

**Effect of probiotic camel
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gastric mucosal toxicity
in Rats**



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Effect of probiotic camel milk-enriched with *Carica papaya* oil or extract against indomethacin-induced gastric mucosal toxicity in Rats

Abstract

Camel milk was known for its unique value which makes it a valuable source in the field of medicine as antidiabetic, wound healing, anti-microbial, hepatoprotective and antiulcer agents. Therefore, the current study was performed to investigate the potential effect of probiotic camel milk-enriched with papaya oil or extract as antioxidant and antiulcer agents on indomethacin-induced gastric ulcers in rats. Thirty-five male albino rats (190 - 200g), were fed on a standard diet and divided into seven groups (5 rats each). Rats of the first group received distilled water and served as normal control. While the other six groups were induced gastric ulceration by a single oral dose of indomethacin (30 mg/kg BW), then these groups were classified into ulcer control, PCM (probiotic camel milk 5 ml /kg BW), PO (papaya oil 5 ml /kg BW), PE (papaya extract 5 ml /kg BW) and their mixture (PCM plus PO), and (PCM plus PE) in 1:1 (v/v) ratio (PCM: PO/or PE). At the end of the study (5 weeks), blood and stomach samples were collected for biochemical analysis. The results revealed that administration of probiotic camel milk significantly ($P < 0.05$) increased gastric pH, the curative ratio of gastric ulcer length, Cyto P450, PGE2 relative to indomethacin-induced ulcer rats. The most effective treated groups were probiotic camel milk incorporated with papaya oil or followed by papaya oil which significantly ($P < 0.05$) decreased gastric ulcer length, the volume of gastric juice, Cox-2 compared with the ulcer group. Activities of glutathione peroxidase, superoxide dismutase in the probiotic camel milk enriched with papaya oil or extract groups were increased significantly compared to the ulcer group ($P < 0.05$). The current study concluded that probiotic camel milk enriched with papaya oil or extract treatment may play a protective role against indomethacin-induced gastric ulcers in rats, which may be due to the enhanced antioxidant enzymes.

Keywords: Antioxidant enzymes, *Carica papaya*, Gastric mucosal toxicity, Probiotic Camel Milk

Introduction

Gastric ulcer considers as the most common multifactorial gastrointestinal disease that associated with various symptoms such as gas, bloating, abdominal pain, fever, nausea, and vomiting. Basic causes include long-term use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), the bacterium *Helicobacter pylori* (*H. pylori*) infection, smoking and alcohol consumption (Yoo *et al.*, 2020). Furthermore, gastric ulcer cause damage in the tissue lining of the stomach and in some cases it can linked with complications such as in perforation, penetration, bleeding (hemorrhage) and obstruction (Chan and Leung, 2002). Among these contributing factors, NSAIDs lead to chronic gastric ulcer through the production of reactive oxygen species (Bandyopadhyay *et al.*, 2002). In Egypt, milk and their products have been widely used in the management of gastric ulcers (Althnaian *et al.*, 2013; Soliman and Shehata, 2019).

Camel milk is considered one of the foods with high nutritional value. It contains high levels of volatile acids and polyunsaturated acids (Solanki and Hati, 2018). It also contains high concentrations of vitamins C, B, B2, E and potassium, magnesium, iron, and zinc (Shori *et al.*, 2012). Camel milk is an easy-to-digest ingredient that has a gentle effect on the gastrointestinal tract, as a result of its high content of whey protein to casein ration compared to other types of milk (Hajian *et al.*, 2020). There are medicinal values and experimental results indicate that camel milk has hepatoprotective (Althnaian *et al.*, 2013), Antiulcer (Hu *et al.*, 2017), antiallergic, antidiabetic and antimicrobial properties (El-Agamy, 2009; El-Salam and El-Shibiny, 2013; Tawfek *et al.*, 2021).

Plants and their extract were widely used for the treatment of gastric ulcers before the discovery of antiulcer drugs (Rozza *et al.*, 2014). However, most populations prefer the use of herbal medicine especially in developing countries because of its safety, cheap and being accepted by different cultures (Kumar, 2011). Thus many plants and their extracts have been screened for their anti-ulcer effects due to the presence of many important bioactive compounds which are responsible of its activity (Patel and Jain, 2010). One of these plants is carica papaya, the fruit and their extracts are widely used in the treatment of gastric ulcerations (Oloyede *et al.*, 2015; Kaur and Sen, 2017). Papaya (*carica papaya L.*) is considered to be one of the world's healthiest fruits, because of its nutrients, such as

vitamin A, dietary fiber, magnesium, potassium, vitamin C, and a reasonable level of calories (Farina *et al.*, 2020). Papaya fruit contains high levels of bioactive compounds such as isothiocyanate, lycopene, alkaloids, flavonoids, phenolic and some proteolytic enzymes like chymopapain and papain (Jaime *et al.*, 2007).

Currently, probiotics are increasingly used as food supplements and in functional milk beverage that enhance digestion and the absorption of nutrients (Yirga, 2015), so maintain healthy gut micro flora and may provide protection against gastrointestinal disorders (Nomato, 2005; Parvez *et al.*, 2006). . It has been reported that the juices and extracts of fruit could use as perfect media for producing probiotic bacteria (Mattila-Sandholm *et al.*, 2002) Therefore, the present study aimed to investigate the potential effect of probiotic camel milk enriched with papaya oil or extract against indomethacin-induced gastric ulcer in rats.

Material and Methods

Plant collection:

Unripe fruits of papaya and their oil were purchased from the Agriculture Research Center, Giza, Egypt.

Preparation of plant extract:

The fruit was washed with water, crushed and dried in air oven at 50 °C then grinded in blender to powder carica papaya. To prepare the methanol extract, 100 gram of carica Papaya powder was added to 1000 ml of 70% methanol (v/v) at room temperature for 20 hours with slowly rotated during this time. After filtration, methanol was evaporated at low pressure at 30 centigrade degree (WHO, 1983).

Camel's milk source:

Fresh Camel's milk was obtained from a private farm in El-Arish, North Sinai Governorate. Milk was collected early in the morning from healthy herd of camels (4 years old) by hand milking and kept in sterile screw bottles and kept under cooling conditions and stored at $5\pm 1^{\circ}\text{C}$ until required. The gross composition of raw camel's milk was: $11.48 \pm 0.21\%$ total solids, $3.31 \pm 0.02\%$ total protein, $3.35 \pm 0.05\%$ fat, $4.25 \pm 0.19\%$ lactose, $0.78 \pm 0.04\%$ ash, $0.18 \pm 0.01\%$, titratable acidity and 6.7 ± 0.02 pH (S=oliman and Shehata, 2019).

Microbial cultures:

Two commercial lyophilized DVS mixed bacterial starters, namely: Yo-Fast1 containing *Lactobacillus* (Lb.) *delbrueckii* ssp. *bulgaricus* and *Streptococcus thermophilus* as a starter, and ABT-5 containing *Bifidobacterium* (B). *Lactis* and *Bifidobacterium cultures* as probiotic, were supplied by the Chr-Hansen company (Horsholm, Denmark). Freeze-dried bacterial starters were activated separately in sterilized (121°C/10 min). The activated cultures were used for inoculation of camel's milk. The cultures were incubated at 42°C for Yo-Fast first starter and 39°C for ABT-5 starter, until curdling of milk.

Preparation of probiotic camels' milk with papaya extract or oil:

Papaya extract or oil were added to camels' milk at a ratio (1:1) and manually blended. The camel milk with a ratios papaya extract or oil were homogenized at 55°C -60°C for 2 min using high speed mixer (30,000 rpm/min⁻¹) (X 520, UAC 30-R, Chicago II 6064). The different treatments were dispensed into bottles and cooled and stored at 5°C ± 1°C for further using.

Chemicals and Reagents:

Indomethacin (Indocin) [®] was obtained from Misr Company for Medical Products Indomethacin Caps 25mg. All other reagents used in the study were freshly prepared and other chemicals used were of the high analytical grade

Animals:

Thirty five male albino rats of Sprague Dawley strain (from Laboratory Animal Colonies, Helwan, Egypt) weighting 120 -150g were used in the current study. The animals were housed under standard condition, 12:12 light-dark cycle, 50% humidity, and 28°C temperature and all rats were supplies with food and water ad libitum, the standard diet was performed according to (NRC, 1995).

HPLC analysis of phenolic compounds:

HPLC analysis of extracts was performed using an Agilent 1200 chromatograph equipped with a PDA model G1315B, a Bin pump model G1312A, an autosampler model G1313A and a RR Zorbax Eclipse Plus C18 column (1.8 µm, 150 mm×4.6 mm). The mobile phase A was 0.2 % formic acid in water and the mobile phase B was acetonitrile. Elution was performed at 0.95 mL min⁻¹ with the following gradient program of solvent B: 0–20 min, 5–16 %; 20–28 min, 16–40 %; 28–32 min, 40–70 %;

32–36 min, 70–99 %; 36–45 min, 99 % and 45–46, min. 99–5 %.³⁰ The injection volume was 10 µL. Wavelengths of 280 nm (for flavan-3-ols and benzoic acid derivatives) and 360 nm (for flavonols and cinnamic acid derivatives) were selected for detection according to (Merfore *et al.*, 1997).

Gas Chromatography- Mass Spectrometry (GC–MS):

The fatty acid profile of ethanolic extract of papaya oil was determined by gas chromatography as described by (Aldai and Osoro, 2006)

Ulcer induction:

Gastric ulceration was induced in the animals according to the procedure described by Sayanti *et al.*, (2007). Briefly, rats (30) were administered with a single oral dose of indomethacin (30 mg/kg body weight). They were deprived of food but had free access to water 24 h prior to ulcer induction. Various degrees of ulceration have manifested 4 h after indomethacin administration.

Study design:

After five days of adaptation then rats were classified into seven groups (each contains on 5 rats) as follows:

Group (1): Normal control (NC) 0.9% saline only.

Group (2): Ulcerated control (UC) administered with a single oral dose of indomethacin (30 mg/kg)

Group (3): Indomethacin + Papaya oil (PO) 5 ml /kg BW.

Group (4): Indomethacin + Papaya extract (PE) 5 ml /kg BW.

Group (5): Indomethacin + Probiotic Camel Milk (PCM) 5 ml /kg BW

Group (6): Indomethacin + Mixture of PCM +PO in 1:1 (v/v) ratio/kg BW.

Group (7): Indomethacin + Mixture of PCM +PE in 1:1 (v/v) ratio/kg BW.

At the end of the experiment period (28 days), rats were sacrificed after overnight fasting under ether anesthesia.

Measurement the length of gastric ulcer:

At the last day of experimental period, all rats were fasted for 12-14hrs and only allowed for drinking water. In the morning of the next day, all rats were sacrificed, and their stomachs were tied around both openings (cardiac & pyloric sphincters) and injected by distilled water (3 ml). The gastric juice was then collected in sterilized tube. The stomachs were opened longitudinally, washed with saline and examined under dissecting microscope for ulcer. The length of gastric ulcer was measured and expressed for each group. The curative ratio was then calculated for each

treated group according to the method described by Akhtar and Ahmed, (1995) by using the following equation:

$$\text{Curative ratio (CR)} = (\text{LC} - \text{LT}) / \text{LC} \times 100.$$

Where: LC = length of ulcer in control ulcer group and LT = length of ulcer in treated group.

Determination of volume and PH of gastric juice:

The PH of centrifuged sample of gastric juice was determined using a pH meter. The volume of gastric juice was measured by graduated cylinder and expressed as ml. The gastric juice decrease percentage was calculated each treated group according to the method described by **Parmar and Desai, (1993)** by using the following equation: Decrease ratio (DR) = (VC - VT) / VC x 100.

Where: VC = volume of gastric juice in control ulcer group and VT = volume of gastric juice in treated group.

Preparation of stomach homogenate and assay of antioxidant indices:

Immediately after ulcer scoring, whole stomach tissues were ground with liquid nitrogen in a mortar. The ground tissues (0.5 g each) were then homogenized in ice cold 0.1 M phosphate saline buffer (1:4 (w/v), pH 7.4) and the homogenates centrifuged at 2500 rpm for 10 min at 4 °C. The resulting supernatants were frozen at -20 °C to ensure maximum release of the enzymes located in the tissue before being used for the enzyme assay. Glutathione peroxidase (GSP), activity of superoxide dismutase (SOD) and level of lipid peroxidation measured as malondialdehyde (MDA) were respectively assayed in the stomach homogenate according to **Vankampen and Ziglstra, (1961)**, **Tapple, (1978)**, **Winterbourn et al., (1975)** and **Yagi, (1987)** respectively.

Measurement of gastric mucosa indices:

Gastric mucosal of cytochrome P450 reductase (Cyto P₄₅₀) activity, cyclooxygenase (Cox-₂) activity, prostaglandin E₂ (PGE₂) and Nitric oxide (NO) levels were determined according to **Mc-Lean and Day, (1974)**, **Hemler and Lands, (1976)**, and **Hamberg and Samuelsson, (1973)** respectively.

Statistical analysis:

The obtained data were statistically analyzed using computerized SPSS (Statistic Program Sigma stat, Statistical Soft-Ware, SAS Institute, Cary, NC). Effects of different treatments were analyzed by one way ANOVA (Analysis of Variance) test using Duncan's multiple range test and p<0.05

was used to indicate significance between different groups (**Snedecor and Cochran, 1967**).

Results and Discussion

The results of phenolic compounds screening of carica papaya methanol extract revealed the presence of ferulic acid (234.14 mg/100g), *p*-coumaric acid (22.54 mg/100g), β -criptoxanthin (12.01 mg/100g), caffeic acid (1.624 mg/100g), β -carotene (1.28 mg/100g) and Lycopene (2.41 mg/100g) (Table 1). **Kaur and Sen, (2017)** reported that papaya fruit plenty with bioactive compounds and these compounds considered as well-known properties which include inhibition of hydrolytic enzymes, free-radical scavenging and anti-inflammatory action.

Table.1. The content of phenolic compounds in unripe carica papaya fruit extract.

phenolic compound	Min standard retention (RT) Min.	Mass (mg/100g)
ferulic acid	3.2	234.14
<i>p</i> -coumaric acid	3.9	22.540
caffeic acid	4.0	1.624
β -criptoxanthin	4.7	12.01
β -carotene	5.2	1.28
Lycopene	6.1	2.41

The results of fatty acids profile of papaya oil extract (Table 1), revealed the presence of palmitic acid (34.10%), stearic acid (6.50%), myristic acid (1.20 %), Arachidic acid (0.90%), with a total percentage of saturated fatty acids reached to 42.70%. Meanwhile, the unsaturated fatty acids content reach to 57.30% which showed as oleic acid (44.20%), linoleic acid (12.10%), palmitoleic acid (0.60%) and eicosanoid acid (0.40%). These results at agreement with (**Sinaga et al., 2020**) reported that the unsaturated fatty acids are higher than saturated fatty acids in papaya (Table 1).

Table 2. The fatty acids profile of *Carica papaya* oil.

Fatty acids	component	Composition (%)
Saturated	Palmitic Acid (C16:0)	34.10
	Stearic acid (C18:0)	6.50
	Arachidic acid (C20:0)	0.90
	Myristic acid (C14:0)	1.20
Total		42.70
Unsaturated	Linoleic acid (C18:2)	12.10
	Palmitoleic acid (C16:1)	0.60
	Oleic acid (C18:1)	44.20
	Eicosanoid acid (C20:1)	0.40
Total		57.30

Table 3 depicts that gastric ulcer length was significantly reduced by administration of probiotic milk (PCM) and when combined with papaya extract or oil compared with ulcer group (UC). The highest reduction in the ulcer length which associated with the increase in the CR% were obtained by using PCM+PO followed by PCM+PE and PCM were (3.89 ± 0.18 mm and 52.62 ± 5.16 % ; 4.05 ± 1.50 mm and 50.69 ± 6.64 % ; 4.28 ± 0.46 mm and 47.86 ± 5.47 % and; 5.77 ± 0.83 mm and 29.84 ± 6.89 %, respectively). However, there were insignificant differences in the ulcer length and CR% between PCM+PO and PCM+PE groups.

Indomethacin produced ulcerative lesions in rats with a gastric ulcer length (8.21 ± 1.98 mm) in ulcerated group that was associated with significant increase in volume of gastric juice. Meanwhile, all treated groups showed significant reduction in the gastric ulcer length and the volume of gastric juice comparing with the ulcerated group (UC). Although none of the treated groups has reached the values of gastric volume juice of the normal control group (NC), the highest reduction in the ulcer length as well as the volume of gastric juice were obtained by using probiotic camel milk enriched with papaya oil (PCM+PO), followed by mixture of (PCM plus PE) , PCM, PO and PE groups. Moreover, treatment with mixture of (PCM plus PO) resulted in higher CR% and DR% than probiotic camel milk or each of them that used alone. These results in agreement with (Abubakar et al., 2018) demonstrated the potential use of camel milk in reversing the damaging effect of ethanol-

induced gastric ulcer. In addition, **Panzarini et al., (2014)** reported that papaya seed has antiulcer and antioxidant activities.

Table 3: Effect of probiotic milk enriched with papaya oil or extract on the length of gastric ulcer and the volume of gastric juice in rats.

Groups	Gastric ulcer length (mm.)	Curative ratio (%)	Volume of gastric juice (1ml)	Decrease Ratio (%)
NC	0.00±0.00	-	2.84±0.08 ^e	-
UC	8.21±1.98 ^a	-	8.05±0.16 ^a	-
PE	5.89±0.22 ^b	28.26±4.22 ^c	5.88±0.18 ^b	26.96±1.22 ^d
PO	5.77±0.83 ^b	29.84±6.89 ^c	5.39±0.25 ^b	33.05±2.38 ^d
PCM	4.28±0.46 ^c	47.86±5.47 ^b	3.85±0.14 ^c	52.18±1.92 ^c
PCM+PE	4.05±1.50 ^{cd}	50.69±6.64 ^{ab}	3.34±0.10 ^c	58.51 ±1.88 ^b
PCM+PO	3.89±0.18 ^d	52.62±5.16 ^a	3.08±0.16 ^d	61.74±1.09 ^a

Note: Different letters between treatments denote significant differences ($p < 0.05$). NC: Normal control, UC: Ulcer control, PE: Papaya Extract, PO: Papaya oil, PCM: Probiotic Camel Milk.

Gastric juice pH value (Figure.1) of ulcerated group (UC) showed significant difference compared to normal control group (2.01 ± 0.41 vs 6.62 ± 0.53 mEq/L), on the other hand the differences between all probiotic camel milk treated groups as compared to each other's was found to be non-significant. NSAIDs was damaged the gastric mucosa by non-selective inhibition of both cyclooxygenase 1 and 2 enzymes which were mainly responsible for the synthesis of prostaglandins. NSAIDs also damage gastric epithelial linings by enhancing the leukocyte infiltration (**Fernanda et al., 2007** and **Yoo et al., 2020**). Generally, necrotizing agents may produce gastric lesion by a combination of many factors which includes but not limited to the following; inhibition of prostaglandins (PGE2) synthesis (**Deshpande et al., 2003**), promotion of acid-pepsin aggression on gastric mucosal, decrease in gastric mucosal barrier/resistance, an increase in gastric acid secretion (**Nafeeza et al., 2002**). Furthermore, these results in the same parallel with (**Oloyede et al., 2015**; **Hu et al., 2017**) as demonstrated that papaya seed and camel milk can be used in ulcer status.

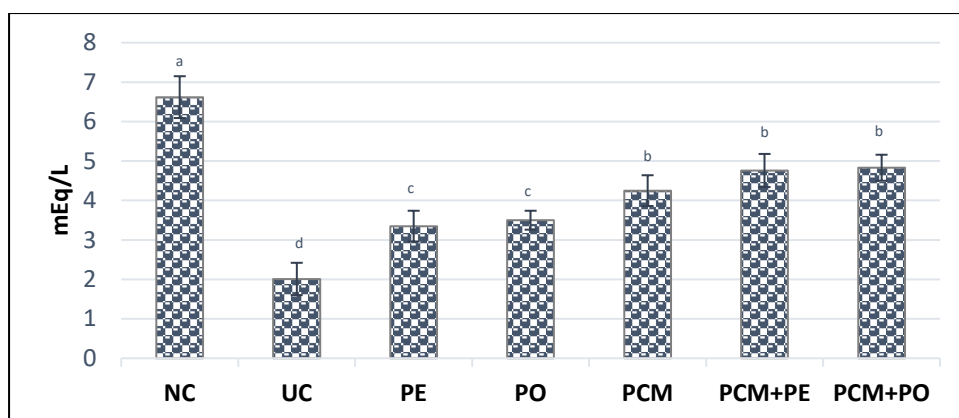


Figure 1. Changes on gastric juice PH values in rats. Different letters between treatments denote significant differences ($p < 0.05$). NC: Normal control, UC: Ulcer control, PE: Papaya Extract, PO: Papaya oil, PCM: Probiotic Camel Milk.

The results (Figure.2) revealed that probiotic camel milk with the addition of papaya oil or their extract causes significant reduction in the level of Cox-2 and significant increase level of Cyto P450 reductase as compared to the Control ulcerated group. Moreover, Cyto P450 reductase level was found to reach the value of the normal group (NC) in treated with probiotic camel milk plus papaya oil (PCM+PO). Insignificant differences were obvious in the levels of Cox-2 and Cyto P45 between (PCM plus PO), and (PCM plus) treated groups. Cytochrome P450 enzymes, consider as enzyme that play a vital role in the metabolism of many drugs. The reduction level of Cyto P450 reductase observed in this study in the control ulcerated group may be related to the higher level of NO produced by iNOS which plays important roles in the suppression of Cyto P450 through modification of their heme moiety and/ or their cysteinyl residues (Takemura *et al.*, 1999). COX-2, the inducible isoenzyme of COX is induced in the presence of gastrointestinal mucosal inflammation. Although it has been reported that COX-2 derived prostaglandins are involved in gastric ulcer repair (Schmassmann *et al.*, 2006), they also contribute to perpetuation of gastrointestinal inflammation (Fiocchi, 1998). In the present study, Indomethacin caused increased level of gastric COX-2. This is consistent with many previous studies which reported that NSAIDs can rapidly up-regulated COX-2 expression in the stomach (D'Argenio *et al.*, 2008). The reduction occurred the papaya addition to

probiotic camel milk associated with its cyclooxygenase inhibition (**Berté et al. 2014**).

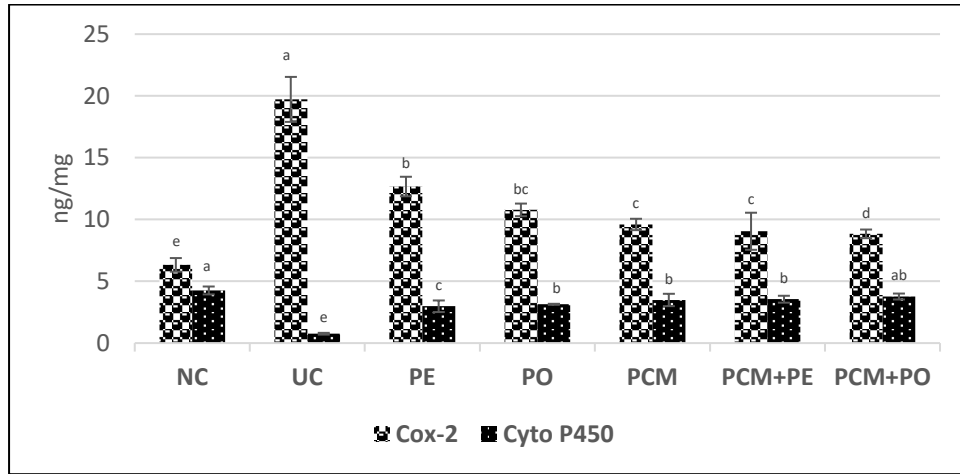


Figure 2. Changes on gastric tissues cytochrome P450 reductase, and cyclooxygenase activities in rats. . Different letters between treatments denote significant differences ($p < 0.05$). Cyto P₄₅₀: cytochrome P₄₅₀ reductase, COX2: cyclooxygenase. NC: Normal control, UC: Ulcer control, PE: Papaya Extract, PO: Papaya oil, PCM: Probiotic Camel Milk.

Results illustrated in Figure. 3 revealed that indomethacin induction causes significant reduction in the level of PGE2 and significant increase of NO level as compared to control ulcerated group. There were insignificant differences in PGE2 level between all probiotic camel milk treated groups. All probiotic treated groups showed significant reduction in NO and increase PGE2 as compared to UC group. There is no significant difference between probiotic camel milk enriched with papaya oil group and normal control group in NO level. Nitric oxide (NO) plays an important role in the control of gastric blood flow as well as in the maintenance of gastric mucosal integrity (**Kwiecien et al., 2002**). Although NO is required for normal gastrointestinal function, there is also some evidence that a large excess of NO may have deleterious effects on the gastrointestinal tract (**Morin et al., 2001**). NO is activated in gastritis induced by NSAID-induced ulcerogenesis, *Helicobacter pylori* infection and inflammatory bowel diseases (**Martin et al., 2001**). In this study, increased nitric oxide (NO) level in the stomach tissue in the control ulcer group suggested that indomethacin-induced gastric ulcer may be caused

high NO production. This finding was in parallel with an earlier study (**Kontureck *et al.*, 2006**). In addition, NSAIDs causes a decreasing on prostaglandins (PGE₂) synthesis (**Zeeyauddin *et al.*, 2011**). The possible mechanisms of improvement here linked with papaya prevention of prostaglandin synthesis through cyclooxygenase inhibition (**Berté *et al.*, 2014**). In addition, a study by **Hu *et al.*, (2017)** found that administration camel milk caused an improvement in damaged tissues ulcer rats.

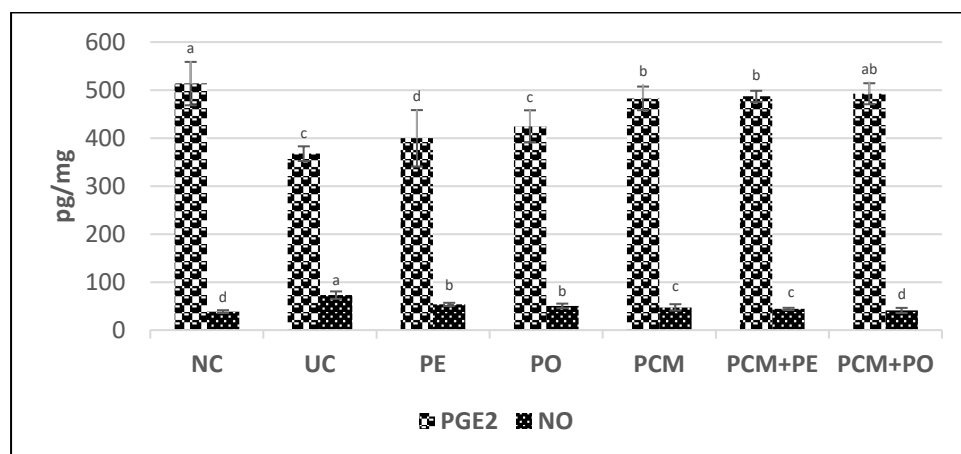


Figure.3. Changes on gastric tissues prostaglandin E₂ (PGE₂) and Nitric acid (NO) concentration in rats. Different letters between treatments denote significant differences ($p < 0.05$). NC: Normal control, UC: Ulcer control, PE: Papaya Extract, PO: Papaya oil, PCM: Probiotic Camel Milk.

The results (Figure. 4) revealed that the SOD and GSP levels significantly increased while MDA level was significantly reduced in all treated probiotic camel milk groups comparing with the control ulcerated group. In addition SOD and MDA levels in all treated groups have reached values slightly similar to the normal group (NC). Insignificant differences were showed in SOD and MDA levels between all treated groups as compared to each other except The GSP levels in probiotic milk enriched with papaya oil or extract (PCM+PO and PCM+PE) groups were increased which their values have nearly similar to the normal group. Oxidative stress has been implicated in the development and pathogenesis of indomethacin-induced gastric injury (**Utsumi *et al.*, 2006** and **Orsi *et al.*, 2014**). NSAIDs such as indomethacin have been reported to decrease the activities of antioxidant enzymes (SOD & GSP) in the stomach and duodenum, thereby

causing gastric ulceration (Halici *et al.*, 2005). The decrease in the activities of these enzymes may be lead to an imbalance in the antioxidant status resulting in the generation of free and oxygen-derived radicals (Ajiboye *et al.*, 2010). The augmentation of the activity of these antioxidant enzymes by consumption of probiotic camel milk enriched with papaya oil or extract may be representing an important mechanism of protection against peroxides, superoxide an ion radicals and hydroxyl radicals (Hu *et al.*, 2017; Kaur and Sen, 2017)

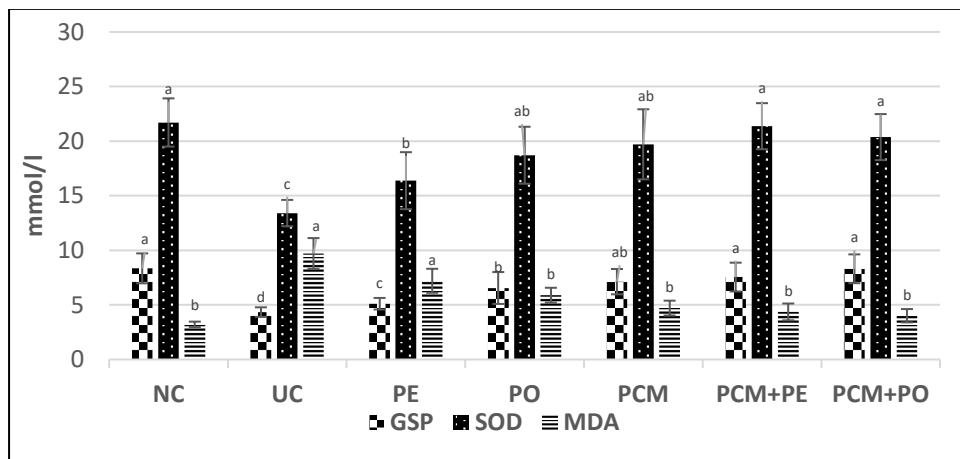


Figure.4. Changes on antioxidant indices in rats. . Different letters between treatments denote significant differences ($p < 0.05$). GSP: Glutathione-peroxidase, SOD: Superoxide dismutase, MDA: Malondialdehyde NC: Normal control, UC: Ulcer control, PE: Papaya Extract, PO: Papaya oil, PCM: Probiotic Camel Milk.

Conclusion

The overall finding of this study demonstrates anti-ulcerogenic and antioxidant effects of probiotic camel milk enriched with papaya oil or extract on indomethacin-induced peptic ulcer in rats as protected the gastric mucosa as shown by significant reduction in gastric juice volume, gastric PH and ulcer length vs control ulcerated suggesting its potent gastro-protective effect on indomethacin- induced gastric ulcer in rats. Also, adding papaya oil or extract to probiotic milk significantly increase the levels of PGE2, Cyto P450 reductase, SOD and GSP while decreasing the levels of Cox-2, NO and MDA vs ulcerated control group thus preventing oxidative damage of the gut mucosa. Therefore, probiotic milk with enrichment of papaya oil or extract can be considered as a promising

material for treatment of gastric mucosal injury and further studies on this fruit are encouraged for deep mechanism.

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