

A Hospital-Based Assessment of the Efficacy and Acceptability of Pomegranate Effervescent Granules (PEGs) in Dyspeptic Patients

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Abstract

Aim: This study aimed to assess the efficacy and acceptability of pomegranate effervescent granules (PEGs) in dyspeptic patients.

Material & Methods: This hospital-based study was conducted by the Department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India for nine months. The granules, prepared from peel extract of pomegranate, were made available in sachets of 2.5 g with dose of, 1 sachet dissolved in 200 ml (1 cup) of water, twice a day after meals for 28 days. Gastrointestinal Symptom Rating Scale (GSRs) scores to assess symptoms of acid peptic disorders at day 0, 15, and 29 along with the taste of formulation were the main study outcomes.

Results: The results showed that in the Punica granatum treatment group with a dose above 500 mg/kg, Ulcer Area (mm²) was 126.44±1.26 and Ulcer Inhibition % was 85.65. In the Punica granatum treatment group with a dose of 250 mg/ kg Ulcer Area (mm²) was 455.60±8.48 and Ulcer Inhibition % 42.83. In the omeprazole treatment group, Ulcer Area (mm²) was 620.20±11.49 and Ulcer Inhibition was 25.55. While in the control group Ulcer Area (mm²) was 822.00 ± 25.75 and Ulcer Inhibition % 15.75 And this Ulcer Inhibition % in the Punica granatum treatment groups was significant compared to the omeprazole treatment group and the control group (P=0.0001). The highest zone of inhibition (13 mm) was recorded against *Y. enterocolitica* and *S. enterica* compared with selected studied bacteria. The second highest zone of inhibition was 10.5 mm observed against *B. cereus*.

Conclusion: PEGs proved to be palatable, patient-friendly, safe, and efficacious in resolving symptoms of dyspepsia in acid peptic disorders.

Keywords: Dyspepsia, effervescence, Gastrointestinal Symptom Rating Scale, Punica granatum.

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Introduction

Acid-related disorders influence the quality of life and productivity of afflicted patients and are common and important causes of morbidity and mortality. [1]

Acid peptic disorders can be counted among the most common ailments occurring in daily life today due to stressful work environments, haphazard

meal timings, increased intake of ready-to-eat foodstuffs, and lowered physical activity. [2] Acid peptic diseases result from distinctive but overlapping pathogenic mechanisms that typically involve acid effects on diminished mucosal defense. Conditions such as acid reflux, damage the esophageal mucosa, and also potentially cause laryngeal tissue injury with subsequent development of pulmonary symptoms. A peptic ulcer is histologically defined as a mucosal defect that extends to or beyond the muscularis mucosa, with mucosal damage due to pepsin and gastric acid secretion. Most ulcers occur in the stomach and proximal duodenum while less commonly in the lower esophagus, the distal duodenum or the jejunum. Gastric ulcer is a condition of the stomach lining that has common symptoms such as vomiting, burning, dull abdominal pain, headache, weight loss, low oral resistance, stenosis, perforation and stomach bleeding. [3] There is a large population who frequently gulps down antacid medications for the same. Over the years, there has been a tremendous revolution in the treatment of acid peptic disorders with assured safety and efficacy which include histamine-2 receptor antagonists (H2RAs) and proton-pump inhibitors (PPIs). [4] Further, H2RAs rapidly develop tolerance with repeat dosing, and exhibit an analgesic effect that may relieve heartburn while leaving the esophagus exposed to acid. [5] Short plasma half-life and necessity for preprandial dosing are significant problems with PPIs. Besides, long-term usage of high-dose PPIs is thought to affect the absorption of essential components such as calcium, magnesium, and Vitamin B12. [6] Thus, a prolonged duration of symptom control preventing symptom remission is an area wherein there is a need for new drugs.

The focus has been on natural plants, partially because certain pharmaceutical medicines are highly harmful to the patient

or cause adverse effects. A plant of the family Lythraceae, *Punica granatum* (pomegranate) has been reported to have several medicinal properties including chemopreventive, antioxidant, antifungal, anti-inflammatory and wound healing. A preventive role against obesity has also been identified. [7] Steroids, triterpenoids, saponins, glycosides, flavonoids, alkaloids, carbohydrate tannins and vitamin C have been found to contain the phytochemical screening of *Punica granatum* extract. [8] Ayurveda has also described use of seeds, fruit peel, and fruit rind of pomegranate in various formulations. The fruit peels of pomegranate are a rich source of tannins. [9] They possess an ability to form a gastroprotective layer which is useful in amelioration of symptoms of gastritis. [10] Apart from the symptomatic relief, which is a conventionally used parameter for studies in acid peptic disorders, we additionally used Gastro Panel, a panel of noninvasive tests to get a clear picture of a morphological and functional status of the gastric mucosa in a group of patients. [11]

This study aimed to assess the efficacy and acceptability of pomegranate effervescent granules (PEGs) in dyspeptic patients.

Material & Methods

This hospital-based study was conducted by the department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India for nine months. A prospective study included 100 patients reported to informed written consent was obtained from all participating individuals before screening and again before recruitment.

Many groups were prepared from patients, the first control group (inoculate with *H. pylori* and fed with standard pellet), the Second group, patients inoculated by *H. pylori* and prevented with *Punica granatum* aqueous extracts (PGAE) in two dosages (250mg/kg, 500mg/kg), and last group inoculated by *H. pylori* and prevented with standard drug omeprazole at the dose (20mg/kg).

Inclusion Criteria

Individuals in the age group of 18–60 years of either sex, suffering from minimum five symptoms out of the various classical symptoms of acid peptic disorders, namely sour or pungent eructation/belching, retrosternal/throat burning, epigastric burning/pain, nausea, regurgitation, vomiting, unsatisfactory digestion, loss of appetite, heaviness in body, and tiredness in absence of physical activity, repetitively for at least once a week for the past 2 months, were recruited. The individuals on the prolonged treatment of NSAIDs for any other clinical condition were also included in the study.

Exclusion Criteria

- Patients with hemoglobin level of ≤ 7 mg%, those with a known history of carcinogenic pathology, and cases of per rectal bleed, coagulopathies, severe cardiac, renal, hepatic, pleural pathologies.
- Those having 2.5 times liver function test values than their upper normal limits, those who had participated in any clinical trial within the past 1 month.
- Pregnant and lactating females were also not considered for inclusion.

Study intervention

Pomegranate effervescent granules (PEGs), prepared from the peel extract of pomegranate, were made available in sachets of 2.5 g.

The patients were asked to drink a mixture prepared by dissolving 1 sachet of PEG in 200 ml (1 cup) of water twice a day after meals for a period of 28 days. The patients were advised to discontinue excessive spicy, heavy food along with observing moderate physical activity. They were asked to return the empty sachets at follow-up to ensure compliance.

All consecutive patients attending the OPDs of the three study sites and suffering from acid peptic disorders were screened for eligibility criteria. They were explained about the study and their detailed medical history was recorded along with demographic details. Their blood investigations, namely hemogram and liver function tests, were carried out and only the participants with test values within normal range were called for recruitment.

On recruitment, per abdomen examination along with recording of vitals (pulse rate and blood pressure) was carried out. This was followed by baseline investigations which included bleeding time (BT), clotting time (CT), and Gastro Panel tests. BT and CT were done to assess the signs of gastrointestinal bleeding seen in cases of peptic ulceration. [12] The Gastro Panel consists of four tests, namely pepsinogen I (Pgl), pepsinogen II (PgII), gastrin 17 (G17), and Helicobacter pylori antibodies (IgG). Pepsinogens (Pgl and II) reflect the histological and functional status of stomach mucosa, particularly inflammation. G17 is the active and abundant form of gastrin and its secretion is influenced by acid concentration in the stomach. H. pylori antibodies denote the presence of H. pylori infection. [13]

The patients were then administered Gastrointestinal Symptom Rating Scale (GSRS), a standardized and validated tool for assessment of symptoms of acid peptic disorders. [14] It comprises 15 points such as abdominal pains, heartburn, acid regurgitation, sucking sensation in epigastrium, nausea and vomiting, borborygmus, abdominal distension, eructation, increased flatus, decreased/increased passage of flatus, stool consistency, urgency of defecation, and feeling of incomplete evacuation. The answer for each question is graded from 0 to 3, where 0 indicates normal physiological condition and 3 represents worsening of symptom. The minimum GSRS score that can be achieved is 0,

while the maximum score is 45. Thus, lower scores denote mild symptomatology and improvement post treatment.

Following this, the sachets of PEG were administered to the patients along with a symptom relief record sheet and drug diary. The patients were expected to fill this sheet daily. This sheet contained information such as presence of symptomatic relief (yes/no), time to relieve symptoms after intake of study drug (categorized as <15 min/≥30 min – 1 h/>1 h), remission of symptoms (yes/no) and its duration (categorized as ≤6 h/≤3 days/≥7 days/≥12 days), need for other antacid (yes/no), and taste of PEG (categorized as good/palatable/bad).

The patients were asked to tick in drug diary daily after taking the study drug to keep an account of drug compliance.

The patients were asked to report the study site on day 15 and then on day 29 (i.e. after finishing the treatment). On both days 15 and 29, GSRS score compliance to treatment and symptom relief was assessed. The blood investigations were repeated only on day 29. At both the visits, empty drug sachets were collected back from the patients to ensure compliance.

Statistical analysis

The parametric data were presented as mean ± standard deviation and analyzed using paired t-test. The nonparametric data were presented as median (range) and analyzed using Wilcoxon rank-sum test. The categorical data were presented as numbers and analyzed using Chi-square test.

Results

Table 1: Anti-ulcer effects of P granatum and omeprazole treatments

Groups	Prevention (5ml/kg) dose	Ulcer Area (mm ²) Mean ± SD	Ulcer Inhibition %	P-value
1	Ulcer control group	822.00±25.75	15.75	0.0001
2	High dose	126.44±1.26	85.65	
3	Low dose	455.45±8.48	42.83	
4	Omeprazole	620.20±11.49	25.55	

The results showed that in the Punica granatum treatment group with a dose above 500 mg/kg, Ulcer Area (mm²) was 126.44±1.26 and Ulcer Inhibition % was 85.65. In the Punica granatum treatment group with a dose of 250 mg/ kg Ulcer Area (mm²) was 455.60±8.48 and Ulcer Inhibition % 42.83. In the omeprazole treatment group, Ulcer Area (mm²) was

620.20±11.49 and Ulcer Inhibition was 25.55.while in the control group Ulcer Area (mm²) was 822.00 ± 25.75 and Ulcer Inhibition % 15.75 And this Ulcer Inhibition % in the Punica granatum treatment groups was significant compared to the omeprazole treatment group and the control group (P=0.0001).

Table 2: Total phenolic acids, total flavonoids, total anthocyanins content, and DPPH radical-scavenging activity% of pomegranate peel powder

	Pomegranate peel
Total phenolic acids (mg GA/g)	412.8±0.80
Total flavonoids (mg QE/g)	18.2±30.04
Total anthocyanins (mg cyanidin-3-O-glucoside /100g)	32.38±0.24
DPPH radical-scavenging activity%	93.7±0.01

Based on DPPH radical-scavenging activity%, pomegranate peel possessed powerful antioxidant activity.

Table 3: Antibacterial and antifungal activities of tested pomegranate peel powder

Strains	Control (sterile distilled water)	Pomegranate peel extract
Zone of inhibition (mm)		
Gram-negative bacteria		
<i>Escherichia coli</i>	0	5.4 ±0.65
<i>Salmonella enterica</i>	0	10.0 ±1.30
<i>Pseudomonas fluorescens</i>	0	0
<i>Yersinia enterocolitica</i>	0	12.0 ±1.35
Gram-positive bacteria		
<i>Bacillus cereus</i>	0	10.3 ±0.72
<i>Listeria monocytogenes</i>	0	0
<i>Staphylococcus aureus</i>	0	0
Fungus		
<i>Aspergillus flavus</i>	0	3.7 ± 0.32
<i>Aspergillus niger</i>	0	7.3 ±0.60
<i>Candida albicans</i>	0	0

The highest zone of inhibition (13 mm) was recorded against *Y. enterocolitica* and *S. enterica* compared with selected studied bacteria. The second highest zone of inhibition was 10.5 mm observed against *B. cereus*.

Discussion

Helicobacter Pylori is a highly motile, spiral-shaped, gram-negative bacterium that colonizes the intestines of 50-80% of people worldwide. [15] Its infection is one of the main and important reasons for continuous bacterial infection among humans. It has a high currency for both genders and all ages. According to the studies, it is directly or indirectly responsible for a diversity of human diseases, the most repeated of which are duodenal ulcers, chronic gastritis, peptic ulcer diseases, pancreatic cancer, and stomach cancer that damage the gastric mucosa. [16-19] The clinical and laboratory analysis exhibited that diabetic patients had more malignant infections in the digestive system than non-diabetic patients. [20] Irregular diets affect the usual operation of the oesophagus, stomach and duodenum. This disease is made by the mucosa internal digestion by gastric acid and pepsin. So, damage to

gastric mucosa will happen and causes ulcer, other factors are effective in making gastric ulcers. [21] Gastric ulcer is a condition of the stomach lining that has common symptoms such as vomiting, burning, dull abdominal pain, headache, weight loss, low oral resistance, stenosis, perforation and stomach bleeding. [22]

Current findings suggest that the anti-ulcer effect is associated with increased secretion of adherent mucus and increased pH of gastric contents [23], which can inhibit the production of oxygen-derived free radicals and keep the contents of MDA in a normal state. Using aspirin in rats is a good method that is helping in studying factors that produced ulcers, prevented or reduced the gastric ulcer [24], and the different changes that may happen in some parameters such as prostaglandins, cytokines, and nitric oxide. [25] Polyphenols rich-plants may control gastric ulcers by activating antioxidant performance, controlling *H. pylori* colonization, balancing the regulation of prostaglandins and anti-angiogenic factors, reducing oxidative mucosal changes, enhancing endothelial nitric oxide synthase derived NO, and increasing endogenous mucosal. [26]

This work evaluated the effect of the pomegranate peel powder as a polyphenol-rich plant in controlling and preventing gastric ulcers. The chemical analysis, including the total phenols, flavonoids, anthocyanins, antioxidant activities, and antimicrobial properties, was done in pomegranate peel powder. The values of these evaluations were acceptable and encouraged to apply this pomegranate peel powder at the level of 10% to a diet that provided to rats (one group) for four weeks, then a dose of 500 mg aspirin /kg-rat-weight were administered to the rats as a gastric ulcer inducer, the results were compared with other tested groups (normal control and ulcer control groups). The present study indicated that pomegranate peel powder contains high levels of total phenols (as gallic acid) and anthocyanins and has a high potency as an antioxidant, natural plant; this agrees with the findings previously described by Morea and Arya. [27] Also, the antimicrobial effects of the pomegranate peel powder were tested, and results showed that pomegranate peel powder has an inhibitory effect against Gram-positive, Gram-negative bacteria, and fungi. These results are in agreement with the previous reports except that *S. aureus* was resistant against pomegranate peel [28], which might be due to using less concentration in the current study compared to previous studies.

Conclusion

The present study concluded that PEGs proved to be palatable, patient-friendly, safe, and efficacious in resolving symptoms of dyspepsia in acid peptic disorders.

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