



Gartroprotective Potential of *Ficus carica* L. Leaves Extract against Ulceration induced via Indomethacin in Rats: Mechanistic Study

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ABSTRACT

Peptic ulcer (PU) is a major health hazard. Ulceration of non-steroidal anti-inflammatory drugs (NSAIDs) has been considered a major health hazard. Several pharmaceutical products have been engaged to protect and treat NSAIDs- induced PU, but there was the incidence of relapses, and many severe side effects were produced during ulcer treatment. Recently, there has been a growing interest in medicinal plants. *Ficus carica* L. leaves' extract (FCLE) has had many biological activities. The present work aimed to evaluate the possible protective utility of FCLE against NSAIDs-induced PU in rats. The PU was induced by interperitoneal (i.p.) injection of indomethacin (IND) (30 mg/kg), while FCLE was given to rats by oral gavage at the dose of 500 mg/ kg, and ranitidine (RNA) was used as a reference drug (50 mg/kg) for 3 weeks before IND injection. Gastric mucosal lesions index (UI) was determined. Total acid outputs (TGA) and pH were assessed in gastric juice. Gastric mucosal malondialdehyde and catalase levels were determined. Gastric prostaglandin E2 (PGE2) and nitric oxide (NO), as well as serum pro-inflammatory cytokines were detected. Histopathological examination for gastric was carried out. There was a significant elevation ($P < 0.001$) in UI, TGA, pepsin, gastric oxidative stress and inflammation along with a significant decline in gastric pH, mucin, PGE2 and NO levels in the PU group compared with the pretreatment PU groups with FCLE, RAN and FCLE+RAN. Moreover, there was a noticeable improvement in the gross structure and histopathological results of the pretreated PU groups compared with PU group. The most effective pretreatment was seen in the PU group co-pretreated with FCLE+ RAN. These protective effects could be explained via the enhanced gastric protective factors, stimulated antioxidant status, and diminished pro-inflammatory cytokines.

Key Words: *Ficus carica*, Indomethacin, Peptic ulcer, Antioxidant, Mechanistic Study.

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INTRODUCTION

Peptic ulcer is a major health hazard, it is caused via several exogenous factors as smoking, increased stress, tension, receiving medications as anticancer, NSAIDs, and therapy that stimulate pepsin and gastric acid secretion [1]. The pathophysiology of PU is caused when a balance between offensive factors; as pepsin, *Helicobacter pylori*, gastric acid, refluxed bile, and

increment of prooxidants, and cytoprotective factors; as prostaglandin, nitric oxide, mucin, bicarbonate, mucosal blood flow and antioxidants is lost. Therefore, diminution the production of gastric acid or boosting the gastric protective mucosal factors are the techniques for treating PU [2].

Inflammatory diseases include different types of rheumatoid arthritis, chronic active hepatitis, and asthma [3]. The NSAIDs as ibuprofen, aspirin, indomethacin etc., are commonly prescribed therapies as pain killers

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and their anti-inflammatory, analgesic, anti-pyretic and other therapeutic actions have been fully agreeable in the treatment of chronic and acute inflammatory conditions to their effectiveness in alleviating swelling pain of inflammation [4]. Receiving NSAIDs caused unlimited hazard effects as gastric mucosal damage and lesions, renal toxicity, cardiovascular events, and hypertension [5, 6]. Almost half of NSAID consumers have had endoscopic injury (such as ulcerations, erosions, and sub-epithelial hemorrhages), mainly located in gastro, usually without medical symptoms [7].

Indomethacin is one of the most commonly used NSAIDs for the treatment of rheumatoid arthritis [8]. It could develop specially with prolonged use of critical systemic toxicity with no appearance of warning symptoms. It generates reactive oxygen species (ROS) which cause extremely tissue cytotoxicity inducing oxidative stress [9]. Researchers detected hepato-renal toxicity and PU relying on the received dose and prolonged use of NSAIDs [10-12]

The accumulation of the ROS and diminution of the antioxidants have been looked upon as being a vital progression in NSAIDs –caused gastric mucosal destruction. Thus, they became the subjects of many investigations [13, 14]. Since that IND is included in the generation of extracellular and/or intracellular ROS. Therefore, antioxidants' cytoprotective role in the protection and curation of PU injuries has been broadly examined.

Ficus carica Linn. (Moraceae family), has been stated in the holy Quran. *F. carica* leaves have been used in alternative therapies to cure several diseases as anti-inflammatory to cure respiratory, cardiovascular, antispasmodic, and gastrointestinal disorders [15, 16]. It has been commonly used for the cure of anemia and jaundice [17]. As well, several researchers reported the antioxidant, hepatoprotective, antispasmodic, anthelmintic, antifungal, antipyretic, and antimutagenic activities [18-22]. Glycemic control of FCLE has been shown in diabetic rats' model [23]. *F. carica* hypolipidemic activity was reported in hyperlipidemic models [24, 25].

Several efforts have been made to find a novel antiulcer drug with potentially less or no side effects. To the best of our knowledge, few scientific works have been carried out on the leaves of FCLE to prove gastro-protective activity. Depending on that FCLE has potent antioxidant activity, the present investigation aimed to assess the potential gastroprotective effect of FCLE on PU caused by IND in rats and compare the FCLE with standard drug RAN, as well, to explore the underling mechanism.

MATERIAL AND METHODS

Experimental rats

Male albino rats (n=50) (180 ± 10 g) were provided from King Fahd Medical Research Center, KAU. Basal diet constituents were purchased from Baghafar Company for Pharmaceutical and Chemical, Jeddah, KSA.

Chemicals and drugs

Indomethacin (IND) and Ranitidine (RAN) were purchased from local Pharmacy, Jeddah, Saudi Arabia. All chemicals were bought from Sigma.

Preparation of *F. carica* leaves extract

F. carica L. Family Moraceae, was obtained from Taif, KSA. Leaves of the plant were authenticated in Faculty of Pharmacy, KAU, KSA. Dried powdered leaves(100 g) were extracted with 80 % ethanol by maceration for 48 h at room temperature. The filtered extract was concentrated under pressure by a rotary evaporator. Finally, the concentrated extract was relocated to freeze dryer at - 20 ° C for 48 h. [26]. A solid extract (6.18 % of dried powder) was reserved at 4 ° C.

Ulceration procedure

Fasted rats (24 h, with water *ad libium*) were i.p. injection with IND (30 mg/kg) at the end of the experimental period (21 days). The rats were sacrificed four h post IND treatment. The different degrees of lesions in the gastric mucosal were measured by a microscope [27].

Experimental grouping

Animals (n=50) were randomly divided into five groups; *Group I* (Contr; rats received saline as negative group). *Group II* (PU; control positive) ulcer rats. *Groups III, IV and V* (protective groups) rats were given the FCLE (500 mg/kg/day p.o), RAN (50 mg/kg/day orally), and both FCLE and RAN; respectively, for three weeks pre-administration of IND to induced PU.

Ulcer index (UI)

Each stomach lesion was measured and used to calculate UI, and the percentage of protection was calculated as follow [(UI (PU) - UI (protected PU))/ UI (PU)] X 100 [28].

Estimation of gastric total acidity, pH, mucin and pepsin levels.

One ml of gastric juice was diluted with distilled water (10 ml), and titrated with sodium hydroxide (0.01 N) after adding phenolphthalein reagent (2-3 drops). The used volume corresponded to gastric (GTA) total acidity [29]. The pH was measured in the gastric content by a digital pH meter [30]. Pepsin and mucin levels were assessed [31, 32]

Estimation of gastric antioxidant status and defensive factors

Gastric malondialdehyde (MDA) and catalase (CAT) were measured using Elisa kits. Nitric oxide (NO) and prostaglandin E2 (PGE2) were estimated by Elisa immunosorbent assay kits following the procedures of the manufacturer.

Estimation of serum pro-inflammatory cytokines.

Serum interleukin-1 beta (IL1- β) and tumor necrosis factor -alpha (TNF- α) were measured by rat Elisa kits following the procedures of the manufacturer.

Histopathological studies

Histopathological of the gastric tissues were examined after being stained with haematoxylin and eosin by a light microscope.

Statistics

The inhibition of ulceration was represented as percentage, while the other obtained results were represented as mean \pm SE. The significant differences between groups in the present study were determined by SPSS, ver. 24.

RESULTS

Gross structure of gastric lesions

In PU rats, the gastric gross showed many ulceration and hemorrhage with dark patches. In pretreated PU rats with FCLE or RAN, there were few linear dark brown lesions, while normal appearance with pink glandular part in PU rats pretreated with FCLE +RAN was seen (Fig 1).

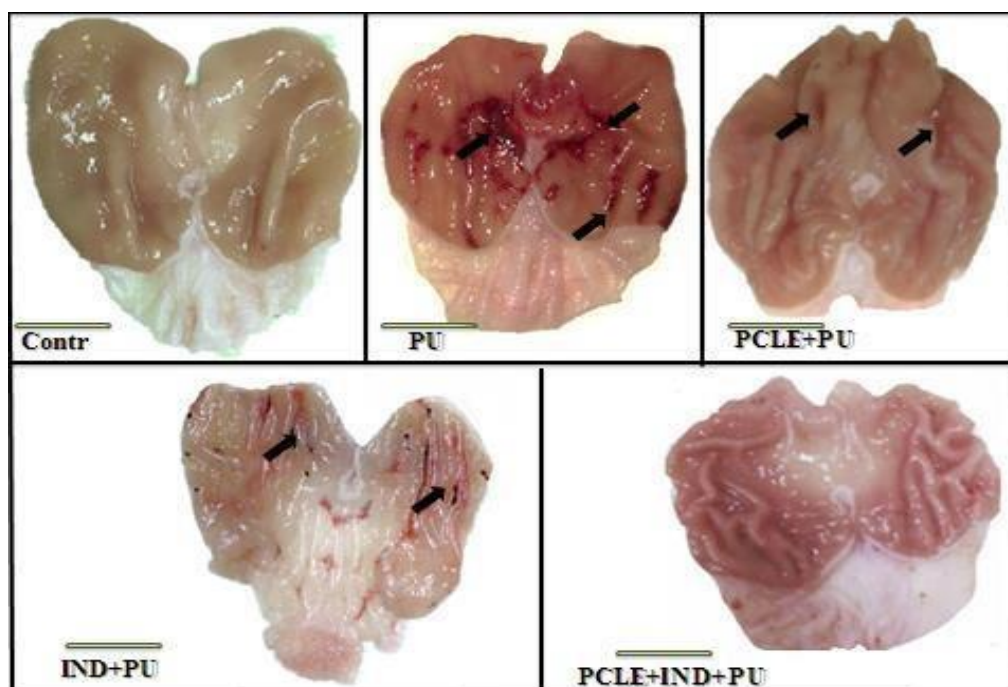


Figure 1: The effect of *F. carica* leaves extract on gastric gross structure in rats. The Contr rats showing, normal rugae with pink glandular part (Contr). In PU rats gastric gross structure showing many ulceration and hemorrhage with dark patches(PU). In PU pretreated with FCLE as well as RAN, the gross evaluation of gastric showing few linear dark brown lesions. while in PU rats pretreated with FCLE +RAN showing normal appearance with pink glandular part.

Ulcer index (UI)

There was a marked decline on ulcer lesions and an elevation on % of ulcer protection in pretreated PU groups compared with PU group. The UI in PU pretreated groups with FCLE, RAN and FCLE+RAN significantly ($p<0.001$) decreased compared with PU group. There was no significant difference between pretreated PU rats with FCLE and pretreated PU rats with RAN, while there were significant differences between PU group pretreated either with FCLE or RAN compared with pretreated

group with FCLE+RAN ($p< 0.05$ and $p<0.01$, respectively). The most effective protective pretreatment was seen in PU group co-pretreated with FCLE+RAN (Table 1).

Gastric defensive factors

There were significant ($p<0.001$) increases in TGA and pepsin levels with significant ($p<0.001$) decreases on gastric pH and mucin levels compared with PU group. There was no significant difference between pretreated PU rats with FCLE and pretreated PU rats with RAN,

while there were significant differences between PU group pretreated with either FCLE or RAN, and PU group pretreated with FCLE+RAN. The most effective protective pretreatment was seen in PU group co-pretreated with FCLE+RAN (Table 2, and Figure 2, 3).

Table 1: Effect of *F. carica* leaves extract on UI and % of protection in PU rats

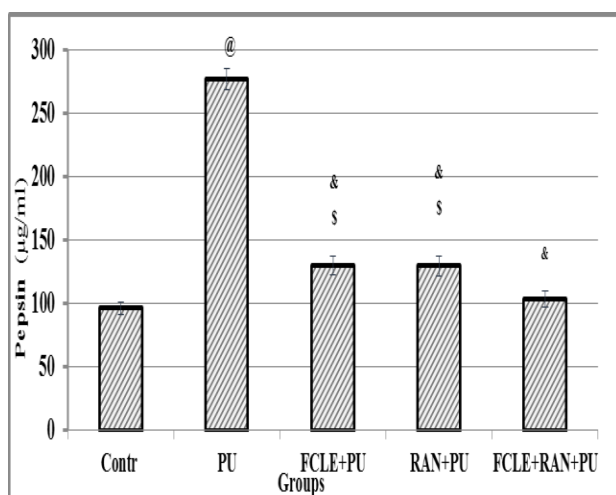
Groups		UI (mm ²)	% of ulcer protection
Contr		-	-
PU		42.64 ± 3.97 ^a	-
Protective PU groups	FCLE (500 mg/kg/day)	23.75 ± 2.28 ^{b,c}	44.30
	RAN	23.90 ± 2.24 ^{b,c}	43.95
	FCLE+ RAN	8.74 ± 0.93 ^b	79.50

P < 0.05, ^a compared with Contr vs. PU, ^b compared with PU, ^c compared with FCLE+ RAN+PU and either FCLE+PU or RAN+PU.

Table 2: Effect of *F. carica* leaves extract on TGA and gastric pH in PU rats

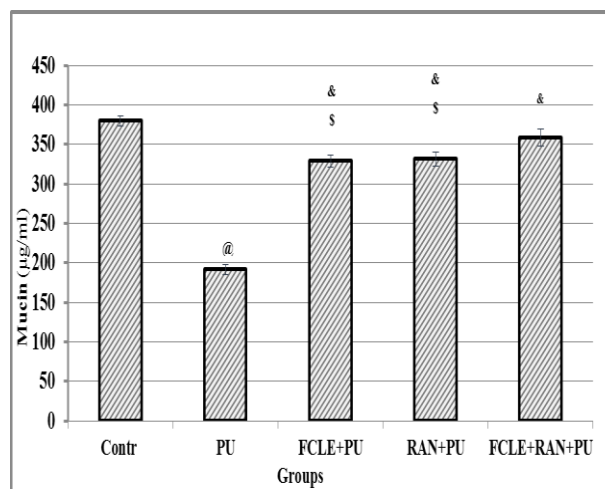
Groups		TGA	Gastric pH
Contr		54.36 ± 3.45	3.42 ± 0.27
PU		183.87 ± 5.37 ^a	1.82 ± 0.23 ^a
Protective PU groups	FCLE (500 mg/kg/day)	87.45 ± 6.22 ^{b,c}	3.02 ± 0.21 ^{b,c}
	RAN	86.83 ± 7.17 ^{b,c}	3.06 ± 0.24 ^{b,c}
	FCLE+ RAN	64.11 ± 5.48 ^b	3.86 ± 0.19 ^b

P < 0.05, ^a compared with Contr vs. PU, ^b compared with PU, ^c compared with FCLE+ RAN+PU and either FCLE+PU or RAN+PU.



P < 0.05, [@] compared with Contr vs. PU, [&] compared with PU, [#] compared with RAN+PU group and protective FCLE + PU group, [§] compared with FCLE+ RAN+PU group and either FCLE+PU group or RAN+PU group.

Figure 2: Effect of *F. carica* leaves extract on pepsin in PU rats



P < 0.05, [@] compared with Contr vs. PU, [&] compared with PU, [#] compared with RAN+PU group and protective FCLE + PU group, [§] compared with FCLE+ RAN+PU group and either FCLE+PU group or RAN+PU group.

Figure 3: Effect of *F. carica* leaves extract on mucin in PU rats

The levels of PGE2 and NO were significantly reduced (p < 0.001) in PU rats compared with the Contr rats. The levels of PGE2 and NO were significantly increased in pretreated groups with FCLE, RAN and FCLE+RAN compared with PU group. There were no significant difference between pretreated PU rats with FCLE and RAN, while there were significant difference between both of them and the PU group pretreated with FCLE+RAN (p < 0.05 and p < 0.01, respectively). The most effective pretreatment was showed in PU group co-pretreated with FCLE+RAN (Table 3).

Table 3: Effect of *F. carica* leaves extract on PGE2 and NO levels in PU rats

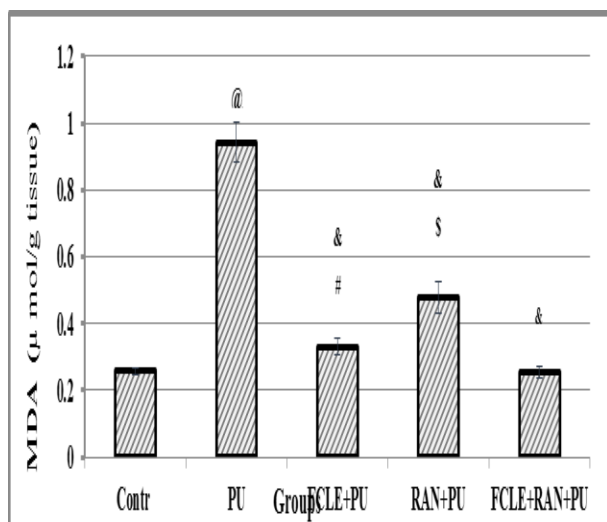
Groups		PGE ₂ (ng/g tissue)	NO (µ mol/g tissue)
Contr		177.05 ± 4.18	0.470 ± 0.018
PU		100.35 ± 3.88 ^a	0.199 ± 0.023 ^a
Protective PU groups	FCLE (500 mg/kg/day)	149.55 ± 8.35 ^{b,c}	0.377 ± 0.021 ^{b,c}
	RAN	142.50 ± 9.12 ^{b,c}	0.334 ± 0.017 ^{b,c}
	FCLE+ RAN	167.95 ± 4.29 ^b	0.449 ± 0.038 ^b

P < 0.05, ^a compared with Contr vs. PU, ^b compared with PU, ^c compared with FCLE+ RAN+PU and either FCLE+PU or RAN+PU.

Gastric antioxidant status

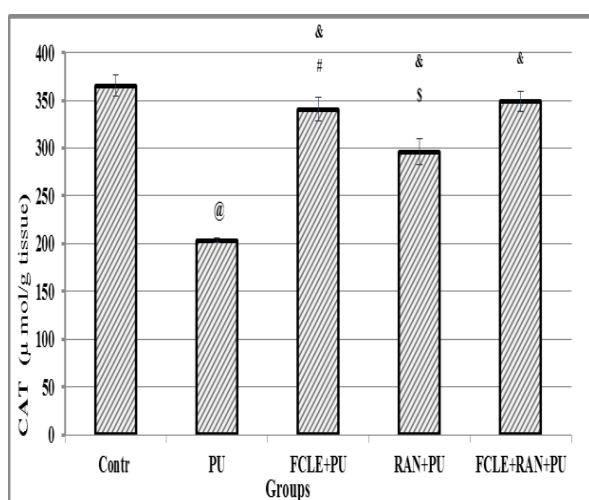
The level of gastric MDA was significantly increased (p < 0.001), while the gastric CAT level was significantly decreased in PU rats compared with the Contr rats. In pretreated groups with FCLE, RAN and FCLE+RAN,

there was a significant decrease in gastric MDA with a significant increase in gastric CAT compared with PU group. There were no significant differences between pretreated PU rats with FCLE and pretreated PU rats with RAN, as well as between pretreated PU rats with FCLE and pretreated PU rats with FCLE+RAN while there were significant differences between PU group pretreated with RAN and PU group pretreated with FCLE+RAN ($p < 0.01$). The most effective pretreatment was seen in PU group co-pretreated with FCLE+RAN (Figure 4 and Figure 5).



$P < 0.05$, @ compared with Contr vs. PU, & compared with PU, # compared with RAN+PU group and protective FCLE + PU group, \$ compared with FCLE+ RAN+PU group and either FCLE+PU group or RAN+PU group.

Figure 4: Effect of *F. carica* leaves extract on gastric MDA in PU rats



$P < 0.05$, @ compared with Contr vs. PU, & compared with PU, # compared with RAN+PU group and protective FCLE + PU group, \$ compared with FCLE+ RAN+PU group and either FCLE+PU group or RAN+PU group.

Figure 5: Effect of *F. carica* leaves extract on gastric CAT in PU rats

Serum pro-inflammatory cytokines

The levels of IL1- β and TNF- α were significantly elevated ($p < 0.001$) in PU rats compared with the Contr rats. The levels of IL1- β and TNF- α were significantly reduced in pretreated groups with FCLE, RAN and FCLE+RAN compared with PU group. Interestingly, there were no significant differences between pretreated PU with FCLE, and pretreated PU with RAN, while there were significant differences between both groups and the PU group pretreated with FCLE+RAN ($p < 0.05$ and $p < 0.01$, respectively). The most effective pretreatment was seen in PU group co-pretreated with FCLE+RAN (Table 4).

Table 4: Effect of *F. carica* leaves extract on IL1- β and TNF- α against IND- induced PU

Groups		IL1- β (ng/ml)	TNF- α (ng/ml)
Contr		13.87 \pm 0.56	1.23 \pm 0.046
PU		26.39 \pm 1.17 ^a	2.94 \pm 0.114 ^a
Protective PU groups	FCLE (500 mg/kg/day)	18.30 \pm 1.34 ^{b,c}	1.62 \pm 0.117 ^{b,c}
	RAN	19.14 \pm 1.02 ^{b,c}	1.83 \pm 0.145 ^{b,c}
	FCLE+ RAN	14.47 \pm 0.77 ^b	1.23 \pm 0.037 ^b

$P < 0.05$, ^a compared with Contr vs. PU, ^b compared with PU, ^c compared with FCLE+ RAN+PU and either FCLE+PU or RAN+PU

Histopathological results

DISCUSSION

Oxidative stress has been involved in several diseases, to avoid it numerous researchers investigate folk medicine, and discovered natural bioactive compounds which have antioxidant properties [33-35]. The present investigation aimed to assess the potential gastroprotective effect of FCLE on PU caused by IND in rats and compare the results of FCLE with the standard drug RAN, as well as, to explore the underlying mechanism.

The present study revealed that IND caused a significant decrease in gastric defensive factors (PGE2 and NO) levels, gastric pH and mucin levels with a significant increase in UI, TGA levels and pepsin activity in PU group compared with Contr group. Similarly, Sabiu et al. [36] and Katary and Salahuddin [37] found that IND caused aggressive factors through increasing gastric acidity and decreasing pH. The high UI in PU group was explained *via* oxidative stress, generation of ROS, inflammation and PGE2 inhibition, which induced the impairment in gastroprotective factors and the increase of gastric damage [38]. The reduction of gastric NO was explained by decline in constitutive nitric oxide synthesis (cNOS) and up-regulation of inducible nitric oxide (iNOS) [30-40].

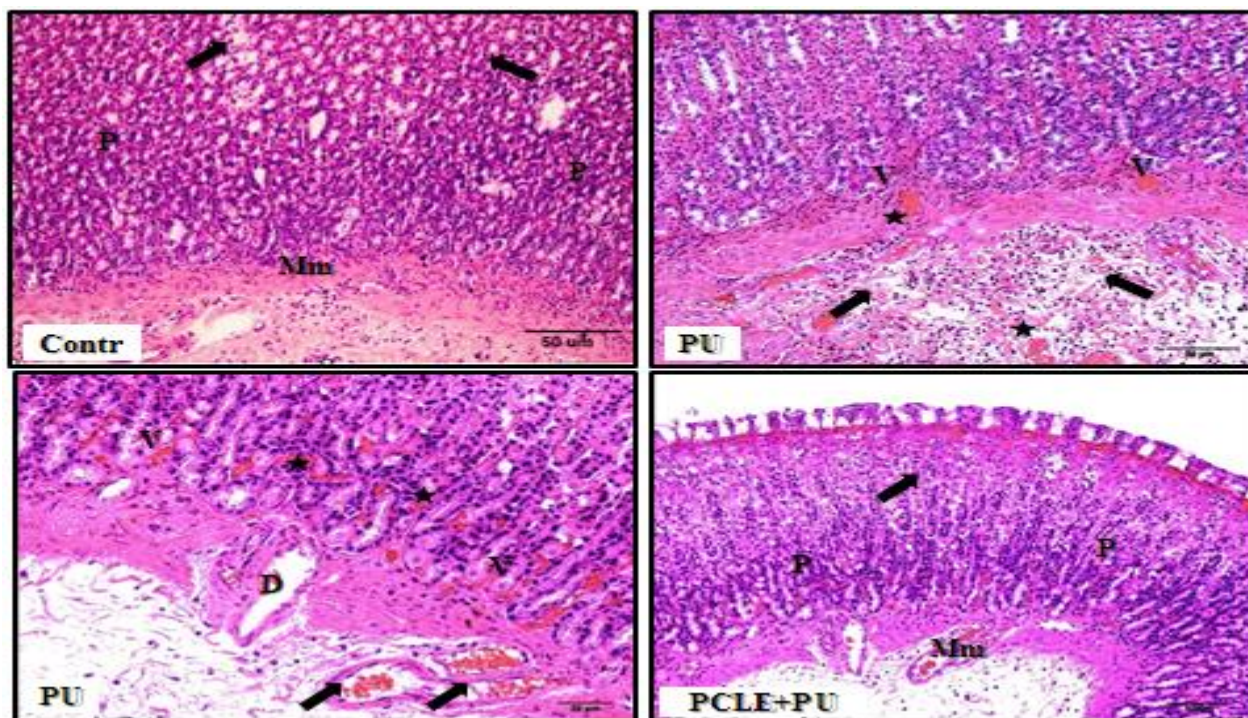


Figure (6): Effect of *F. carica* leaves extract on histopathological alteration on gastric tissue in PU rats (Haematoxylin and eosin staining). The gastric of Contr group showing normal structure of fundic glands with basal oval nuclei, Parietal cells (P) with pale foamy cytoplasm (stars), and muscularis mucosa (Mm) (Fig Contr). In PU group fundic glands of the gastric showing loss of architecture of epithelium vacuolization (V) of the cytoplasm of P cells with nuclear fragments (arrows) (Fig PU-1). Inflammation and dilatation (D) in the gastric gland (stars) (Fig PU-2). In PU group treated with FCLE the fundic mucosa of gastric showing near normal architecture, few area of partial erosion and dilatation are seen (Fig FCLE+PU).

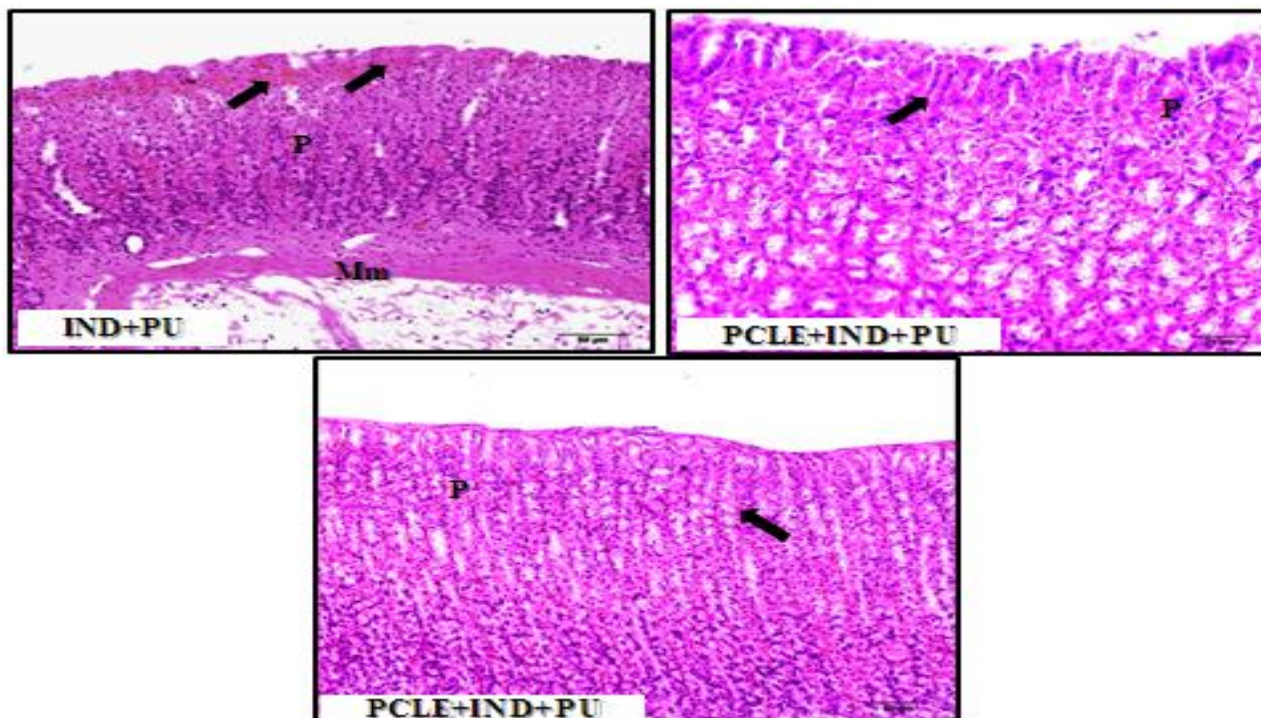


Figure (7): Effect of *F. carica* leaves extract on histopathological alteration on gastric tissue in PU rats (Haematoxylin and eosin staining). In PU group pretreated with RAN The epithelial surface in the gastric was near normal, expect some area of (arrows) (Fig RAN+PU). While co-pretreatment with FCLE + RAN to PU rats showed improved in the architecture of epithelium surface in the gastric which seen as normal (Fig FCLE+RAN+PU).

The pretreatment of PU rats with FCLE showed a significant increase in gastric defensive factors as evidenced by the marked increase in (PGE2 and NO) levels, gastric pH and mucin levels with significant decreases in UI, TGA levels and pepsin activity compared with PU group. To the best of the authors' knowledge, relatively few researches were available regarding the gastroprotective effect of FCLE; however, this effect could be explained through the high flavonoid and phenol compounds in FCLE [41-43]. These compounds had high antioxidant activities which attenuated the damage effect induced by IND.

The NSAIDs was reported to induce the side effects through oxidative stress in several studies [9-12]. In this study, the administration of IND induced oxidative stress (significant increase MDA and decrease CAT) and inflammation (significant increase IL1- β and TNF- α levels). The decrease in CAT and increase in MDA could be explained through free radicals generated from the infiltration of neutrophils which caused oxidation in membrane fatty acids and increased lipid peroxidation thus induced further aggravation of the gastric damage [44, 45]. The depletion in antioxidant as CAT was reported in several studies, caused IND to induce PU [40, 46]. The increase in cytokines was explained *via* activated neutrophils which induced excessive infiltration of the mucosal tissue in gastric [47, 48]. The elevation of pro-inflammatory cytokines had an essential role in aggravation of gastric damage.

A marked significant antioxidant and anti-inflammatory effects were seen in the groups pretreated with FCLE compared with the PU group. The obtained finding explained the potent antioxidant activity in the FCLE [49-50]. Many studies proved the antioxidant effect of FCLE. The low level of stable free radicals DPPH assay by FCLE indicated the stronger antioxidant substance activity of the extract [51]. The anti-inflammatory effect was attributed to the antiradical effect of FCLE [52, 53]. Interestingly, significant differences were found between pretreated groups with FCLE+RAN+PU and with RAN as a reference drug in the antioxidant and anti-inflammatory tested parameters, thus it was indicated that FCLE had potent antioxidant and anti-inflammatory activities, which had a synergistic effect along with RAN. In this study, the gastric gross structure and histopathology results showed a lot of ulceration, hemorrhage, mucosal damage and inflammation in the PU group injected with IND. These findings have been reported by several studies, the researchers explained pathogenesis of PU by IND through inhibition of PGE2,

depletion of blood flow in gastric mucosal which infiltrated neutrophils and leucocytes to gastric tissue, thus activated myeloperoxidase enzyme which increased inflammation [30-40, 54, 55]. On the other hand, the pretreatment with FCLE showed a marked decrease in gastric mucosal damages that could be explained through antioxidant and anti-inflammatory activities, as well as scavenging free radicals of flavones and phenolic compounds as found in many studies [49-50].

CONCLUSION

This work proved that FCLE possessed gastroprotective activity in IND induced PU by restore the antioxidant status, decrease the inflammation and increase the gastric defensive factors. The PU group pretreated with FCLE+RAN is the most effective pretreatment compared with either FCLE or RAN alone.

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