conventional treatments, such as anti-inflammatory medications (e.g., 5-amino salicylic acid, steroids) and immunosuppressants, provide little therapeutic advantage. However, their non-specific effects on the immune system may lead to side effects such as allergic reactions, nausea, and pancreatitis, emphasizing the urgent need for novel therapeutic approaches for IBD[5]. The supra-physiological amounts of growth factors generated from activated platelets, including transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF), are largely responsible for PRP's regenerative potential. Numerous studies have demonestrated that these growth factors show critical roles in tissue regeneration[6].

Exosomes play a crucial role in cell-to-cell communication by regulating certain signalling pathways through interactions with receptors on the surface of the target cell[7]. Exosomes are biological particles that are discharged by cells and range in size from 30 to 130 nm. They are encased in a bilayer membrane[8]. Exosomes are found in physiological fluids such as blood, urine, breast milk, and saliva and can be released by almost all metabolically active cells[9].

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Exosomes were isolated from PRP, and their role in tissue regeneration was first reported[10]. Studies have shown that PRP exhibits reduction of oxidative stress and anti-inflammatory effects in a model of colitis[11].

AIM OF THE STUDY

The present work was designed to evaluate the possible therapeutic role of PRP versus PRP- derived exosomes in healing of experimentally induced ulcerative colitis in rats.

MATERIAL AND METHODS

Animals

The study included 40 male albino Wistar rats aged 8 weeks weighing 250 - 280g. Throughout the experiment, the rats lived in hygienic plastic cages covered with mesh wire and had unrestricted access to tap water and an ordinary rat chow diet. The proper amount of light, temperature, and humidity were maintained for them. The examination was carried out at the Medical Research Centre in ASU, Faculty of Medicine (MASRI). It was carried out in compliance with the rules established by the US Office for Human Research Protections, the US Code of Federal Regulations, the International Council on Harmonization (ICH), and the Islamic Organization for Medical Science (IOMS). Federal Wide Assurance No FMASU MS581/2023 covers this study.

Experimental animal models

Following 7 days acclimatization, the rats were classified into 4 groups. Control group involved 20 rats divided into four subgroups: subgroup Ia, which remained without intervention for 15 days; subgroup Ib, which received a daily dose of phosphate buffered saline for 7 days; subgroup Ic, which received a daily dose of platelets rich plasma for 7 days; and subgroup Id, which received a daily dose of PRP derived exosomes then all rats were left for further one week. Group II involved 10 rats in two subgroups: Subgroup IIa, which experienced ulcerative colitis, and Subgroup IIb, which was left as the recovery group, both receiving a single transrectal injection of 4% acetic acid and 0.5 ml PBS intraperitoneally for 7 days. Rats of Subgroup IIa were sacrificed after 24 hours, while Rats of Subgroup IIb were left for further one week. Group III (the PRP-treated group) Five rats received 0.5 ml of PRP intraperitoneally as a daily dose for seven days following the establishment of colitis (as in group II) and were then left for an additional week[11,12]. Group IV (PRP derived exosomes treated group) Five rats received 0.5 ml of PRP derived exosomes intraperitoneally as a daily dose for seven days following the establishment of colitis (as in group II) and were then left for an additional week[11,12].

Induction of Colitis

Rats were fasted overnight with water access. After anesthetizing with ether, a 2.7 mm catheter was placed into the colon through the rectum. 2 ml solution of 4% acetic acid (El Nasr Pharmaceutical Chemicals Company, Egypt) was introduced into the colon, and in order to prevent leaking, the rats were placed in a supine Trendelenburg position for 30 seconds.

Mortality rates

Daily, the number of dead rats was noted, and the mortality rate for each group was calculated using this formula:

No. of dead rats X 100

Total No. of rats

Preparation of PRP[13]

A total of 90 ml of venous blood was collected from a healthy adult donor into sodium citrate tubes after obtaining informed consent. Centrifugation of blood was done at 195 ×g for 8 minutes at room temperature, resulting in three layers: red blood cells (bottom), buffy coat (middle), and plasma (top). Plasma layer was further divided into three sub-layers in a 2:1:1 ratio: platelet-poor plasma (PPP), platelet-average plasma (PAP), and PRP. The PPP and PAP layers were removed, and the PRP layer was isolated and centrifuged again under the same conditions for 5 minutes. The supernatant plasma was removed, and the remaining 20 ml of PRP was collected for intraperitoneal injection in subgroup Ic and Group III.

Preparation of platelet rich plasma derived exosomes[14]

Following PRP preparation, exosomes were isolated using differential ultracentrifugation at the National Research Center, Cairo, Egypt, using a Sorval MTX150 ultracentrifuge .

The procedure included

- Initial centrifugation: 20 ml of PRP was centrifuged at 2200 ×g (G - Force)
- for 8 minutes at room temperature.
- Resuspension: pellet was resuspended in 20 ml of PBS, and 20 µl of $CaCl_2$ (10% w/v; 10 µl per ml PRP) was added.
- Incubation: suspension was incubated at 37 °C for 30 minutes.
- Second centrifugation: centrifugation of the mixture was done at 4000 ×g for 10 minutes at 4 °C.
- Supernatant processing: After discarding the pellet, the supernatant was gathered and centrifuged for 30 minutes at 4°C at 10,000 ×g.

Sample collection & preparation of tissues

On day 16, all rats were sacrificed by decapitation except subgroup IIa, which was sacrificed after 24 hours. A 5 cm segment of the distal colon was collected, washed with PBS, and fixed in 10% buffered formalin. Tissues were dehydrated, cleared, embedded in paraffin, and sectioned at 5 µm thickness to be stained with hematoxylin

and Eosin stain (H&E) and Combined Alcian blue-PAS Technique for demonstration of goblet cells.

Immunohistochemical Detection of TNF-α and PCNA

Avidin-biotin complex (ABC) immunoperoxidase approach was used to measure TNF-α and PCNA expression in tissue sections that were formalin-fixed and paraffin-embedded. After being first deparaffinized in xylene, the sections were rehydrated through descending alcohol concentrations to distilled water. Hydrogen peroxide was used to suppress endogenous peroxidase activity (5 minutes for TNF-α and 15 minutes with 10% H_2O_2 for PCNA).

For TNF-α, antigen retrieval was carried out by microwaving the samples at 90°C for 3 minutes. Sections were then incubated with hydrogen peroxide for 20 minutes and blocked with Ultra V Block for 8 minutes to reduce nonspecific staining. A rabbit polyclonal TNF-α antibody (1:50, 100 µg/ml; Santa Cruz Biotechnology, sc1350) was applied. The slides underwent overnight incubation at 4°C, and the next day,a secondary antibody (Histostain-Plus Kit, In*vitro*gen) and streptavidin-HRP were added sequentially for 20 minutes each. DAB was used for 10 minutes to visualize the reaction, followed by counterstaining with Harris's hematoxylin for 45 seconds. Sections were dehydrated, cleared in xylene, and mounted with DPX. Positive TNF-α immunoreactivity appeared as brown cytoplasmic staining[15].

For PCNA, antigen retrieval was done. Citrate buffer (pH 6) was used in a microwave at 2 watts for 10–20 minutes., then allowed to cool for 20 minutes. Slides were blocked with normal goat serum for 10 minutes before incubation with a monoclonal anti-PCNA antibody (LABVISION, USA) overnight. The next day, biotinylated goat anti-mouse secondary antibody and streptavidin-HRP were applied, followed by DAB for 10 minutes and counterstaining with hematoxylin for 30 seconds. The sections were subsequently dehydrated, cleared, and mounted[16].

Negative control sections for both markers were prepared by substituting the primary antibody with PBS. Positive PCNA immunoreactivity appeared as brown nuclear staining.

For microscopic inspection, a microscope (Leica, DM2500) was utilized, with a Canon EOS 1100D Digital SLR camera, with the magnification set to 10 (ocular) x 10 and 40 (object lens).

Histomorphometric Study and statistical analysis

Histomorphometric measurements were conducted using ImageJ software. For each rat, three different slides were analyzed, and five non-overlapping fields per slide were selected to determine goblet cell counts in sections stained by combined Alcian blue-PAS, the mean area % of PCNA and TNF-α immunoreactivity. Collected morphometric data were statistically analyzed using SPSS software (version 21, IBM, Chicago, IL, USA). The mean and standard deviation (SD) were calculated for each group. Comparisons among groups were made using one-way ANOVA, followed by the LSD post-hoc test to identify significant variations. Statistical significance was established at $p < 0.05$, and the results were displayed as mean ± SD.

RESULTS

In present study, an experimental model of colitis was done in adult male albino rats. Colon specimens were collected after one day and fifteen days.

The results include all the following:

I. Characterization of exosomes by TEM.

II. Histological results.

III. Morphometric results and statistical analysis

Characterization of exosomes by TEM

The exosomes were characterized in terms of their size and morphology by TEM using phosphotungstic acid as a staining agent. Exosomes appeared as rounded or oval membrane bounded electron lucent vesicles with a mean diameter of 71.5 nm. (Figure 1).

General observation

Group II rats showed calm behavior, general weakness, and developed clinical signs indicative of colitis, including bloody diarrhea and apparent body weight loss as compared with the control group. Bloody diarrhea manifested as a reddish-brown stain on the rat's fur together with apparent inflammation and congestion at their anal orifices which most probably indicates the occurrence of inflammation. Rats in the PRP-treated group (group III) and the PRP-derived exosome-treated group (Group IV) exhibited a generally good condition, although the rats were somewhat active rather than calm. Notably, no bloody diarrhea, redness and congestion in anal orifices were observed.

Mortality rate

One rat in Group II died during this study, resulting in a mortality rate of 20%, while no deaths were observed in the other groups.

Gross examination of the colon

Gross examination of colonic specimens from ulcerative colitis group revealed marked hyperemia (the colon appears more red or dark pink), erosions, and bleeding ulcers. Treatment with PRP and PRP-derived exosomes significantly improved these pathological manifestations, as no ulcers or erosions were observed; however, mild hyperemia persisted.

Histological Findings

H&E-stained sections

Examination of sections of the colon from rats of subgroups Ia, Ib, Ic and Id showed no histological difference

between the different subgroups by using different histological and immunohistochemical techniques. Histological examination of the distal colon in rats in group I revealed the normal architecture comprising the muscularis externa, serosa, mucosa, and submucosa. The outside longitudinal and inner circular layers of smooth muscle fibers made up the muscularis externa. Beneath the mucosa, the submucosa formed of connective tissue that contained blood veins, fibers, and cells. Inner circular and outer longitudinal smooth muscle fibers were visible in the muscularis externa.

Smooth muscle appeared fusiform with oval central nuclei. Nerve cells of Auerbach's plexus appeared in the connective tissue between the two layers of the muscularis externa (Figure 2A). The mucosa exhibited regularly arranged, closely packed, elongated crypts. Their lining epithelium showed columnar cells with basal oval nuclei. Most of the cells lining the crypts were goblet cells with apical rounded vacuolated cytoplasm. Between the crypts, the lamina propria was visible beneath the epithelium and contained mononuclear cells (Figure 2B). While, in subgroup IIa (acetic acid induced colitis), loss of the colonic mucosal architecture was apparent. Colonic crypts and their lining epithelium were completely lost. A large area of granulation tissue, rich in mononuclear cellular infiltration, was seen to be covering the inflamed submucosa. Additionally, submucosa exhibited dilated and congested blood vessels. (Figure 2C). Inflammatory cells such as neutrophils and lymphocytes were seen in submucosa (Figure 2D).

In subgroup IIb (recovery group), sections showed incomplete recovery of the colonic mucosal architecture. Most of the areas showed short regularly arranged closely packed crypts. However, the length of the crypts was apparently less than that of the control. Also, there was a massive area of mononuclear cellular infiltration seen in submucosa and some inflammatory cells in mucosa. Some areas demonstrated disruption of the colonic mucosal architecture, characterized by shortened, irregular, or completely absent crypts (Figure 2E). The inflammatory cells which infiltrate submucosa were mainly lymphocytes and some neutrophils (Figure 2F).

Group III (PRP treated group), displayed signs of regeneration with apparently normal mucosa, and few inflammatory cells. In most areas, the crypts appeared regularly arranged and closely packed, lined by surface columnar cells with basal oval nuclei and interspersed goblet cells (Figures 2G,H)

In Group IV (PRP-derived exosomes), histological examination revealed almost total restoration of the normal colonic architecture. The mucosa displayed an intact structure with regularly arranged, closely packed, elongated crypts (Figure 2I). These crypts were lined by surface columnar cells with basal oval nuclei, along with numerous goblet cells (Figure 2J).

Combined Alcian blue-PAS-stained section (Figure 3, Histogram 1)

Examination of section of rats in the control group showed alcian blue-PAS positive mucin secreted by goblet cells along the crypts that appeared blue in color. While, in subgroup IIa section showed focal areas with absence of positive alcian blue reaction indicating absence of goblet cells. Also, there were few alcian blue positive goblet cells lining the distorted crypts. In subgroup IIb, significant decrease goblet cells number in most crypts compared to control group. Group III showed positive alcian blue goblet cells in the lower half of most of the crypts and significant decrease in the number of goblet cells in some crypts compared to group I. Examination of sections of group IV exhibited significant rise in the number of positive alcian blue goblet cells compared to ulcerative colitis group.

Immuno - histochemically - stained sections for TNF α: (Figure 4, Histogram 2)

Negative reaction for TNFα was found in the control group (Figure 4A). While Subgroup IIa showed positive brown cytoplasmic reaction for TNF α in some connective tissue cells in the mucosa and submucosa respectively (Figures 4 B,C). Also Subgroup IIb showed few positive cytoplasmic expression for TNF α in the mucosa and submucosa (Figure 4D). Group III showed weak positive cytoplasmic reaction for TNFα in the mucosa and submucosa (Figure 4E). However, in group IV negative cytoplasmic reaction was detected (Figure 4F).

Immuno-histochemically stained sections for PCNA: (Figure 5, Histogram 3)

Control group showed positive nuclear expression in the cells lining the lower 2/3 of the crypts. In subgroup IIa, positive nuclear expression in few cells in the submucosa was observed, while in other areas most of the cells lining the distorted crypts showed positive nuclear expression for PCNA even in the cells of the upper 1/3 of the crypt and cells lining colonic lumen. Subgroup IIb, revealed positive nuclear expression in the cells lining the lower half of the crypts was seen with some cells in the lamina propria. Sections of group III showed positive nuclear expression for PCNA in the cells lining the lower 2/3 of the crypts. Group IV showed positive nuclear expression in the cells lining the lower 2/3 of the crypts with minimal reaction seen in the upper 1/3.

Morphometric and statistical studies

After colon specimens had been collected, prepared for staining and examined, they were subjected to the following measurements:

1. Number of goblet cells in sections stained by combined Alcian blue PAS
2. Mean area % of TNF-α positive cells using anti TNF- α antibody-stained sections
3. Mean area % of PCNA using anti PCNA antibody-stained sections.

All subgroups of control rats (Group I) exhibited similar morphometric results.

Number of goblet cells in combined Alcian blue PAS-stained sections. (Table 1, Histogram 1)

Using one way ANOVA, a significant reduction in number of goblet cells ($P < 0.05$) was noticed in all groups when compared to control group (Group I). Meanwhile, a considerable increase in the number of goblet cells in the PRP derived exosomes treated group (Group IV) compared to ulcerative colitis subgroup (Subgroup IIa), recovery subgroup (Subgroup IIb) and PRP treated group (Group III) was detected.

Mean area % of TNF-α positive cells using anti TNF-α antibody-stained sections. (Table 1, Histogram 2)

One-way ANOVA indicated a notable rise in the mean area percentage of TNF-α ($P < 0.05$) in the ulcerative colitis group and the recovery subgroup as compared to control group. With administration of PRP and PRP derived exosomes, there was a significant drop in the mean area percentage of TNF-α in PRP treated group (Group III) and PRP derived exosomes treated group (Group IV) in comparison to ulcerative colitis group and recovery group. Meanwhile, there was a significant reduction in the mean area percentage of TNF-α in PRP derived exosomes treated group when compared to PRP treated group and non-significant increase in the mean area percentage of TNF-α in PRP derived exosomes treated group as compared to control group.

Mean area percentage of Proliferating cell nuclear antigen (PCNA) using anti PCNA antibody-stained sections. (Table 1, Histogram 3)

One-way ANOVA demonstrated a significant rise in mean area % of PCNA ($P < 0.05$) in both the ulcerative colitis group and the recovery group as compared to the control group. With administration of PRP and PRP derived exosomes, there was a significant decrease in the mean area % of PCNA in PRP treated group and PRP derived exosomes treated group compared to ulcerative colitis group (Subgroup IIa) and recovery group (Subgroup IIb). Meanwhile, there was a significant reduction in the mean area % of PCNA in PRP derived exosomes treated group (Group IV) as compared to PRP treated group (Group III) and non-significant increase in the mean area % of PCNA in PRP derived exosomes treated group in comparison to control group.

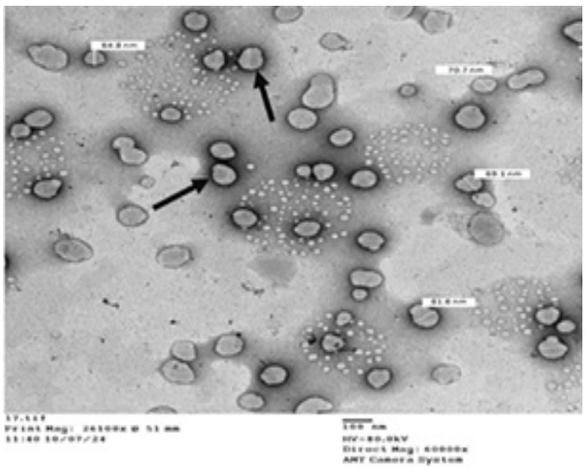

Fig. 1: An electron photomicrograph showing exosomes of different diameters. Exosomes have rounded to oval shape. Phosphotungstic acid is seen concentrated on the outer surface of cell membrane of exosomes (↑). TEM X 60000

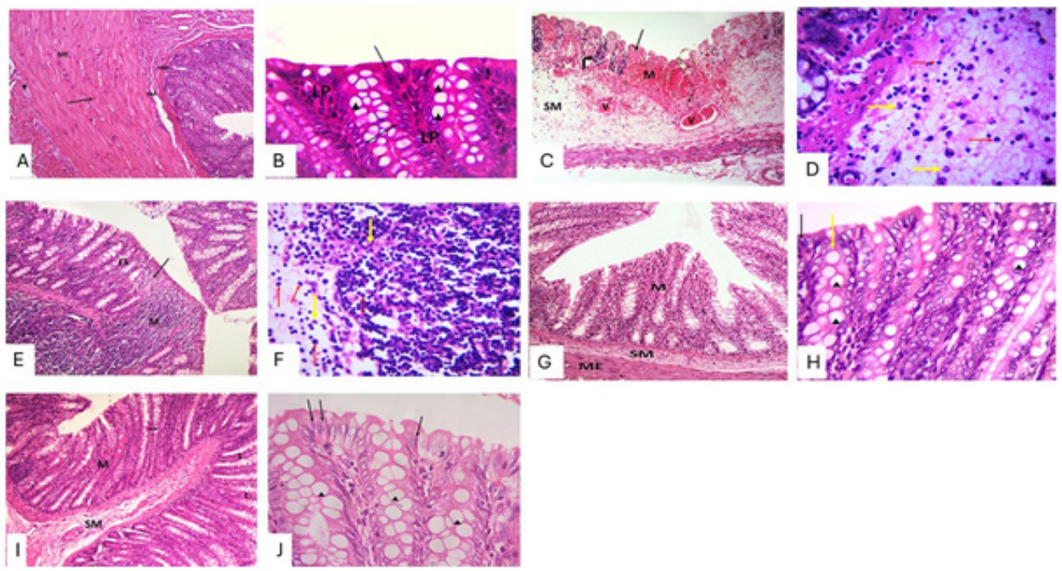

Fig. 2: Sections stained with H&E- in the distal colon from different groups [A&B]: control group (group I), A, showing the muscularis mucosa (MM) and the muscularis externa (ME) and in between thin layer of submucosa (SM). The smooth muscle fibers (↑) are fusiform with oval central nuclei. The nerve cells of Auerbach's plexus ( ) are also seen in connective tissue between the two layers of the muscularis externa X100. B, showing regularly arranged closely packed crypts (↔). Goblet cells with apical rounded vacuolated cytoplasm (▲) and columnar cells with basal oval nuclei (↑) line them. The lamina propria (LP) is present in between the crypts underlying the epithelium and contains mononuclear cells X 400. [C&D]: UC group (subgroup IIa), C, showing disturbed mucosal architecture (M). There is complete loss of the colonic crypts (↑) with the appearance of wide area of granulation tissue contains mononuclear inflammatory cells ( ) that extend deep to the submucosa (SM). Also submucosa contain dilated congested blood vessels (V) X 100. D, showing the inflammatory cells infiltrate. Notice neutrophils (yellow arrow) and lymphocytes (red arrow) X 400. [E&F]: recovery group (subgroup IIb), E, showing some short, irregular crypts ( ) and some lost crypts (↑). Notice inflammatory cells in mucosa (M). X100. F, showing inflammatory cells mainly lymphocytes (red arrow). and some neutrophils (yellow arrow). X400. [G&H]: PRP treated group (group III), G, showing regeneration with apparently normal mucosa (M), submucosa (SM) and muscularis externa (ME), and showed regularly arranged closely packed crypts in most areas. X 100. H, showing relatively long regular crypts (yellow arrow) lined by surface columnar cells with basal oval nuclei (↑) and goblet cells (▲). X400. [I&J]: PRP derived exosomes treated group (group IV), I, showing the mucosa (M) having long crypts that are intact and regularly positioned in close proximity (↔).X100. J, displaying lengthy, evenly spaced crypts that are lined with many goblet cells (▲) and surface columnar cells with basal oval nuclei (↑). X 400.

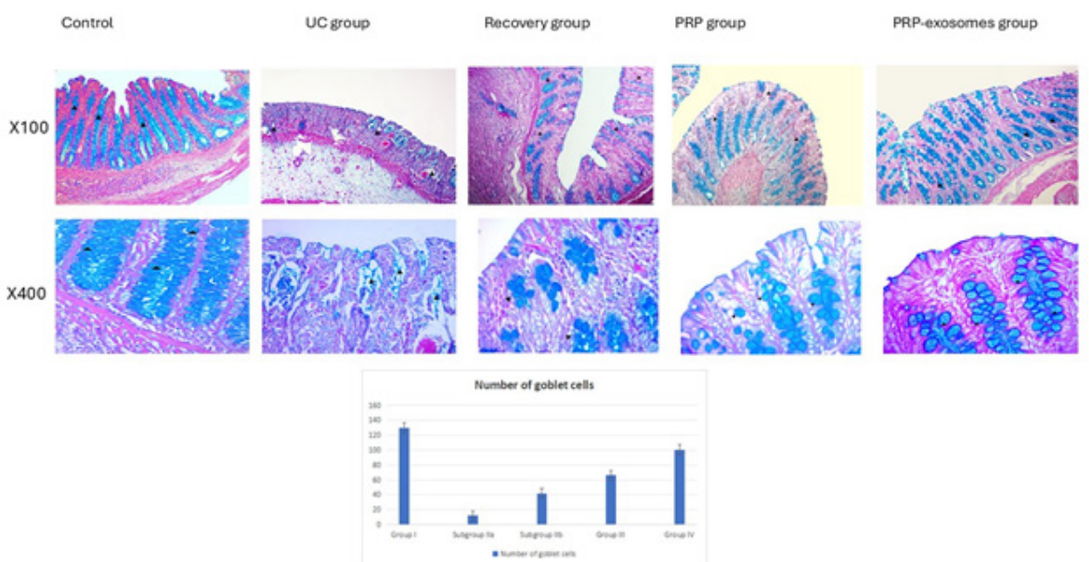

Fig. 3: sections stained with Combined Alcian blue-PAS of distal colon from different groups. Positive alcian blue reaction of goblet cells along the crypt (▲). Histogram (1): Showing the mean ± SD of number of goblet cells in different groups.

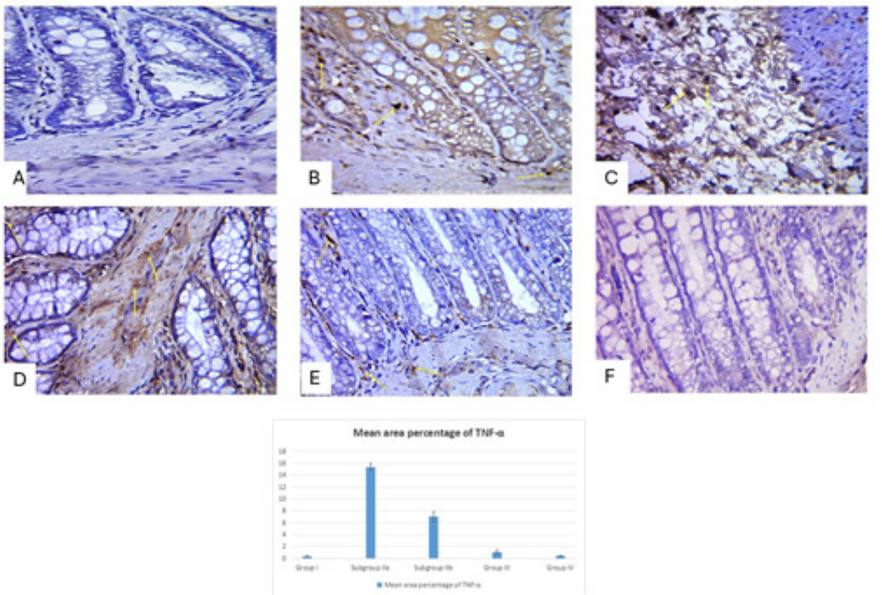

Fig. 4: Sections of distal colon from different groups stained with Streptavidin-biotin peroxidase for TNFα x400. [A] Group I: showing negative cytoplasmic reaction for TNF α. [B&C]: UC group, showing positive expression of TNF α (yellow arrow) in the cytoplasm of some connective tissue cells in the mucosa and submucosa respectively [D] Recovery group, showing relatively few positive cytoplasmic expressions for TNF α (yellow arrow) in the mucosa and submucosa. [E] PRP treated group, showing weak positive cytoplasmic reaction for TNFα (yellow arrow) in the mucosa and submucosa. [F] PRP derived exosomes treated group, showing negative cytoplasmic reaction for TNFα. Histogram (2): Showing the mean area percentage of TNF-α positive cells ± SD in different groups.

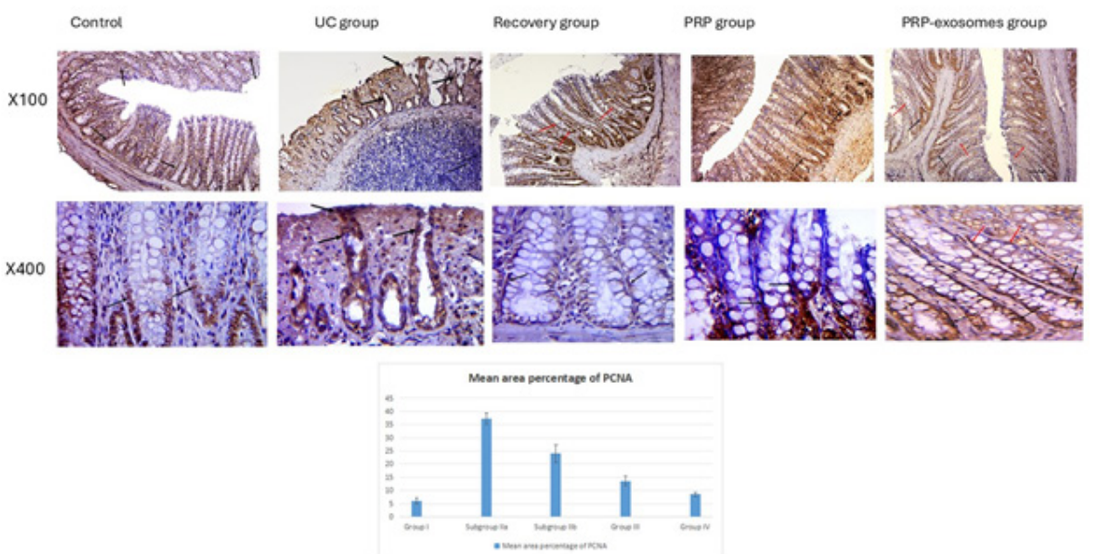

Fig. 5: Sections in the distal colon stained with Streptavidin-biotin peroxidase for PCNA from different groups. Positive nuclear expression for PCNA in the cells (↑). Histogram (3): Showing the mean area percentage of PCNA ± SD in different groups.

Table 1: Showing the mean number of goblet cells, mean area % of TNF-α positive cells and PCNA ± SD in different groups

Group	Number of goblet cells mean ± SD	Mean area % of TNF-α positive cells ± SD	Mean area % of Proliferating cell nuclear antigen (PCNA) ± SD
Group I (control)	129.6 ± 6.8	0.376 ± 0.097	6.096 ± 1.091
Subgroup IIa (ul-cerative colitis)	12 ± 6.32▲	15.366 ± 0.616▲	37.2178 ± 2.161▲
Subgroup IIb (re-covery group)	42 ± 6.32▲■	7.02 ± 0.807▲■	23.9848 ± 3.270▲■
Group III (PRP)	66 ± 6.55▲■●	1.112 ± 0.304▲■●	13.6364 ± 1.878▲■●
Group IV (PRP derived exosomes)	100.2 ± 6.64 ▲■●Δ	0.418 ± 0.100 ■●Δ	8.4938 ± 0.779 ■●

▲ significant difference from control group

■ significant difference from UC group

● significant difference from recovery group

Δ significant difference from PRP group

DISCUSSION

Ulcerative colitis is an inflammatory bowel illness that flares up and goes away with increasing in incidence and prevalence. It is a disease affecting the quality of life with high morbidity[17]. Determining the optimal treatment approaches requires an understanding of the pathophysiology of UC disease.

Animal model of experimental UC was produced using acetic acid, in this study. Ahmed *et al*.[18] reported that colitis induced by acetic acid is a widely used ulcerative colitis experimental model due to its simplicity, reproducibility, and close resemblance to the clinical symptoms of human UC.

In the present study, induction of ulcerative colitis (UC) in the rats of subgroup IIa led to a marked disruption of the normal mucosal architecture. The colonic crypts were completely destroyed, and extensive granulation tissue was observed, infiltrated with mononuclear inflammatory cells such as neutrophils and lymphocytes. This granulation tissue covered a severely inflamed and hemorrhagic submucosal layer.

According to Bahrami *et al*.[19], the inflammatory response triggered by acetic acid begins when its protonated form penetrates the epithelial layer. Once inside, it dissociates, releasing protons that lower the pH and damage epithelial cells by acidifying their environment. Moreover, acetic acid-induced colitis is known to elevate levels of reactive oxygen species (ROS). Activated and infiltrating neutrophils in affected tissue are key contributors to this oxidative stress, as they generate substantial amounts of reactive oxygen and nitrogen species.

Similarly, Pei *et al*.[20] observed intestinal epithelium necrosis in the UC model, as well as inflammatory infiltration in the submucosa that extended through the colonic wall's muscular layers.

Drury *et al*.[21] reported the importance of neutrophils in driving gut inflammation in IBD. These cells generate elevated levels of ROS, which contribute to the disruption of epithelial barrier. In addition, they secrete proteases, proinflammatory cytokines, and mediators such as IL-8 and TNF-α, further damaging the epithelium and promoting the recruitment of monocytes and more neutrophils to the inflamed gut tissue.

In this study, mucin content and types in goblet cells were assessed using combined Alcian blue–PAS staining, revealing that acidic mucin was the predominant type. This is considered a protective response to inflammation caused by UC.

Similarly, Danquah *et al*.[22] reported that there is a low concentration of neutral mucin and a high concentration of acidic mucin in healthy colonic tissues.

Moreover, Hamam *et al*.[23] stated that acidic mucins are a sign that the colonic epithelium is functioning properly in terms of secretion.

According to Gomes *et al*.[24] in his study of the development of goblet cells in intestine of rat, the expression of various types of mucins depends on the food intake phases. Goblet cells differentiation starts intrauterine and continues postnatally. At birth, goblet cells are acidic, neutral and mixed. With weaning and introduction of solid food which is contaminated with pathogens, goblet cells tend to increase in number and acidic goblet cells predominates.

In the current study, The quantity of goblet cells significantly decreased in subgroup IIa, that was also observed by Morampudi *et al*.[25] who mentioned that numerous research on the tissues of UC patients who were inflamed showed that there were less goblet cells.

In addition, Wang *et al*.[26] mentioned that Mucin glycoproteins (Muc2) is produced and secreted by intestinal goblet cells, which provide a protective mucus layer that keeps the luminal contents away from the epithelial surface and is crucial for defending against luminal assaults. Therefore, the defect in the mucus barrier and decreased goblet cells observed in ulcerative colitis facilitate increased bacterial translocation and perpetuate inflammation, contributing to the relapsing and incurable nature of the disease.

TNF-α plays a key role in IBD by promoting intestinal inflammation and mucosal barrier damage, as supported by Souza *et al*.[27], explaining its increased expression in the mucosa and submucosa of the UC subgroup.

In the ulcerative colitis subgroup of this study, most of the cells lining the distorted crypts showed positive nuclear expression for PCNA even in the top cells lining the upper

third and cells lining the colonic lumen, increased PCNA expression indicates heightened proliferative activity, including in the upper crypt regions and colonic lumen. This shift, essential for tissue repair, was also reported by Lin *et al*.[28].

However, as noted by Talero *et al*.[29], such hyperproliferation may signal an elevated risk of colon cancer, making PCNA a useful marker for early diagnosis and prognosis assessment.

In the present study, the recovery subgroup showed incomplete recovery of the mucosal architecture. Most areas showed short regularly arranged closely packed crypts. The length of the crypts was apparently less than that of the control. There was a massive mononuclear cellular infiltration mainly lymphocytes in the lamina propria and at base of the crypts that was extended deep in the submucosa. This finding may be attributed to Ali *et al*.[30], who reported that during spontaneous healing, ulcerative colitis (UC) can transition into an inactive or quiescent phase. Inactive colitis is histologically defined by a notable architectural distortion without active inflammation, particularly neutrophil-mediated epithelial injury. The most frequently noted abnormalities include crypt atrophy, irregularity, and shortening. These features could account for the reduced crypt length observed in the current study.

Ali *et al*.[30] identified crypt distortion and basal lymphocytosis as markers of chronic UC, supporting the classification of the recovery subgroup as representing a chronic state. In line with this, the current study observed mild expression of TNF-α in the mucosa and submucosa of recovery subgroup, consistent with findings by Diab *et al*.[31].

Siqing Chen *et al*[32] reported that cell proliferation in colonic crypts is site-dependent, with stem cells located in the lower third actively dividing and differentiating as they migrate upward. In contrast, cells in the upper third are mostly fully differentiated and non-proliferative.

So, in the recovery subgroup of the current study with the incomplete recovery of the mucosal architecture, showed positive nuclear expression for PCNA in the cells in lower 1/2 of the crypts and also some cells in lamina propria.

The treatment of IBD traditionally involves a range of medications, including salicylates, corticosteroids, and antibiotics[33].

Pai *et al*.[34] underlined that evaluating disease activity is essential to creating and choosing the best treatment for UC patients. To effectively measure disease activity, endoscopic and clinical grading systems have been validated. In UC patients, histology has recently been recognized as a major prognostic marker and a possible therapeutic target.

Moreover, Gupta *et al*.[35], noted that persistent histologic activity is associated with increased relapse rates in UC patients in endoscopic remission.

Dulai *et al*.[36] mentioned that Sulfasalazine which is the medication most frequently used to treat and manage IBD, caused serious adverse effects, including ulcerogenic, hepatotoxic, blood disorders, male infertility, and some patients might require intestinal resection.

Katsanos *et al*.[37] recommended anti-TNF-α biological therapy for inducing remission in glucocorticoid-refractory or -dependent IBD patients, citing its benefits in reducing hospitalizations, enhancing the patients' quality of life and encouraging mucosal healing. However, 30–40% of patients may lose their response during the first year, and up to 30% of patients might not respond at first, necessitating dose adjustments or switching therapies.

Due to the limitations of current therapies, ongoing efforts aim to develop alternative treatments that achieve remission, healing of mucosa, and improving the patients' quality of life with fewer side effects. Although not yet standard care for IBD, PRP and PRP-derived exosome therapy show promise, as PRP is rich in growth factors and cytokines that support tissue regeneration and healing[38].

Samadi *et al*.[39] also highlighted PRP's sustained release of bioactive factors and its strong regenerative potential.

In this work, treatment with PRP in rats with experimentally induced ulcerative colitis (group III) resulted in signs of tissue regeneration, with an apparently normal appearance of mucosa, submucosa, and muscularis externa with regularly arranged closely packed crypts in most areas. The length of the crypts was apparently more than the UC subgroup. This could be explained by Mazzaro *et al*.[40] who reported that PRP can both promote tissue regeneration and modulate immune responses, so it is important in regenerative medicine. They clarified that growth factors including PDGF and Transforming Growth Factor Beta (TGF-β), which are abundant in PRP, support the three stages of wound healing: remodeling, proliferation, and inflammation.

In this study, the PRP-treated group exhibited an increased goblet cells count in most crypts, though still fewer than in the control group. This aligns with El-Kholy *et al*.[41], who highlighted PRP's role in goblet cell restoration.

Additionally, the weak TNF-α expression observed in the PRP group may be attributed to PRP's anti-inflammatory effects, as noted by Yousefi-Ahmadipour *et al*.[12], who reported that platelets reduce TNF-α production and promote regulatory monocyte differentiation. Mazzaro *et al*.[40] further emphasized PRP's importance in lowering inflammation and encouraging growth factor expression to improve wound healing.`

Also, Lyles *et al*.[42] mentioned that PRP is rich in molecules such as serotonin, histamine, dopamine, calcium, and adenosine which may increase permeability of cell membranes and decrease inflammation

The PRP derived exosomes treated group exhibited restoration of the colon's layers' histological architecture. The mucosa displayed complete architecture, with lengthy crypts that were consistently placed and densely packed. The length of the crypts was apparently more than that of the PRP treated group. Surface columnar epithelium and abundant goblet cells were seen lining the crypts. These results were evidenced by statistical analysis that showed significant increase in the number of goblet cells in comparison to PRP treated group.

This could be explained by the findings of Torreggiani *et al*.[10], who isolated exosomes from PRP and were the were the initial ones to report the regenerative role of PRP-derived exosomes (PRP-Exos) in tissue repair.

Boilard[43] reported that PRP-derived exosomes can encapsulate main growth factors like PDGF, TGF-β, and VEGF following PRP activation, protecting them from degradation and enabling effective delivery to target cells during tissue regeneration. Additionally, Ridder *et al*. (2014) noted that exosomes can carry large molecular cargo, shield their contents from degradation, and transmit signals across species, making them ideal candidates for nano delivery therapies.

Beit-Yannai *et al*.[44] highlighted that exosomes are essential for intercellular communication because they carry bioactive lipids, proteins, mRNAs, and miRNAs, so they transfer specific signals from platelets to other healing-related cells. The negative TNF-α expression noticed in the PRP-exosome–treated group in the current study aligns with Liu *et al*.[45], who reported the anti-inflammatory properties of PRP-Exos, including their ability to downregulate TNF-α.

Similarly, Wu *et al*.[46] noted that PRP-Exos can suppress inflammation by inhibiting pro-inflammatory cytokines as TNF-α and IL-8 from immune cells.

Moreover, Saumell-Esnaola *et al*.[14] mentioned that PRP-Exos are rich in the molecular mediators and growth factors that account for the healing effect of PRP.

Shams *et al*.[47] stated that numerous PDGF molecules found in PRP-Exos are shielded from degradation and effectively transported to target cells.

Also, Xu *et al*.[48] demonstrated that treatment with PRP-derived exosomes (PRP-Exos) was adequate to encourage wound healing more successfully than PRP applied directly. These findings clarify why PRP-Exosomes outperform PRP in angiogenesis and cell mitosis.

Therefore, in this study, the examination of sections stained immuno-histochemically of PRP and PRP derived exosomes treated groups for PCNA showed positive nuclear expression in the cells of the lower 2/3 of the crypts like control group. This could be explained by Siqing Chen *et al*[32] who observed that the proliferative activity of the cells varies according to their sites along the crypt. The lower third of the crypts is the place where most colonic stem cells present. They are rapidly proliferating cells while the majority of the cells at the upper third are fully differentiated and are non-proliferative.

CONCLUSION

From the current study, it was concluded that using both PRP and PRP derived exosomes proved to be effective in the treatment of ulcerative colitis. However, treatment with PRP derived exosomes resulted in better amelioration of the inflammatory reactions observed in ulcerative colitis. The increased crypt length and increased number of goblet cells following treatment with PRP derived exosomes indicated their promising therapeutic efficiency in treating ulcerative colitis.

CONFLICTS OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

التأثير العلاجي المحتمل للبلازما الغنية بالصفائح الدموية مقابل المستخلصات المشتقة من البلازما الغنية بالصفائح الدموية على التهاب القولون التقرحي المستحدث تجريبيًا في ذكور الجرذان البيضاء البالغة. دراسة نسيجية

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مقدمة: التهاب القولون التقرحي هو مرض التهاب الأمعاء المزمن، الذي يسبب تلف القولون. لا يزال لا يوجد علاج سريري فعال. تعد البلازما الغنية بالصفائح الدموية (PRP) وا الإكسوزومات المشتقة منها هي تدابير صعبة للعلاج.
الهدف من العمل: تقييم الدور العلاجي المحتمل للبلازما الغنية بالصفائح الدموية مقابل الإكسوزومات المشتقة منها في شفاء التهاب القولون التقرحي المستحدث تجريبيًا في الجرذان.
المواد والطرق: تم تضمين أربعين من ذكور الجرذان البيضاء البالغة في هذه الدراسة. تضمنت المجموعة الأولى (المجموعة الضابطة) تم التضحية بالمجموعة الفرعية الثانية أ (التهاب القولون التقرحي)، بعد إجراء حقنة شرجية واحدة مقدارها ٢ مل من حمض الأسيتيك ٤٪، بعد ٢٤ ساعة؛ وتم الإبقاء على المجموعة الفرعية الثانية ب (مجموعة التعافي) للشفاء التلقائي بعد تحفيز التهاب القولون ثم تم التضحية بها في اليوم السادس عشر؛ أما المجموعة الثالثة (المعالجة بالبلازما الغنية بالصفائح الدموية) فقد تم إعطائها ٠,٥ مل يوميًا من البلازما الغنية بالصفائح الدموية عن طريق البطن لمدة ٧ أيام بعد ٢٤ ساعة من تحفيز التهاب القولون، ثم تم الإبقاء على الجرذان لمدة أسبوع آخر، والمجموعة الرابعة (الإكسوزومات المستخلصة من البلازما الغنية بالصفائح الدموية) تم إعطاؤها ٠,٥ مل يوميًا من الإكسوزومات المستخلصة من البلازما الغنية بالصفائح الدموية عن طريق البطن لمدة ٧ أيام بعد ٢٤ ساعة من تحفيز التهاب القولون ثم تم الإبقاء على الجرذان لمدة أسبوع آخر.
النتائج: سبب حقن حمض الأسيتيك ضررًا كبيرًا في القولون. تم الكشف عن فقدان البنية المخاطية، ومنطقة كبيرة من أنسجة التئام الجروح تحتوي على خلايا التهابية وحيدة النواة وغياب خلايا الكأس. أظهر العلاج بالبلازما الغنية بالصفائح الدمويةوأيضا بالإكسوزومات المستخلصة من البلازما الغنية بالصفائح الدموية تحسنًا ملحوظًا. كان هناك انخفاض ملحوظ في كل من نسبة مساحة PCNA وTNF-α في هذه المجموعات مقارنة بمجموعة التهاب القولون التقرحي. ومع ذلك، فإن الجرذان التي تم علاجها بالإكسوزومات المستخلصة من البلازما الغنية بالصفائح الدموية أظهرت تحسنًا أفضل.
الخلاصة: أظهرت الإكسوزومات المشتقة من بلازما الصفائح الدموية تأثيرًا علاجيًا أفضل من بلازما الصفائح الدموية في نموذج التهاب القولون التقرحي.