Original Article

Protective Effects of Autologous Platelet Rich Plasma Versus Glutamine against Aspirin Induced Acute Gastric Ulcers in Adult Male Albino Rat (Histological and Immunohistochemical study)

Enas Anwar Bekheet and Hala Taha Shalan

Department of Anatomy and Embryology, Faculty of Medicine, Ain Shams University, Egypt

ABSTRACT

Introduction: Gastric ulcers greatly affect the quality of a patient's life and they may lead to major complications such as perforation, bleeding, and even death. Treatment is mainly medical. However, the medications are not effective in the treatment of all cases and may cause many adverse effects.

Aim of the Work: This work aimed to assess the protective effects of autologous platelet-rich plasma versus glutamine against aspirin-induced acute gastric ulcers in adult male albino rats.

Material and Methods: Fifty male albino rats were used, aged 6-8 months, weighing 180-200 grams each, randomly divided into six groups. Group I (Control group): subdivided into two subgroups: subgroup Ia: rats were kept without any treatment and subgroup Ib: each rat received a single oral dose of carboxymethylcellulose. Group II: each rat received 0.5ml/Kg prp subcutaneously two days/week for three weeks. Group III: each rat received 500 mg/kg/day of glutamine orally for three weeks. Group IV (gastric ulcer group): each rat received a single oral dose of aspirin (300 mg/Kg). Group V: each rat received a dose of 0.5ml/Kg of prp subcutaneously two days/week for three weeks then a single oral dose of aspirin. Group VI: each rat received a dose of 500 mg/kg /day of glutamine orally for three weeks and then a single oral dose of aspirin.

Results: No histological difference between gastric mucosa of rats of groups I, II and III. Whereas, numerous changes were noticed in the gastric mucosa of the rats of group IV (aspirin group) while the rats of group V (prp protective group) and of group VI (glutamine protective group) showed nearly a regular structure of their gastric mucosa with better results of prp.

Conclusion: Platelet-rich plasma and glutamine have good protective effects against aspirin-induced acute gastric ulcers in rats but prp is preferable to glutamine.

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Key Words: Aspirin, gastric ulcer, glutamine, platelet rich plasma.

Corresponding Author: Enas Anwar Bekheet, MD, Department of Anatomy and Embryology, Faculty of Medicine, Ain Shams University, Egypt, **Tel.**: +20 12 2403 7554, **E-mail:** eno.anatomy@yahoo.com

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INTRODUCTION

Gastric ulcer is considered the most common gastrointestinal disease which affects 10-15% of the population worldwide. It is defined as an interruption of the continuity of the gastric mucosa. Gastric ulcers either acute or chronic greatly affect the quality of a patient's life and they may lead to major complications such as perforation, bleeding and even death. Risk factors of gastric ulcers include emotional stress, smoking, systemic non-steroidal anti-inflammatory drugs such as aspirin, chronic infection by helicobacter pylori and systemic corticosteroids[1-7].

Treatment of gastric ulcers is mainly medical unless there is a complication that needs surgical intervention. The medications depend on decreasing gastric acid secretion including histamine receptor antagonists, antacids, anticholinergics and proton pump inhibitors. However, medications are not effective in treating all cases also; they have many adverse effects with a high recurrence rate[8,9]. Therefore, there is a need for an alternative safe product against gastric ulcers. Platelet-rich plasma (prp) gained by blood centrifugation is used by researchers as a new product in regenerative medicine as platelets have a pivotal role in tissue repair and wound healing that's because platelets contain more than 800 different types of proteins inside their α-granules. Platelet-rich plasma also activates the stem cells with subsequent speeding up of tissue repair[10]. It differs from normal body plasma in containing a high concentration of platelets within a little amount of plasma. It contains several growth factors that are necessary for the healing process and regeneration, including vascular endothelial growth factor, platelet-derived growth factors αα, αβ, and ββ, and transforming growth factors β1 & β2[11,12].

Glutamine (non-essential amino acid) is the most plentiful amino acid in the body. It is a building unit for making body proteins. Under certain conditions, glutamine is considered an essential amino acid and must be obtained from the diet when its level is decreased due to increased consumption during periods of stress or illness (inflammation, sepsis, and surgery). It plays a key role in the regulation of acid-base balance, nucleic acid synthesis, cellular metabolism, and cellular immune function[13]. Therefore, the present study was conducted to assess the

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protective effects of autologous platelet-rich plasma versus glutamine against aspirin-induced acute gastric ulcers in adult male albino rats.

MATERIALS AND METHODS

Chemicals

- Acetylsalicylic acid (Aspirin) was purchased in the form of powder from Sigma-Aldrich Chemical Co., St. Louis. Mo. USA.
- Carboxymethyl Cellulose 1% (aspirin solvent) was obtained from Central Drug House Pvt. Ltd., New Delhi, India.
- L-glutamine (Universal glutamine) R was purchased in the form of powder from Universal Nutrition Co. USA.

Preparation of platelet-rich plasma (prp)

Under aseptic technique and ether anesthesia, 2 ml of blood was obtained from the tail vein of each rat via a capillary tube (previously dipped in 3.2% sodium citrate). The blood was then delivered to tubes containing 0.5 mL of acid citrate dextrose and subjected to double centrifugation, firstly at 1600 rpm for 10 minutes, where three layers of different densities were formed with the superior layer containing the plasma. The plasma was pipetted and centrifuged again for 10 minutes at 2000 rpm. The upper part containing the platelet-poor plasma was removed, and the lower part remained in the tube, then gently agitated to get the platelet suspension (prp). For confirmation, each sample was checked for platelet count in an automatic apparatus (more than 1,000,000/µl). The calculated dose for each rat of prp was diluted by phosphate buffer saline (1:1) and then placed in a sterile insulin syringe and each rat was injected subcutaneously with its autologous prp[14]. The preparation of prp was carried out at the Medical Research Center, Faculty of Medicine, Ain-Shams University.

Induction of gastric ulcer

It was done by a single oral dose of aspirin (300 mg/ Kg) dissolved in 1% carboxymethylcellulose (0.6 ml) by an orogastric tube after overnight fasting[15,16].

Animals

Fifty adult male albino rats were used, aged 6-8 months, weighing 180-200 grams each. They were obtained and kept at the Medical Research Center, Faculty of Medicine, Ain-Shams University. Rats were kept in medium-sized metal cages at room temperature with good ventilation and regular light/dark cycles. All rats were housed under the same circumstances throughout the experiment with free access to food and water ad libitum. The experiment followed the guidelines of Ain Shams University Ethical Committee.

Rats were randomly divided into six groups

Group I (control group): contained ten rats which were further subdivided into two subgroups, five rats each: subgroup Ia (negative control subgroup); rats were kept without any treatment and subgroup Ib (carboxymethyl cellulose vehicle control subgroup); each rat received 1% carboxymethyl cellulose (0.6 ml) orally by an orogastric tube once after overnight fasting then five hours later rats were sacrificed.

Group II (prp group): included five rats, each rat received 0.5ml/Kg prp subcutaneously; two days/week for three weeks.

Group III (glutamine group): included five rats; each rat received 500 mg/kg/day of glutamine in 2ml of distilled water by an orogastric tube for three weeks then sacrificed.

Group IV (gastric ulcer group): contained ten rats, each rat received a single oral dose of aspirin (300 mg/ Kg) dissolved in 1% carboxymethyl cellulose (0.6 ml) and given by an orogastric tube after overnight fasting. Five hours later rats were sacrificed[15,16].

Group V (prp protective group): contained ten rats, each rat received 0.5ml/Kg of prp subcutaneously, two days/ week for three weeks. One hour after the last dose of prp, a single oral dose of aspirin was administered as in group IV. Five hours later rats were sacrificed[17].

Group VI (glutamine protective group): contained ten rats, each rat received 500 mg/kg /day of glutamine in 2ml of distilled water by an orogastric tube for three weeks. One hour after the last dose of glutamine, a single oral dose of aspirin was administered as in group IV. Five hours later rats were sacrificed[18].

By the end of the experiment, rats were sacrificed under anesthesia (inhalation of diethyl ether 1.9%). The anterior abdominal wall was opened, and the stomach of each rat was obtained and washed gently with saline. The body of the stomach of each rat was divided longitudinally into two parts, one part was fixed in neutral-buffered 10% formalin and the other part was fixed in 2.5% glutaraldehyde. Then, the specimens were processed for paraffin and epon blocks respectively, sectioned, stained histologically and immunohistochemically to be examined by a light microscope.

Paraffin Sections

Specimens were fixed in 10% neutral-buffered formalin, dehydrated, and embedded in paraffin blocks, then 5µm sections were cut and stained with Hematoxylin and eosin (Hx. & E.) for the histological examination[19], Periodic Acid–Schiff stain (PAS) for mucins detection[20]and Masson's trichrome stain for collagen fibers detection[21].

Immunohistochemical stain for cleaved caspase-3 was used as an indicator of apoptosis as follows: sections were washed with phosphate-buffered saline (for 5 minutes) and incubated with primary antibody to cleaved caspase (In*vitro*gen, Sweden AB Stockholm Sweden 1:200) at 4°C, sections then washed and incubated with secondary goat-anti-rabbit antibody (In*vitro*gen, Molecular Probes, Eugene, Oregon, USA 1:500) for 1h at room temperature. Slides

were incubated in 3,3-diaminobenzidine for 10 minutes, counterstained by Mayer's hematoxylin, and mounted by dibutyl phthalate in xylene[22]. Positive immunoreactive cells were detected by the brown coloration of their cytoplasm. Tonsils were used as a positive control staining. Negative control staining was done by omitting the primary antibody.

Semithin sections

Specimens were fixed in 2.5 % glutaraldehyde, washed with phosphate buffer saline and fixed in 1 % osmium tetroxide, then dehydrated in alcohol and embedded in epon blocks. 1um semithin sections were cut by L.K.B. ultra-microtome and stained with toluidine blue[23].

Olympus light microscope supported by an automatic photomicrographic camera system was used to examine and photograph the stained sections at the Anatomy Department, Faculty of Medicine, Ain Shams University.

Morphometric analysis

Morphometric analysis was achieved by using Image-J software on a computer connected to an Olympus microscope connected with a digital camera (BX3M series, Olympus, Tokyo, Japan). Ten randomly chosen non-overlapping fields in ten different sections from ten rats of the same group were examined to measure the mean area % of collagen (on Masson's trichrome stained sections), the mean area % of mucin stain (on PAS-stained sections) and the mean area % of caspase-3 immunoreactivity. The magnification used was x100 with an objective lens of x10. Pixels were calibrated for actual measurements using a stage micrometer.

Statistical analysis

Data analysis was performed by SPSS freeware (Version 20, IBM Corp., Armonk, NY, USA). One-way ANOVA and Bonferroni Post Hoc test were used to compare the differences between every two groups. Data were offered as the mean value ± standard deviation (SD). Results were considered highly significant when $P\text{-}value \leq 0.001$, significant when $P\text{-}value \leq 0.05$ and nonsignificant, when $P\text{-}value > 0.05$.

RESULTS

General histological picture

Groups I (control), II (prp group) and III (glutamine protective group)

Light microscopic examination of Hx. & E.- stained sections of the rat gastric wall of group I (control subgroups Ia, Ib), as well as group II (prp group) and group III (glutamine group) showed almost the same regular histological structure of the mucosa, the submucosa, and the muscularis externa. The gastric mucosa showed numerous closely packed tubular glands with surface invaginations (gastric pits). The detected parts of the gastric glands consisted of the surface cells, the ismuth, the neck, and the base. The submucosa showed loose connective tissue and blood vessels with an underlying thick layer of the muscularis externa (Figures 1,2).

Examination of semithin sections of groups I, II and III stained with toluidine blue showed the gastric mucosal neck cells with different shapes and sizes having foamy cytoplasm and basal nuclei. Some rounded parietal cells were also detected with central vesicular nuclei. The basal parts of the gastric glands were composed mainly of darkly stained chief cells surrounding narrow, regular and rounded lumens. They appeared conical or pyramidal in shape with granular apical cytoplasm and basal spherical nuclei with prominent nucleoli. Few large spherical parietal cells were noticed between the chief cells having mottled cytoplasm, central spherical nuclei, and prominent nucleoli. (Figures 3,4).

Group IV (gastric ulcer group)

Light microscopic examination of Hx. & E.- stained sections of the rat gastric wall of group IV showed numerous structural changes. The gastric mucosa showed large ulcers with a loss of the whole thickness of the gastric mucosa. Cellular remains were seen at the base of the ulcers. Congested submucosal blood vessels were detected mainly in the non-ulcerated areas (Figures 5,6).

Examination of semithin sections stained with toluidine blue of the gastric mucosa of non-ulcerated areas showed loss of alignment of mucous neck cells with irregular shapes and pyknotic nuclei. The basal parts of most gastric glands showed distorted and dilated lumens, parietal cells with lost nuclei, and light-stained chief cells with loss of their apical granules. Inflammatory cells and Mast cells were also detected between the mucosal cells (Figures 7,8).

Group V (prp protective group)

Light microscopic examination of Hx. & E.- stained sections of the rat gastric wall of group V showed intact gastric mucosa with numerously closely backed gastric glands (Figures 9,10).

Examination of semithin sections stained with toluidine blue showed regularly aligned mucous neck cells with foamy cytoplasm and basal nuclei. The basal part of the gastric glands showed darkly stained chief cells surrounding rounded narrow lumens and having granular apical cytoplasm and vesicular nuclei with few large vesicular parietal cells in-between (Figures 11,12).

Group VI (glutamine protective group)

Light microscopic examination of Hx. & E.- stained sections of the gastric wall of group VI showed nearly regular layers of the gastric wall with minimal mucosal loss (Figures 13,14).

Examination of semithin sections stained with toluidine blue showed regularly aligned mucous neck cells with less foamy cytoplasm, some cells were having pyknotic nuclei. Few inflammatory cells between the mucosal cells and slightly dilated lumens of the basal parts of the gastric glands were noticed (Figures 15,16).

PAS stain

Examination of PAS-stained sections of groups I, II and III showed a strong PAS-positive reaction mainly in the surface mucous layer, filling the pits, and the isthmus region (Figure 17).

In sections of the rat gastric wall of group IV (gastric ulcer group) a weak interrupted PAS-positive reaction was observed in the surface mucous layer, in the pits with an almost negative reaction in the isthmus region (Figure 18).

However, sections of rats in group V (prp protective group) showed a strong positive PAS reaction in the surface mucous layer, in the pits, and in the isthmus region (Figure 19). In sections rat gastric wall of group VI (glutamine protective group), slightly interrupted positive PAS reaction in the surface mucous layer and in the pits with a weak reaction in the isthmus region was noticed (Figure 20).

Masson trichrome stain

Examination of Masson's trichrome-stained sections of rat gastric wall of groups I, II and III showed a regular distribution of collagen fibers in the lamina propria which were more noticeable in-between and below the basal parts of the glands and in the submucosa (Figure 21). In sections of the rat gastric wall of group IV (gastric ulcer group), an irregular distribution of few collagen fibers in the lamina propria in-between and below the basal parts of the glands and in the submucosa were observed (Figure 22).

Examination of rats' gastric wall sections of group V (prp protective group) showed the regular distribution of thick collagen fibers in the lamina propria in-between and below the basal parts of the glands and in the submucosa (Figure 23). Moreover, in group VI (glutamine protective group), Masson's trichrome stained sections showed an almost regular distribution of collagen fibers in the lamina propria in-between and below the basal parts of the glands and in the submucosa (Figure 24).

Caspase-3 immunohistochemical stain

Examination of caspase-3-stained sections of rats' gastric wall of groups I, II and III showed a negative cytoplasmic reaction of most of the glands' cells (Figure 25).

In rats of the gastric ulcer group (group IV), strong positive cytoplasmic immunoreactivity to caspase- 3 was observed in most of the glands' cells (Figure 26).

Whereas examination of caspase-3-stained sections of rats in group V (prp protective group) showed a negative cytoplasmic reaction of most of the glands' cells (Figure 27). Also, in rats of group VI (glutamine protective group), negative immunoreactivity to caspase-3 was noticed in the cytoplasm of most of the glands' cells (Figure 28).

Morphometric results and statistical analysis

Morphometric measures for the mean area % of Masson trichrome positive reaction for collagen fibers, PAS-positive reaction for mucin, and caspase-3 positive immunoreaction for apoptosis were summarized in (Histogram 1, Table 1).

Highly significant statistical differences (*P-value* <0.001) were observed between the control group (group I) and the gastric ulcer group (group IV) for the three measures. Moreover, highly significant differences were observed between group IV and groups V and VI for the three measures. On the other hand, highly significant differences were noticed between groups V and VI for area % of collagen fibers and mucin and nonsignificant statistical difference (*P-value* > 0.05) for area % of caspase-3 positive immunoreaction.

Nonsignificant statistical differences (*P-value* > 0.05) were seen between group I and group VI for area % of collagen fibers and for caspase-3 positive immunoreaction and a highly significant statistical difference (*P-value* < 0.001) for mucin. Moreover, there were nonsignificant statistical differences (P-value > 0.05) between group I and group V for area % of caspase-3 positive immunoreaction and for mucin and a highly significant statistical difference (P-value <0.001) for area % of collagen fibers.

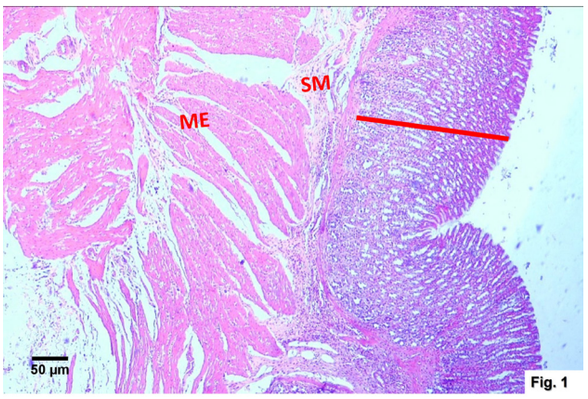


Fig. 1: A photomicrograph of a section of a rat's stomach of group I showing the layers of the gastric wall, the mucosa (red line), the submucosa (SM) containing loose connective tissue and blood vessels, and the muscularis externa (ME). (Hx. & E., x40)

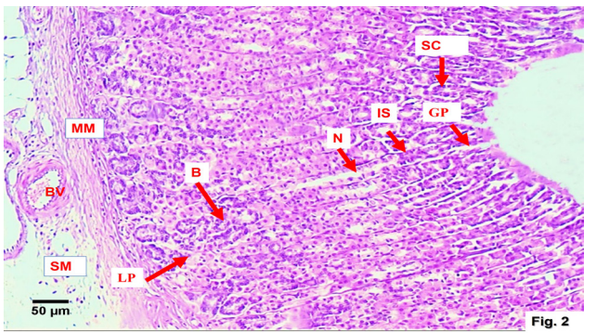


Fig. 2: A photomicrograph of a section of rat's gastric mucosa of group I showing numerous closely packed tubular glands with surface gastric pits (GP with red arrow), the parts of the gastric glands; the surface cells (SC with red arrow), the ismuth (IS with red arrow), the neck (N with red arrow), and the base (B with red arrow). Notice, the intervening lamina propria (LP with red arrow), the muscularis mucosa (MM) under the basal parts of the glands, and the submucosa (SM) with its blood vessels (BV). (Hx. & E., x100)

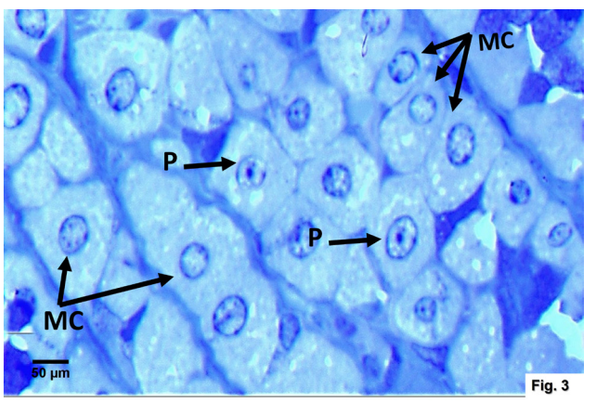


Fig. 3: A photomicrograph of a semithin section of the neck part of rat's gastric mucosa of group I showing regularly aligned mucous neck cells (MC with black arrows) having different shapes and sizes, foamy cytoplasm, and basal nuclei. Some rounded parietal cells (P with black arrow) were also seen with central vesicular nuclei. (Toluidine blue, x1000)

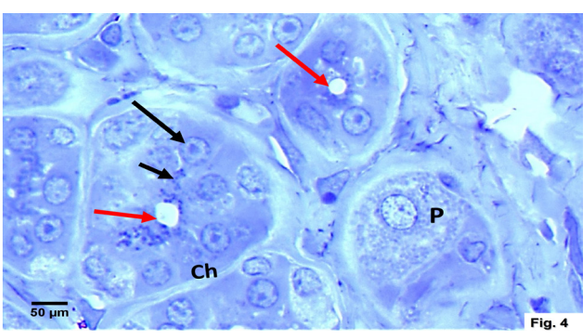


Fig. 4: A photomicrograph of a semithin section of the basal part of rat's gastric mucosa of group I showing the basal parts of the gastric glands which formed mainly of chief cells (Ch) having granular apical cytoplasm (short black arrow) and basal spherical nuclei with prominent nucleoli (long black arrow), few large parietal cells (P) having mottled cytoplasm, central spherical nuclei, and prominent nucleoli. Notice, the rounded, regular, and narrow lumens of the glands (long red arrows). (Toluidine blue, x1000)

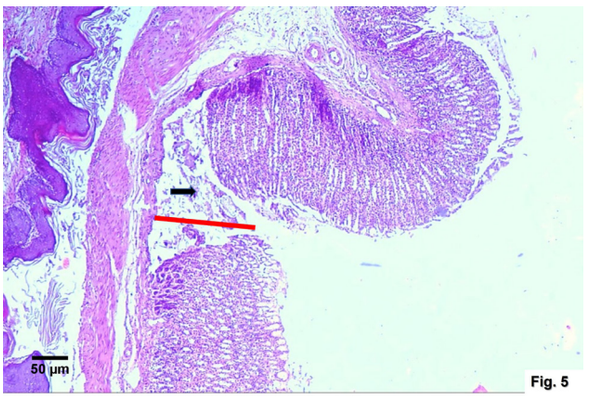


Fig. 5: A photomicrograph of a section of a rat's stomach of group IV showing an ulcer with loss of the whole thickness of the gastric mucosa (red line). Notice the cellular remains at the base of the ulcer (black arrow). (Hx. & E., x40)

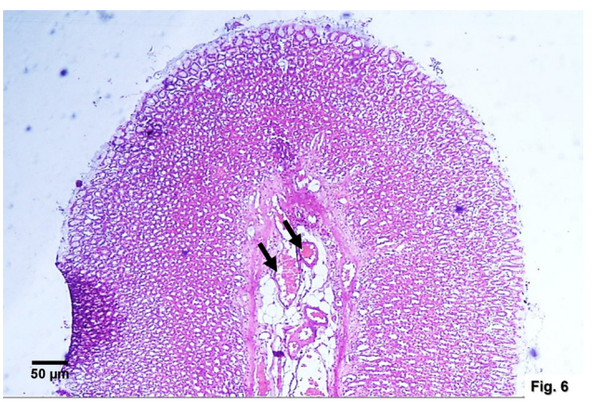


Fig. 6: A photomicrograph of a section of rat's gastric mucosa of group IV showing congested submucosal blood vessels (black arrows). (Hx. & E., x100)

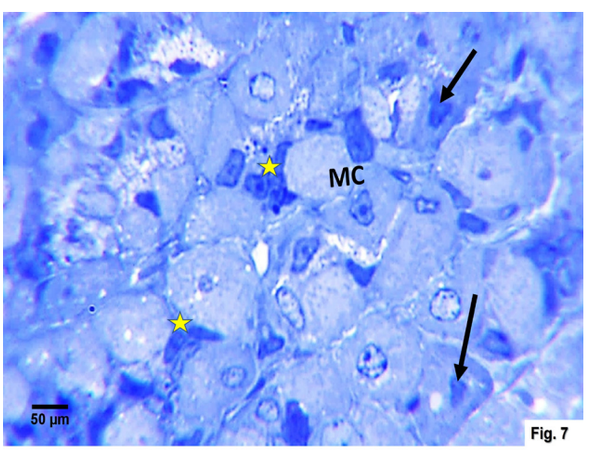


Fig. 7: A photomicrograph of a semithin section of rat's gastric mucosa of group IV showing loss of alignment of mucous neck cells (MC) with pyknotic nuclei (black arrows). Notice, the inflammatory cells (*). (Toluidine blue, x1000)

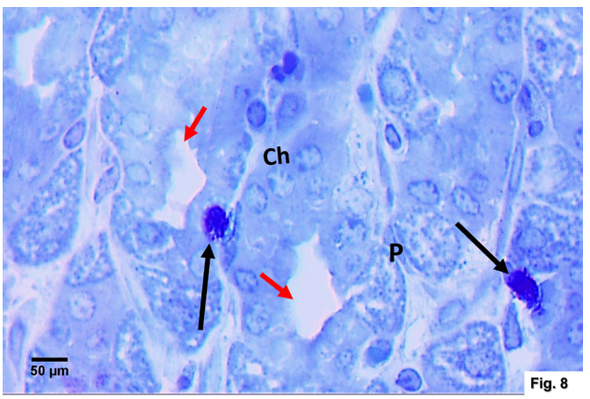


Fig. 8: A photomicrograph of a semithin section of rat's gastric mucosa of group IV showing the basal parts of the gastric glands with distorted and dilated lumens (short red arrows), parietal cells with lost nuclei (P), and light-stained chief cells with loss of their apical granules (Ch). Notice, the mast cells (long black arrows). (Toluidine blue, x1000)

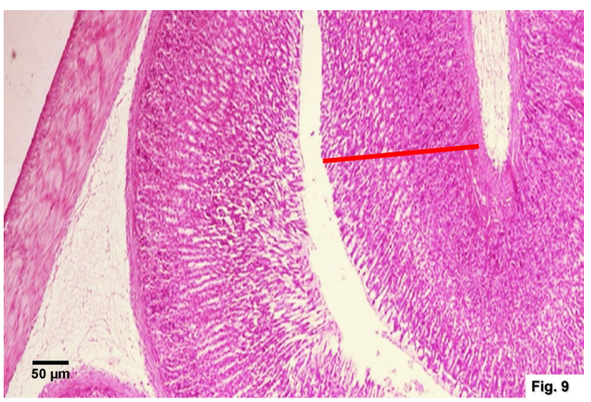


Fig. 9: A photomicrograph of a section of rat's stomach of group V showing intact gastric mucosa (red line). (Hx. & E., x40)

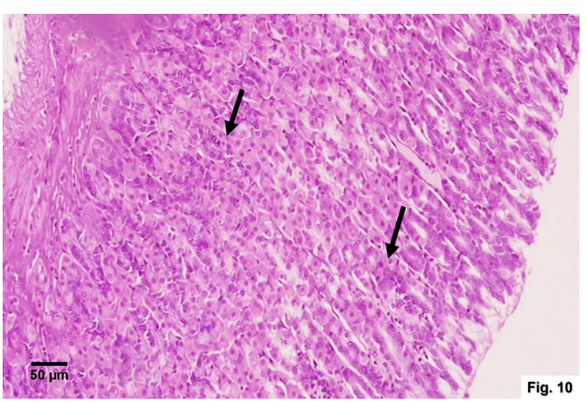


Fig. 10: A photomicrograph of a section of rat's gastric mucosa of group V showing numerous closely backed gastric glands (black arrows). (Hx. & E., x100)

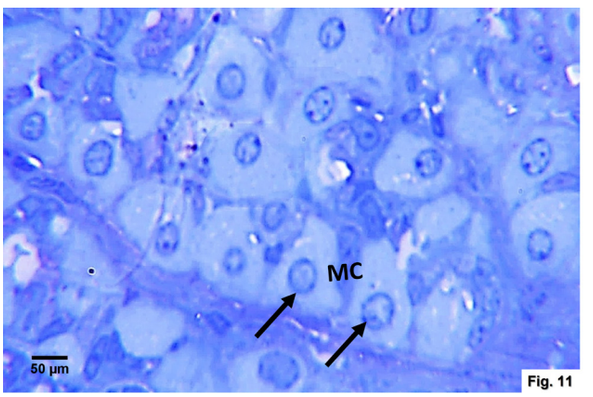


Fig. 11: A photomicrograph of a semithin section of rat's gastric mucosa of group V showing regularly aligned mucous neck cells (MC) having foamy cytoplasm with basal nuclei (black arrows).(Toluidine blue, x1000)

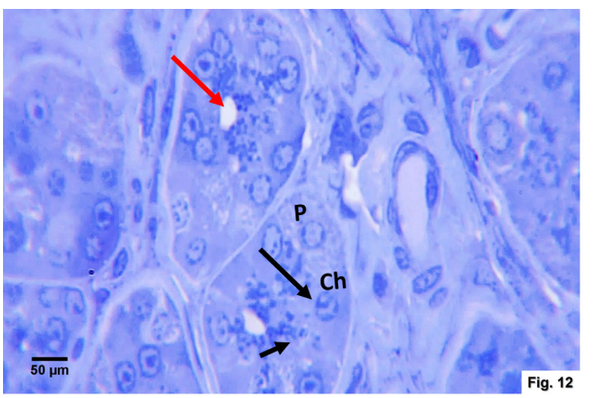


Fig. 12: A photomicrograph of a semithin section of rat's gastric mucosa of group V showing the chief cells of the basal part of the gastric glands (Ch) having granular apical cytoplasm (short black arrow) and vesicular nuclei (long black arrow), and a large parietal cell with central nucleus (P). Notice, the narrow lumen of the gland (long red arrow). (Toluidine blue, x1000)

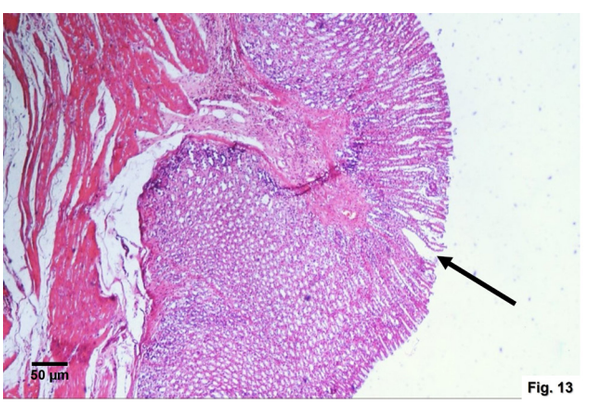


Fig. 13: A photomicrograph of a section of a rat's stomach of group VI showing nearly regular layers of the gastric wall with minimal mucosal loss (black arrow). (Hx. & E., x40)

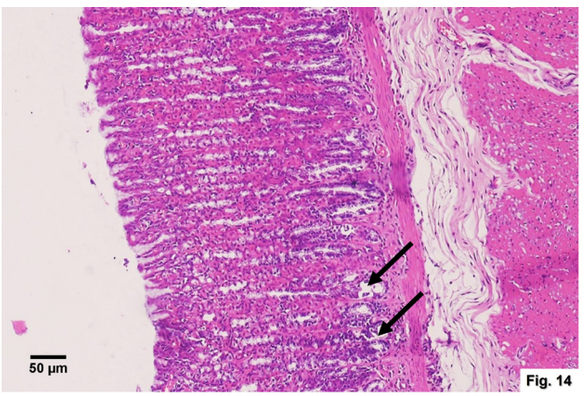


Fig. 14: A photomicrograph of a section of the gastric mucosa of group VI showing nearly regular gastric glands with slight dilatation of the lumens (black arrows). (Hx. & E., x100)

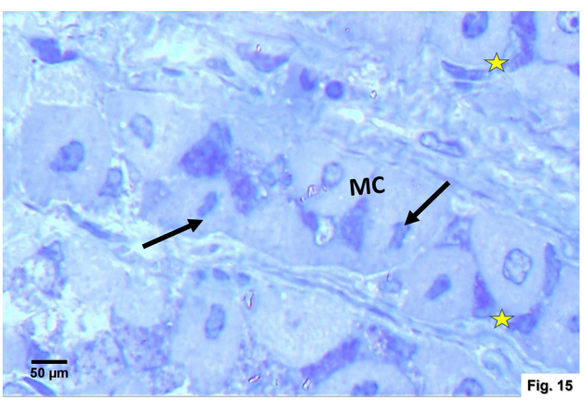


Fig. 15: A photomicrograph of a semithin section of rat's gastric mucosa of group VI showing regularly aligned mucous neck cells (MC) with less foamy cytoplasm but, some of them have pyknotic nuclei (long black arrows). Notice few inflammatory cells (*). (Toluidine blue, x1000)

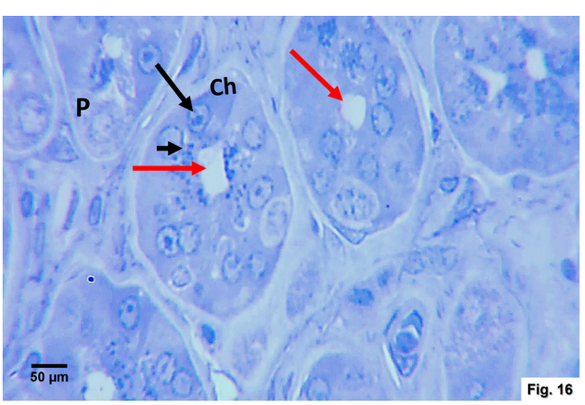


Fig. 16: A photomicrograph of a semithin section of rat's gastric mucosa of group VI showing the basal parts of the gastric glands formed mainly of darkly stained chief cells (Ch) with granular apical cytoplasm (short black arrow) and vesicular nuclei (long black arrow) and rounded parietal cell (P) between the chief cells. Notice, the slightly dilated lumens (long red arrows). (Toluidine blue, x1000)

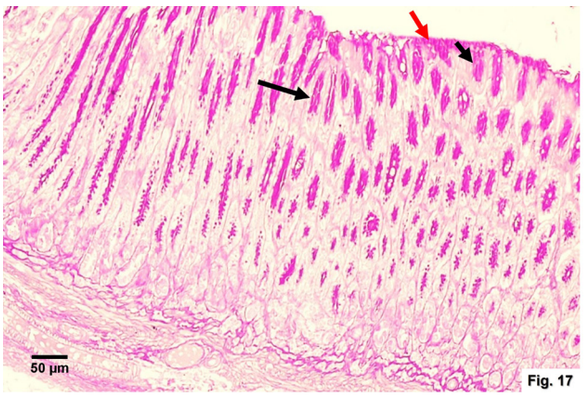


Fig. 17: A photomicrograph of a section of rat's gastric mucosa of group I showing strong PAS-positive reaction mainly in the surface mucous layer (short red arrow), in the pits (short black arrow), and in the isthmus region (long black arrow). (PAS, x100)

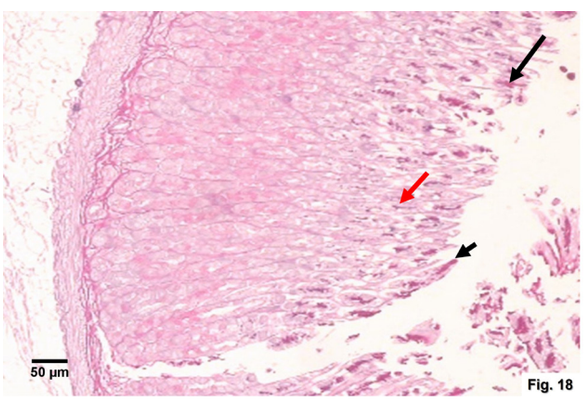


Fig. 18: A photomicrograph of a section of rat's gastric mucosa of group IV showing weak interrupted PAS-positive reaction of the surface mucous layer (short black arrow), in the pits (long black arrow) and with an almost negative reaction of the isthmus region (red arrow). (PAS, x100)

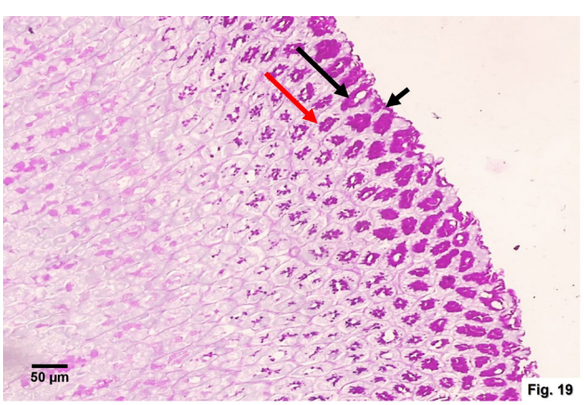


Fig. 19: A photomicrograph of a section of rat's gastric mucosa of group V showing strong PAS-positive reaction mainly in the surface mucous layer (short black arrow), in the pits (long black arrow), and in the isthmus region (long red arrow). (PAS, x100)

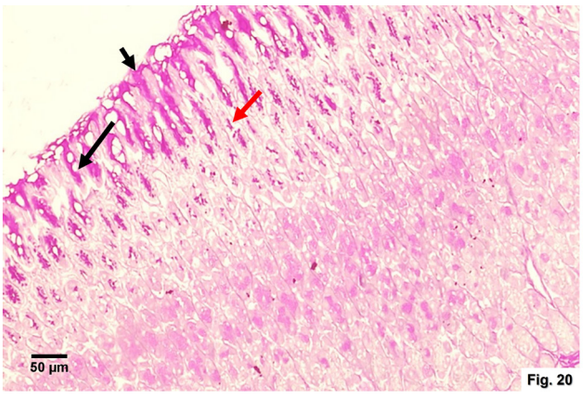


Fig. 20: A photomicrograph of a section of rat's gastric mucosa of group VI showing slightly interrupted PAS-positive reaction in the surface mucous layer (short black arrow) and in the pits (long black arrow) with weak reaction in the isthmus region (red arrow). (PAS, x 100)

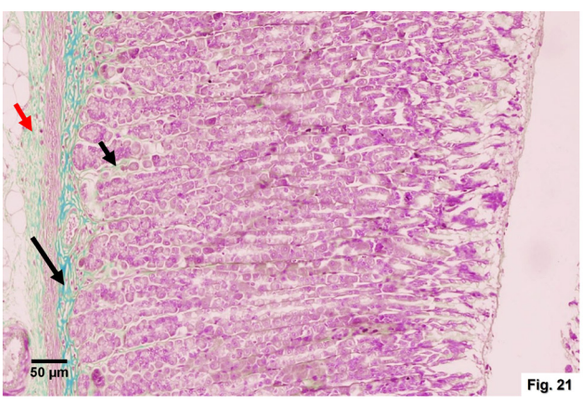


Fig. 21: A photomicrograph of a section of rat's gastric mucosa of group I showing the regular distribution of collagen fibers of lamina propria in-between the basal parts of the glands (short black arrow) and below the basal parts of the glands (long black arrow) and in the submucosa (short red arrow). (Masson's trichrome, x100)

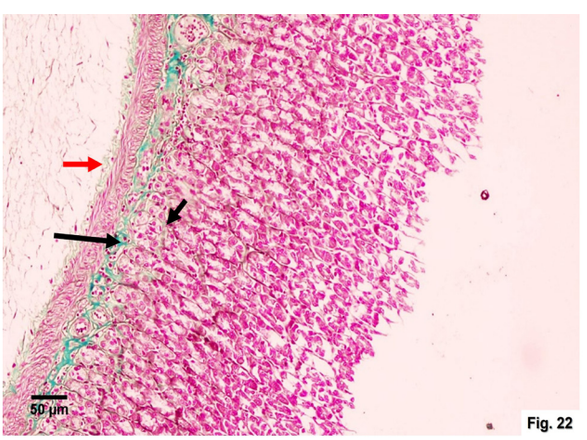


Fig. 22: A photomicrograph of a section of rat's gastric mucosa of group IV showing an irregular distribution of few collagen fibers in the lamina propria in-between the basal parts of the glands (short black arrow), below the basal parts of the glands (long black arrow), and in the submucosa (red arrow). (Masson's trichrome, x100)

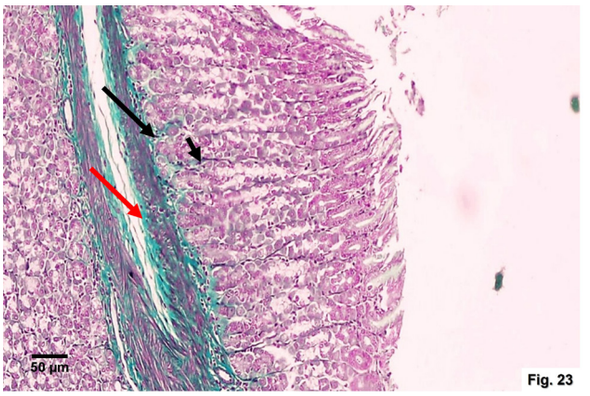


Fig. 23: A photomicrograph of a section of rat's gastric mucosa of group V showing a regular distribution of thick collagen fibers in the lamina propria in-between the basal parts of the glands (short black arrow), below the basal parts of the glands (long black arrow) and in the submucosa (red arrow). (Masson's trichrome, x100)

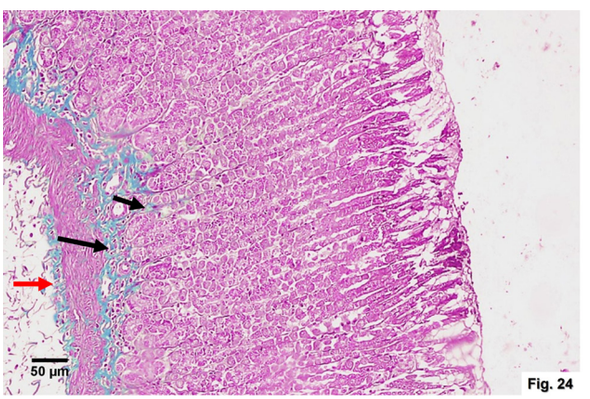


Fig. 24: A photomicrograph of a section of rat's gastric mucosa of group VI showing an almost regular distribution of collagen fibers in the lamina propria in-between the basal parts of the glands (short black arrow), below the basal parts of the glands (long black arrow) and in the submucosa (red arrow). (Masson's trichrome, x100)

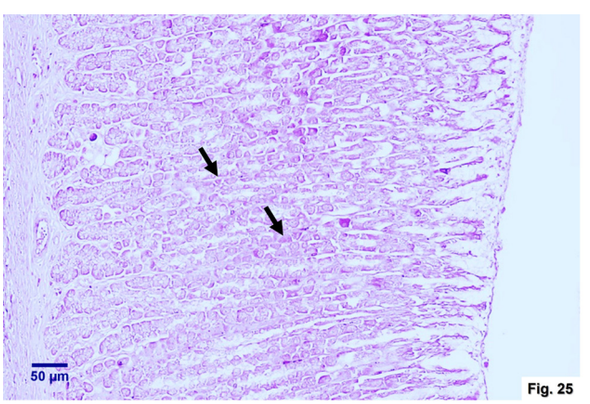


Fig. 25: A photomicrograph of a section of rat's gastric mucosa of group I showing negative cytoplasmic reaction for caspase-3 of most of the glands' cells (black arrows). (Caspase 3, x100)

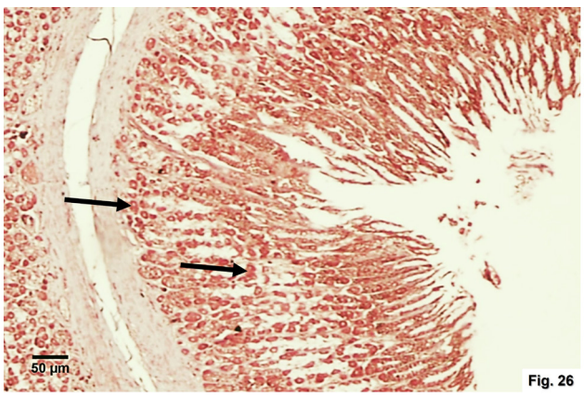


Fig. 26: A photomicrograph of a section of rat's gastric mucosa of group IV showing a strong positive cytoplasmic reaction for caspase-3 of most of the glands' cells (black arrows). (Caspase 3, x100)

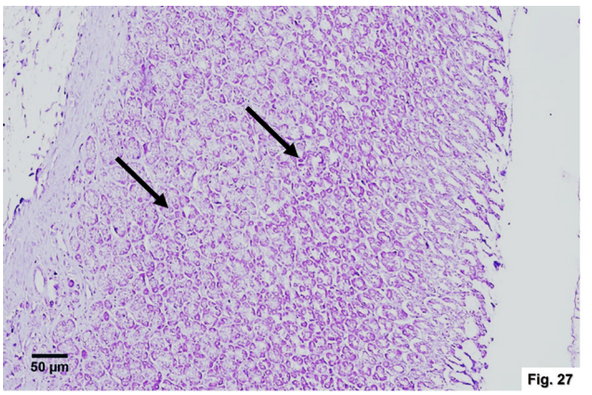


Fig. 27: A photomicrograph of a section of rat's gastric mucosa of group V showing negative cytoplasmic reaction for caspase-3 of most of the glands' cells (black arrows). (Caspase 3, x100)

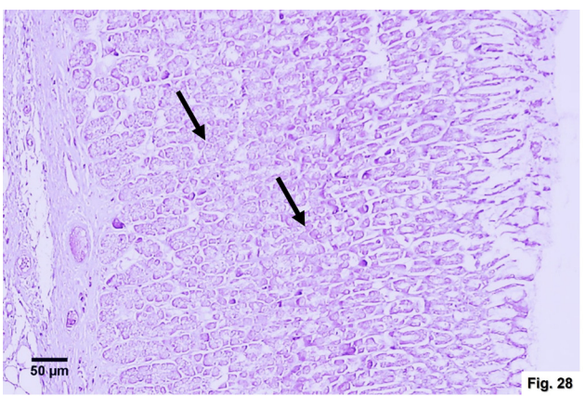
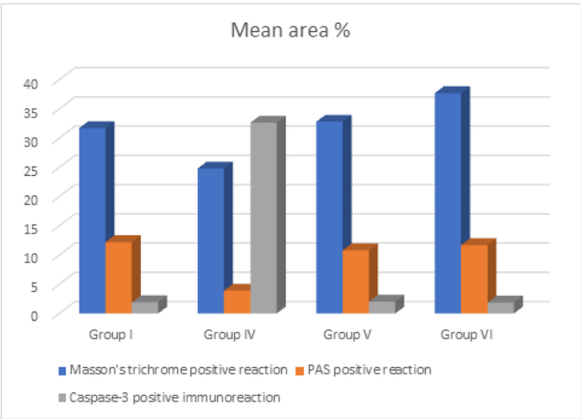


Fig. 28: A photomicrograph of a section of rat's gastric mucosa of group VI showing negative cytoplasmic reaction for caspase-3 of most of the glands' cells (black arrows).(Caspase 3, x100)

Table 1: Comparing the mean area % of Masson's trichrome positive reaction, PAS-positive reaction, and caspase-3 positive immunoreaction of the experimental groups.

	Masson's trichrome positive reaction	PAS-positive reaction	Caspase-3 positive immunoreaction
	Area%	(Mean ± Standard deviation)	
Group I (control group)	31.7 ± 1.5	12.2 ± 0.8	1.9 ± 0.1
Group IV (gastric ulcer group)	24.8 ± 5.2	3.9 ± 0.7	32.6 ± 5.0
Group V (prp protective group)	37.7 ± 4.4	11.7 ± 1.1	1.9 ± 0.2
Group VI (glutamine protective group)	32.8± 3.0	10.8 ± 0.6	2.0 ± 0.1
	(*P-value* between every two groups)		
Groups I& IV	0.000*	0.000*	0.000*
Groups I& V	0.000*	0.274**	0.617**
Groups I& VI	0.12**	0.001*	0.413**
Groups IV & V	0.000*	0.000*	0.000*
Groups IV & VI	0.000*	0.000*	0.000*
Groups V & VI	0.000*	0.044*	0.737**

P-value, highly significant (*) and nonsignificant (**)



Histogram 1: Demonstrating the morphometric comparison between the experimental groups regarding the mean area% of Masson's trichrome positive reaction, PAS-positive reaction, and caspase-3 positive immunoreaction.

DISCUSSION

Gastric ulcers occur due to alterations of the gastric defense mechanisms either due to an increase in the exposure of the mucosa to harmful factors such as free radicals, gastric acid and pepsin, or due to a decrease in the protective factors of the mucosa including bicarbonates, prostaglandins, and mucus[6,24]. Aspirin is a commonly used drug in preventing thrombosis and in the treatment of rheumatoid arthritis due to its potent anti-inflammatory and analgesic effects[25,26]. Peptic ulcer including gastric and duodenal ulcers is considered one of the major side effects of using oral nonsteroidal anti-inflammatory drugs such as aspirin[27-29].

The aim of the present study was to assess the protective effects of autologous platelet-rich plasma versus glutamine (non-essential amino acid) against aspirin-induced acute gastric ulcers in adult male albino rats.

The results of the present study revealed numerous structural changes in the gastric wall of group IV rats that received a single oral dose of aspirin. There were mucosal ulcerations and congested submucosal blood vessels. Most of the non-ulcerated areas showed loss of alignment of mucous neck cells with irregular shapes and pyknotic nuclei. The basal parts of most gastric glands showed distorted and dilated lumens, degenerated parietal cells, and light-stained chief cells with loss of their apical granules. Inflammatory cells and Mast cells were also detected between the mucosal cells.

Aspirin leads to gastric mucosal ulceration through reduction of the mucosal prostaglandins via inhibition of the cyclooxygenase-1 enzyme. Prostaglandins protect mucosal integrity by improving the blood flow and encouraging the secretion of mucus and bicarbonate. The acidic media of the stomach causes aspirin to retain in the nonionized form, making it accumulates in the mucosal cells, which alters the cells' permeability with subsequent loss of these cells and ulceration of the mucosa.

Aspirin effects on the mucosa of the stomach can be detected by an endoscope within a few minutes after topical application[30,31]. The inflammatory cellular infiltration between the mucosal cells could be attributed to the loss of the mucosal barrier which is formed by the tight junctions between the cells that prevent back diffusion of acid and pepsin[32,33]. The changes that occurred in the chief and the parietal cells with the distorted lumens of the basal parts of the glands could be assigned to the destruction of the cells by gastric acid and pepsin leakage[34].

In the present study, both prp and glutamine showed good protective effects against aspirin-induced acute gastric ulcers with more positive effects of prp. The gastric wall of rats in group V that received prp before aspirin showed intact gastric mucosa and regularly aligned mucous neck cells with foamy cytoplasm. The basal parts of the gastric glands were nearly like those of the control group. Whereas, the rats in group VI that received glutamine before aspirin, showed nearly regular layers of the gastric wall, and regularly aligned mucous neck cells. Though, the mucosa was still showing minimal loss of the surface cells. Also, the mucous neck cells were having less foamy cytoplasm and some of them showed pyknotic nuclei. Few inflammatory cells between the mucosal cells and slightly dilated lumens of the basal parts of the gastric glands were also detected.

The possible mechanisms by which prp protected the gastric mucosa might be accredited to its ability to decrease lipid peroxidation, produce antioxidants and increase the mucosal immune response. Also, prp is well known to be rich in multiple growth factors such as platelet-derived growth factor, vascular endothelial growth factor, epidermal growth factor, and fibroblast growth factor. That's why it has a great protective and healing capability for ulcers. Epidermal growth factor has also other potent biological effects on gastric mucosa which include suppression of acid secretion and stimulation of mucous production[11,14,35-37]. Jeong *et al*.[25] investigated the effectiveness of the endoscopic application of prp in the treatment of gastric ulcers resulting from endoscopic submucosal dissection and reported a marked decrease in the ulcer size measured by an endoscopic ruler without any adverse effects from its application.

Regarding glutamine, it was reported that it can block the harmful effects of aspirin on gastric mucosa by preventing the back diffusion of gastric acid and pepsin into the mucosa and by inhibiting the absorption of aspirin into the mucosal cells. Additionally, it increases glucagon-like peptide-1, which in order reduces the release of acetylcholine and the secretion of gastric acid[38-40].

In the present study examination of PAS-stained sections of group IV (gastric ulcer group) showed a weak interrupted PAS-positive reaction in the surface mucous layer and in the pits with an almost negative reaction in the isthmus region. In group V, PAS-stained sections showed a strong positive PAS reaction in the surface mucous layer,

in the pits, and in the isthmus region. While group VI showed slightly interrupted PAS-positive reaction in the surface mucous layer and in the pits with a weak reaction in the isthmus region.

The depletion of the surface mucous with aspirin administration was in accordance with Abdelatif *et al*.[16] who attributed this to either surface cell lysis and/or failure of gastric adaption. On the other hand, remarkable surface mucous was detected in the prp protective group than that detected in the glutamine protective group. The evident mucous detected in the prp protective group could be attributed to its ability to induce cellular proliferation and secretion by its growth factors[17,25]. On the other hand, glutamine greatly affects the function of the mucous cells as they not only utilize extracellular glutamine but also synthesize it. So, glutamine synthesis inhibition in mucosal cells culture led to inhibition of the proliferation and the differentiation of the cells suggesting that glutamine activates the genes linked to cell cycle progression in the mucosal cells[41].

Additionally, in the present study examination of Masson's trichrome stained sections of group IV showed an irregular distribution of few collagen fibers in the lamina propria and in the submucosa. While examination of sections in groups V and VI revealed regular distribution of collagen fibers in the lamina propria and in the submucosa. Though, regular, and thick collagen fibers were more evident in the prp protective group.

Decreased collagen observed in the aspirin group was in accordance with Alese *et al*.[42] who reported compromised collagen integrity in aspirin-induced gastric lesions which were considered a part of the gastric tissue inflammation that led to the destruction of both the glands and the connective tissue. Preserved collagen distribution in prp protective group could be attributed to the sensitivity of fibroblasts to prp growth factors which might help in maintaining collagen integrity, fast maturation and new synthesis[43,44].

Concerning the noticed preserved collagen distribution in the glutamine protective group. It was reported that glutamine increases hydroxyproline cellular content which is one of the products of glutamine metabolism essential for collagen production. Hydroxyproline is a highly abundant amino acid in collagen that promotes the triplet-helix formation of collagen and exports collagen out of the cells[45,46].

Finally, examination of immunohistochemically stained sections for caspase-3 of group IV showed a strong positive cytoplasmic reaction of most of the glands' cells. While in groups V and VI there was negative cytoplasmic reaction of most of the glands' cells.

Apoptosis is achieved by the intracellular caspases which present as dormant precursors and are activated through either extrinsic or intrinsic apoptotic pathways. The extrinsic pathway is stimulated upon activation of specific receptors by specific antibodies while the intrinsic pathway is triggered by a stimulus that damages the mitochondria. Both pathways activate the caspases with subsequent destruction of the structural proteins and the DNA[47].

The apoptotic effect of aspirin on gastric mucosal cells was traditionally attributed to its direct toxic action resulting in cell death[48,49] but, other researchers reported that mucosal cellular death by aspirin resulted from an acceleration of the cellular apoptosis by its effect on the mitochondria[50,51].

The ability of prp to decrease cellular apoptosis might be accredited to its high content of cytokines and growth factors[52-54]. The effect of subcutaneous injection of prp on internal organs was reported in previous studies. It showed to enhance pancreatic islet regeneration in experimentally induced diabetes in rats[14] and to ameliorate gamma radiation-induced nephrotoxicity in rats through modulating oxidative stress and apoptosis[55].

With reference to glutamine as an apoptotic suppressor, it was reported to block apoptosis induced by heat shock, irradiation, and hepatocyte apoptosis in obstructive jaundice. Glutamine is thought to regulate signal transduction pathways for cellular proliferation and apoptosis[56,57]. Even though glutamine and prp showed good protective effects against aspirin-induced acute gastric ulcers in rats, prp proved to be better in preserving the general architecture of the mucosa, its collagen, and its mucin contents.

CONCLUSION

In view of the above discussion, it could be concluded that platelet-rich plasma (prp) and glutamine have good protective effects against aspirin-induced acute gastric ulcers in adult male albino rats but prp has better results.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

التأثيرات الوقائية للبلازما الذاتية الغنية بالصفائح الدموية مقابل الجلوتامين ضد قرح المعدة الحادة التي يسببها الأسبرين في ذكر الجرذ الابيض البالغ (دراسة نسيجية وكيميائية مناعية)

ايناس انور بخيت ـ هالة طه شعلان

قسم التشريح والاجنة، كلية الطب، جامعة عين شمس

المقدمة: تؤثر قرحة المعدة بشكل كبير على نوعية حياة المريض ، وقد تؤدي إلى مضاعفات كبيرة مثل ثقب المعدة والنزيف ويمكن ايضا ان تصل الى الموت. العلاج بشكل أساسي يكون دوائى. ومع ذلك ، فإن الأدوية ليست فعالة في علاج جميع الحالات وأيضًا لديها العديد من الآثار الضارة.

الهدف: يهدف هذا العمل إلى تقييم التأثيرات الوقائية للبلازما الذاتية الغنية بالصفائح الدموية مقابل الجلوتامين ضد قرحة المعدة الحادة التي يسببها الأسبرين في ذكور الجرذان البيضاء البالغة.

المواد والطرق: تم استخدام خمسين جرذ ابيض ذكر تتراوح أعمارهم بين ٦-٨ شهور واوزانهم بين ١٨٠-٢٠٠ جم وقسمت الجرذان عشوائياً إلى ست مجموعات. المجموعة الأولى (المجموعة الضابطة): والتي قسمت إلى مجموعتين فرعيتين: المجموعه الاولى أ : تم الاحتفاظ بالجرذان دون أي علاج ، المجموعة الاولى ب : تلقت الجرذان جرعة واحدة عن طريق الفم من الكربوكسي ميثيل سيليولوز، المجموعة الثانية : تلقى كل جرذ ٠,٥ مل لكل كجم من وزن الجسم من البلازما الغنيه بالصفائح الدموية تحت الجلد يومين فى الاسبوع لمدة ثلاث اسابيع، والمجموعة الثالثة : تلقى كل جرذ ٥٠٠ ملجم لكل كجم من وزن الجسم من الجلوتامين يوميا عن طريق الفم لمدة ثلاث اسابيع. المجموعة الرابعة (مجموعة القرحة): تلقى كل جرذ جرعة واحدة عن طريق الفم من الأسبرين (٣٠٠ ملجم لكل كجم من وزن الجسم). المجموعة الخامسة (مجموعة الوقايا بالبلازما الغنية بالصفائح الدموية): تلقى كل جرذ جرعة ٠,٥ ملجم لكل كجم من وزن الجسم من البلازما الغنية بالصفائح الدموية تحت الجلد يومين في الأسبوع لمدة ثلاثة أسابيع ثم جرعة واحدة من الأسبرين عن طريق الفم. المجموعة السادسة (مجموعة الوقاية بالجلوتامين): تلقى كل جرذ جرعة مقدارها ٥٠٠ ملجم لكل كجم من وزن الجسم من الجلوتامين يوميا عن طريق الفم لمدة ثلاثة أسابيع ثم جرعة واحدة من الأسبرين عن طريق الفم.

النتائج: لا يوجد فرق نسيجي فى الغشاء المخاطي للمعدة بين جرذان المجموعات الأولى والثانية والثالثة بينما لوحظ العديد من التغيرات في الغشاء المخاطي للمعدة فى جرذان المجموعة الرابعة (مجموعة الأسبرين) بينما أظهرت الجرذان في المجموعة الخامسة (مجموعة الوقاية بالبلازما الغنية بالصفائح الدموية) والمجموعة السادسة (مجموعة الوقاية بالجلوتامين) هيكل منتظم للغشاء المخاطي في المعدة ولكن البلازما الغنية بالصفائح الدموية أعطت نتائج أفضل.

الخلاصة: البلازما الغنية بالصفائح الدموية والجلوتامين لهما تأثيرات وقائية جيدة ضد قرح المعدة الحادة التي يسببها الأسبرين في الجرذان ولكن البلازما الغنية بالصفائح الدموية أفضل من الجلوتامين.