Pomegranate Juice Attenuates Anti-Ulcer in Indomethacin-Induced Peptic Ulcer

Ali Omar Yaseen [1], Payam Jamal Muhamed [1], Hacer Haltas [1], Subasini Uthirapathy [1*]

Abstract

Introduction: *Pomegranate* (*Punica granatum L.*) is a well-known fruit that grows in tropical and subtropical areas. In this study, we wanted to find out how pomegranate juice (POMJ) affected rats with gastric ulcers caused by standard drugs. Indomethacin is the most common drug causes gastric ulcer also, most of the NSAID drugs have harmful side effects, so studies have focused on finding an alternative natural solution. **Methods:** In this study, 25 male albino rats were split into four groups of five rats each. These groups were called control, pomegranate, indomethacin, and standard. The examination took one week to complete. Indomethacin saline suspension (100 mg/kg rat weight) caused gastric ulcers. Pomegranate peel juice (5-10%) reduced stomach ulcer area and ulcer index, gastric juice volume, and acidity. Pomegranate juice restores stomach mucus content and tissue at the histological level. **Results:** Rats given indomethacin and pomegranate juice were significantly less likely to get a gastric ulcer. It also lowered the ulcer index to 0.7093±0.36 showing that 52.25 % prevention. **Conclusion:** The study's macroscopical and microscopical results showed that pomegranate juice might reduce the ulceration caused by indomethacin in a rat model. Pomegranate as a protective food supplement against gastric ulcers.

Keywords: *Punica granatum,* Indomethacin, gastric ulcer, Antioxidant, Pomegranate

Significance | Study on using pomegranate juice supplements to treat ulcers caused by pain medications.

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Introduction

When the mucosal epithelium of the stomach or duodenum is exposed to acid and pepsin, it wears away. This is called a peptic ulcer. The number of people who get gastric ulcers goes up when they smoke, are stressed, don't eat enough, or take nonsteroidal anti-inflammatory drugs (Belaiche *et al.,* 2002). NSAIDs reduce mucosal blood flow, mucus bicarbonate secretions, platelet aggregation, epithelial cell renewal, and leukocyte adhesion, all of which contribute to the development of ulcers. Indomethacin is a NSAIDs drug that is made from the chemical indol. It works by reducing inflammation, relieving pain, and lowering fever. Because it can cause ulcers better than other NSAIDs, indomethacin was chosen as the first drug to use in an experimental ulcer model (Allen *et al.*, 1993; Suleyman *et al.,* 2010).

The current medical treatment for a peptic ulcer is mostly based on H2-antagonists, like omeprazole and antimuscarinics, which stop the stomach from making acid, and acid-independent therapies, like sucralfate and bismuth, which don't depend on stomach acid (Bighetti *et al.,* 2005). The most important problem with ulcer treatment is that between 40 and 80% of ulcers come back within a year after treatment stops (Miller and Faragher 1989). In addition to a number of side effects, such as hepatotoxicity and anaphylaxis, these products have a lot more to

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offer (Kohn *et al.*, 2012). From this point of view, several natural products, such as apple bananas, papeeta, and brindle berry, have been said to have antiulcerogenic activity because of their effects on mucosal defensive factors (Umashanker and Shruti 2011).

Inedible pomegranate peel has therapeutic properties. Pomegranate peel is known for its wound healing, immunological modulatory, antibacterial, anti-atherosclerotic, and anti-oxidative capabilities. The seeds and juice treat throat, eye, gum, and skin issues, cancer, cardiovascular disease, diabetes, baby brain ischemia, and male infertility (Satheesh et al., 2012). Phytochemical screening of extracts indicates phenols, glycosides, flavonoids, terpenoids, carbohydrates, proteins, and amino acids. Pharmaceutical qualities of phytochemicals are vital to human health. These substances can be used as medications or supplements to treat or prevent ailments (Karthikeyan and Vidya, 2019; Yasoubi et al., 2007)

Pomegranate (*Punica granatum* L.) in the family *Lythraceae* is a well-known fruit that grows in tropical and subtropical areas. But most authorities put it in the family Punicaceae because it is the only genus in that family (Bhandari, 2012). Pomegranate (PG) has been studied in many ways, including in vitro, in vivo, and clinical studies. Most of the good effects have to do with protecting the heart and brain, lowering blood sugar, and fighting cancer, especially prostate, colon, and breast cancer. The anticancer effect has only been seen in in vitro and animal studies (Johanningsmeier and Harris 2011). This study aimed to find out how pomegranate affects rats with gastric ulcers caused by indomethacin. Pomegranate has powerful efficacy of antiulcer properties.

Materials and Methods

Materials

Indomethacin was bought at a local pharmacy, and the *P. granatum* Linn. Peel was bought at the Erbil market. Rats were given 0.35 mg/kg body weight orally once after fasting for 24 hours. Omeprazole is a standard drug for peptic ulcer. They were bought at a local pharmacy and mixed with saline water. The doses of omeprazole and Indomethacin were 20 mg/kg body weight and 100 mg/kg body weight, respectively.

Preparation of plant extract

The POMJ was made by crushing, squeezing, and treating pomegranate fruit (POMJ) with the enzyme pectinase. This produced the inner and outer peels and the seeds as byproducts. The juice was strained and put in a freezer at -18 C (Aviram *et al.*, 2010).

Methods

Experimental animal

This study was done on 25 adult male albino rats that were bought from the Department of Pharmacology at Animal House (250-280 g). The animals were kept in a controlled environment (with a temperature of 22 2°C) for 24 hours. The rats were kept in normal conditions. They had free access to water from the tap and ate normal pellets. Rats lived in these conditions for a week before the experiment started. The Ethical Committee for the College of Medicine at Hawler Medical University in Erbil gave the go-ahead for the plan for testing on animals. After the animal's acclimatization period, they were put into five groups, each with five rats.

Experimental protocol

Twenty-five male albino rats were split into five groups of five rats each as follows.

Group I: This group was used as a control and given with normal food and water.

The rats in Group II were given 100 mg/kg (1 ml) of Indomethacin (diseases group)

The rat s in Group III were given omeprazole at a dose of 20 mg/kg (1 ml/rat) (standard group)

The rats in Group IV were given 50 mg/kg (3 ml/rat) of pomegranate juice (POMJ) (low dose)

The rat in Group V were given 100 mg/kg (5 ml/rat) of pomegranate juice (POMJ) (high dose)

Indomethacin was given to groups II rats by mouth to make them get ulcers (induction). Before the experiment, the rats went fasting for 8 hours. All of the drug solutions were given 8 hours after Indomethacin, and the tested POMJ juices were given with food and lasted for 5 days. At the end of the experiment, the animals fasted for 24 hours before their blood was taken. The blood was taken through the retroorbital route using capillary tubes and put into clean tubes.

Evaluation of Mucosal Lesions of the Stomach

Rats were given 100 mg/kg of body weight of indomethacin once, five hours before they were sacrificed (Russell, 2001). This caused them to get acute gastric ulcers. The transparency graph sheet marked the area of a bleeding ulcer and a small hole in the glandular part of the stomach. After that, the stomachs were put in a 10% formalin solution with a buffer to keep them still so that histopathologists could study them.

The formula was used to figure out the ulcer index (UI),

Ulcer Index = 10 / X

Where, X = total mucosal area of glandular part of stomach / total ulcerated area

The protective index (PI) of a drug was calculated from the following equation:

$$PI = \frac{[\text{UI of diseased group}] - [\text{UI of POMJ treated group}]}{[\text{UI of diseased group}]} \times 100$$

Analysis of the stomach's tissues and lesions at a macroscopic level

Each stomach was cut along its larger curve, and linear hemorrhagic lesions in the glandular area were looked for. The level of damage to the gastric mucosa was measured by the ulcer index (UI) (Abdallah, et al., 2011; Nassar, et al., 2013), which is based on a lesion index that is calculated by giving each lesion a score from 0 to 5 based on how severity it is. The length of the lesions was used to figure out the severity factor. Severity factor: 0 = no lesions, 1 = small red spots, 2 = erosions less than 1 mm, 3 = erosions between 1 and 2 mm, 4 = erosions between 2 and 4 mm, and 5 = erosions larger than 4 mm.

Gross pathology study

The stomachs were taken out and cut open along the larger curve. Then, they were washed with ice-cold phosphate-buffered saline (PBS) and scored for gross mucosal lesions that could be seen with the naked eye. The lesions observed in the rats during the post-mortem examination of stomachs are given in Table 3.

Histopathology

Histopathological tests were done on the treated and untreated parts of the stomach. Both the control group and the treated group of animals were looked at from a histopathological point of view. Figures 1 and 2 show the results of observing those groups of animals for 7 days after giving them POMJ juice at the highest dose of 100 mg/kg. Stomach mucosa sections were stained using the hematoxylin and eosin (H&E) staining method (x40).

Statistical analysis

All of the results were shown as mean ± standard error, and a one-way ANOVA in SPSS was used to compare the experimental groups (Version 2.1). At the level of $P<0.05$, a difference was significant value.

Results and Discussion

The polyphenols found most often in PG juice are ellagitannins and anthocyanins (Heber, 2011). This part of the fruit has ellagitannins like punicalagins and other minor tannins like gallagic acid and punicalin (Gil, et al., 2000). Gastric mucosa protection requires COX-1 prostaglandins, especially PGI2 and PGE2. NSAIDs increase ulcer risk by inhibiting endogenous prostaglandin synthesis, but indomethacin also alters stomach secretion and barrier permeability (Fiorucci, et al., 2001). Omeprazole reduced ulcer area and thickness by 30% compared to the control group.

In this study, stomach ulcer activity was significantly lower in the peptic ulcer group than in the control group, which shows that indomethacin caused an increase in oxidative stress (Table 1) So, it is known that indomethacin causes reactive oxygen metabolites in animal models, which may cause damage to the mucosa. These free radicals also damage the antioxidant enzymes in cells, which are the first line of defense against oxidative stress. This could worsen tissue damage in a stomach ulcer (Alam, et al., 2010). Indomethacin interferes with the protective functions of the stomach, such as the production of mucus and bicarbonate, the ability of the surface epithelium to repel water, and blood flow to the mucosa. By stopping cyclooxygenase (COX), acetylsalicylic acid mostly stops the body from making cytoprotective prostaglandins. This causes the body to make too many leukotrienes and other products of the 5-lipoxygenase pathway. The PG methanol peel extract demonstrated significant anti-H. pylori activity in vitro, as evidenced by the inhibition zone size in the disk diffusion method, which was similar in size to that of metronidazole, the reference chemical mentioned by (Saniee, et al., 2009). In rats with ethanol-induced gastritis, PG fruit rind methanolic extract significantly decreased the ulcer index (UI), according to an in vivo investigation (Ajaikumar, et al., 2005). His result was the same as what we found.

Pathological results in this study confirmed the pharmacological parameters. So, no lesions were found when the stomachs of the control and pomegranate juice-given animals were looked at in a general way. However, almost all of the indomethacin given animals had lesions, such as petechiae and erosions in the gastric mucosa (Fiorucci, et al., 2001). On the other hand, very mild lesions were seen in pomegranate juice that had been treated with indomethacin first (Table 1). Compared to the control group, the ulcer index was very high (1.4853±0.66)) after Indomethacin was given. Rats that were given indomethacin and then given pomegranate juice before the experiment were significantly less likely to get a stomach ulcer. The ulcer index went down to 0.7093±0.36, 52.25 % of reduction displayed in Table 1. The mechanism of action by which POMJ shows antiulcer activity is partially attributed to the inhibitory effect on the gastric H+, K+-ATPase, and the healing of the ulcers (Rao, et al., 2008).

Normal Control (Group I) No gross pathological changes were evident in the gastric mucosa of the rats of this group. **Diseased control (Group II)** Marked bleeding ulcers in the glandular part of stomach, mild to moderate petechiation and diffuse congestion of moderate intensity were existed in four out of five animals sacrificed. A total of 32 bleeding ulcers (Table 3) of different grades were evident as haemorrhagic streaks covering 12.38 % of the total area of the glandular stomach (Table 2). A total of 8 petechiations were observed along with mild to moderate congestion of the gastric mucosa (Table 4). **Group III – Standard drug:** Post–mortem examination of the rats' stomach of this group revealed a total of 20 bleeding ulcers (Table 3) covering 10.40 % of the total area of glandular stomach (Table 2). A total of 9 petechiations (Table 4). **Low dose (Group IV)** In this group, a total of 25 ulcers (Table 3) covering 6.43 % of the total area of the glandular stomach (Table 2). A total of 13 petechiations (Table 4)

Table 1. Effect of Pomegranate Juice (POMJ) on ulcer index and protective index

Group	Treatment	Ulcer index (mean ± SEM)	Protective index
I	Normal control	-	-
II	Disease control	1.4853±0.66	-
III	Standard drug (Omeprazole 20 mg/kg, i.p.)	1.0395±0.36	30.0141
IV	POMJ -Low dose (50 mg/ Kg, i.p.)	0.7717±0.27	48.0442
V	POMJ-High dose (100 mg/ Kg, i.p.)	0.7093±0.36	52.2453

Pomegranate Juice (POMJ)

Table 2. Effect of Pomegranate Juice (POMJ) on the area of ulcer formation

S. No.	Total ulcerated area in square millimeter				
	Normal Control	Disease control	Standard drug	POMJ- (50 mg/Kg, i.p.)	POMJ- (100 mg/Kg, i.p.)
1	0	40.41	15.97	0.00	0.87
2	0	10.05	0.13	5.74	9.83
3	0	14.03	17.20	6.87	20.19
4	0	0.00	3.05	3.43	0.00
5	0	5.56	4.69	4.27	4.45
6	0	4.22	21.34	18.28	0.13
Mean ± S.D	0	12.38±14.56	10.40 ± 8.82	6.43 ± 6.26	5.91 ± 7.94
% Decrease *			**15.99 %**	**48.06 %**	**52.26 %**

***%** Decrease as compared with diseased control, Pomegranate Juice (POMJ)

Table 3. Effect of POMJ on the numbers of Haemorrhagic ulcers formed

S. No.	Total numbers of Haemorrhagic ulcers observed				
	Normal Control	Disease control	Standard drug	POMJ-5 (50 mg/Kg, i.p.)	POMJ-5 (100 mg/Kg, i.p.)
1	0	4	2	0	1
2	0	8	0	6	7
3	0	8	5	3	8
4	0	0	2	5	0
5	0	4	4	3	6
6	0	8	7	8	1
Total No. of Ulcers	0	32	20	25	23
Mean ± S.D	0	5.33 ±3.27	3.33 ±2.50	4.17 ±2.79	3.83 ±3.54
% Decrease *			**37.52 %**	**21.76 %**	**28.14 %**

*% Decrease as compared with diseased control, Pomegranate Juice (POMJ)

Table 4. Summary of Gross Pathology

S. No.	Group	No. of Animals	Haemorrhagic Ulcer in Numbers	Petechiation (foci in Numbers)	Congestion
1	Control	5	NAD	NAD	NAD
2	Diseased control	5	4 (Massive diffuse haemorrhage- approx. 60 % involvement)	2 (Moderate)	Mild
3	Standard	5	2	4 (Moderate)	Mild
4	POMJ-Low dose	5	5	3 (Mild)	-
5	POMJ-High dose	5	6	1 (Moderate)	Mild

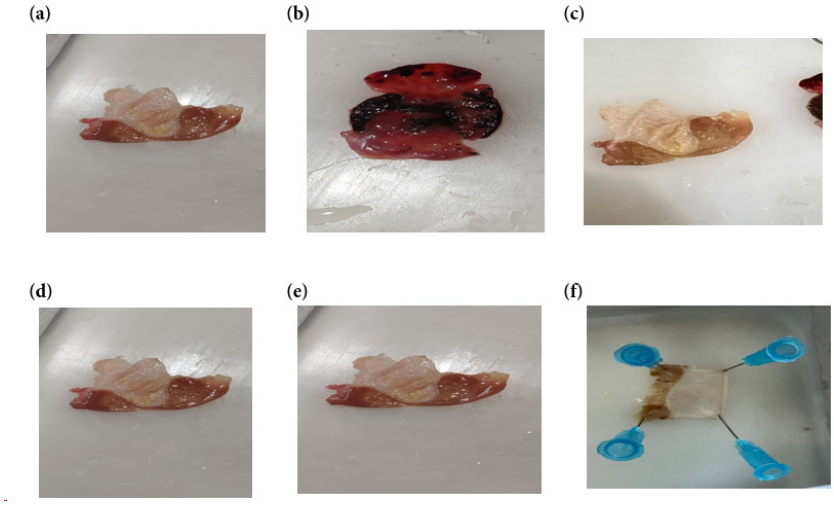

Figure 1. Macroscopic appearance of gastric mucosa in the (a)Control group, (b) Indomethacin treated group (IND), (c) Omeprazole group, (d) POMJ-low dose, and (e) POMJ-high dose group

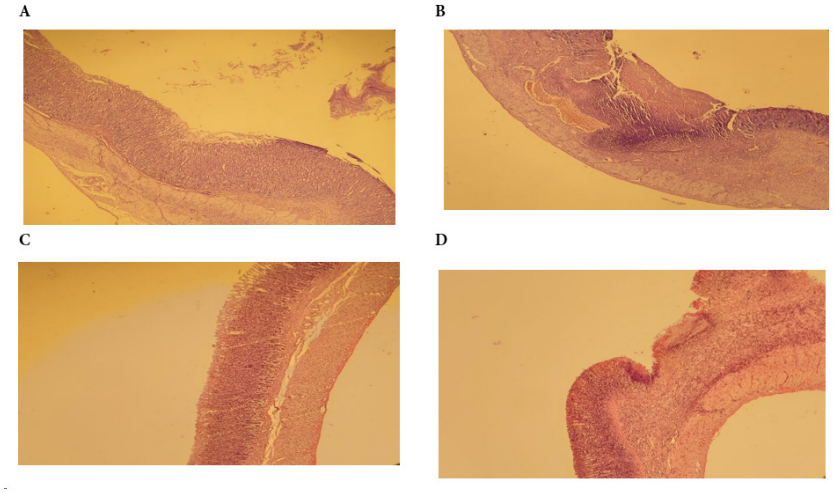

Figure 2. (A) shows normal stomach mucosa, while (B) displays stomach mucosa from rats induced with ulcers using indomethacin, at day 1 after the induction. Wide and severe ulceration, along with necrosis, is observed. (C) shows stomach mucosa from indomethacin-administered rats that were pretreated with PPI. In this group, only superficial erosion is seen. (D) displays stomach mucosa from another group of indomethacin-administered rats that were pretreated with pomegranate juice. Here, a single ulceration is visible.

were noticed in the gastric mucosa of the rats of this group. **High dose (Group V)** A total of 23 ulcers (Table 3) covering 5.91 % of the total area of the glandular stomach (Table 2) was observed in this high dose treated group. A total of 8 petechiations (Table 2 and 4) were observed in the gastric mucosa of the rats of this group. No significant pathological changes were observed in the non-glandular part of stomach of the rats of all the groups (Sabiu, et al., 2015).

The histopathological findings of the present investigation demonstrated that the introduction of Indomethacin into the gastric mucosal layer caused several modifications to glandular and surface mucous cells. Pyknosis and vacuolation were observed within the parietal cells of the isthmus region of the gastric mucosa layer during the study. The findings presented here are consistent with prior histology research documented by (Alazzouni, et al., 2020; Beck, et al., 2000). Control Group: No ulcers or erosions were found in the gastric mucosa of any of the rats in this group. Diseased control group: "V"-shaped loss of the epithelium of the gastric mucosa, which is a sign of ulcers, was seen in 4 of the 5 stomach sections that were checked. The lack of ulcers on diseased control animal No.4 was in line with the gross pathological observation. Standard drug group: Histologically, ulcers were found in 4 out of 5 stomach sections. The absence of ulcers in the stomach of the standard drug-treated animal No.2 was in line with the animal's outward appearance. Low dose group: In this group, the stomach section of low dose animal No. 1 had a few small holes, and the stomach sections of the other 5 low dose animals had ulcers. In the high dose group, ulcers were found in 4 out of 5 stomach sections that were checked. Animal No.4 that was given a high dose of the drug showed that there was no ulcer in the gastric mucosa.

The Ulcer index was found to be 0.7717±0.27 for the 50 mg/kg, i.p. POMJ group, 0.7093±0.36 for the 100 mg/kg, i.p. POMJ group, and 1.0395±0.36 for the 20 mg/kg, i.p. omeprazole group. 1.4853±0.66 is the ulcer index for disease control. The ulcer protective index was 48.05% for the 50 mg/Kg, i.p. POMJ group, 52.23 % for the 100 mg/kg, i.p. POMJ group, and 30.01% for the 20 mg/kg, i.p. omeprazole group. The ulcer area decreased by 15.99%, 48.06%, and 52.26 % in the standard drug group, the low dose group, and the high dose group, respectively. NSAIDs cause histological alterations in gastric tissue by blocking prostaglandin synthesis, resulting in higher acid levels (Adhikary, et al., 2011). These processes result in diminished cytoprotective mucus synthesis and, as a result, stomach ulcers. In this regard, it has been reported that indomethacin administration could lead to accumulation of lipid peroxidation in the gastric tissue, and hence could cause peptic-ulcer (Bialonska, et al., 2009). This means that the test drug protected about 50% of the ulcer area. The test drug was found to cause ulcers in more than three times the size of the area that the standard drug did it. The number of bleeding ulcers decreased by 37.52 %, 21.76 %, and 28.14 % in the 20 mg/kg, i.p. omeprazole group, 50 mg/kg, i.p. POMJ group, and 100 mg/Kg, i.p. POMJ group, respectively. The stomach appears to be a site of absorption for free ellagic acid, whereas ellagitannins are not. Pomegranate ellagitannins release ellagic acid in the stomach, which is weakly absorbed in the small intestine; nevertheless, ellagic acid is substantially converted into urolithins by human gut microbiota in the intestinal lumen (Cryer, and Mahaffe, 2014). Prostaglandins play an essential role in preserving the gastric mucosa against the NSAIDs drug's ulcerative effect by an increase in blood flow and production of mucus and bicarbonate (Talaa et al., 2004). The bicarbonate acts to decrease the acid in the gastric lumen (Lai, et al., 2009). In this regard, it has been previously reported using cyclooxygenase-2 as a marker for inflammatory processes on the surface epithelium and lamina propria of the gastric mucosa (Musumba, et al., 2009; Mahmoud, et al., 2019).

Conclusion

Various animal models show high antiulcer effect from entire fruit or juice, peel, and flowers in vivo. In animal models, the Juice's high ellagic acid and tannin content caused gastroprotective and ulcer-healing properties. In the end, the results of this study showed that taking pomegranate juice supplements is an important way to stop ulcers caused by NSAIDs. It also helps the liver and kidneys work better and reduces hepatotoxicity and nephrotoxicity due to its strong antioxidant activity. The above results show that pomegranate juice has about 50 % gastro-protection against indomethacin-induced ulcers in albino wistar rats at a dose of 100 mg/kg, i.p., while omeprazole at 20 mg/kg, i.p., only has 30% gastro-protection.

Author Contributions

S.U. prepared method, supervised, and performed the animal study and biochemical analysis,; H.H. prepared graphs, supervised and performed histology analysis; A.Y. wrote, revised and edited; P.J.M.A. conceptualized and performed software analysis. All authors participated in the study design, and data analysis, and manuscript review.

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Competing financial interests

The authors have no conflict of interest.

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