

A Study to Assess 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: A prospective study including 50 patients reported to ANMMCH, Gaya, Bihar, India and informed written consent was obtained from all participating individuals before screening and again before recruitment. 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: In the group treated with Punica granatum at a dosage above 500 mg/kg, the Ulcer Area (mm²) was measured to be 128.42±1.28, and the Ulcer Inhibition % was found to be 84.66. In the group receiving Punica granatum therapy at a dosage of 250 mg/kg, the Ulcer Area was measured to be 458.42±8.52 mm², with an Ulcer Inhibition rate of 41.89%. In the group receiving omeprazole treatment, the Ulcer Area (mm²) was measured to be 622.18±12.48, with an Ulcer Inhibition of 24.56%. In comparison, the control group had an Ulcer Area of 832.00±24.86 and an Ulcer Inhibition of 14.76%. The Ulcer Inhibition percentage in the Punica granatum treatment groups was significantly higher than that of both the omeprazole treatment group and the control group (P=0.0001). Pomegranate peel exhibited significant antioxidant activity, as shown by its DPPH radical-scavenging activity percentage. The greatest zone of inhibition was seen against *Y. enterocolitica* and *S. enterica* in comparison to the other microorganisms examined. An inhibition zone of 10.5 mm was reported as the second greatest against *B. cereus*.

Conclusion: PEGs shown their ability to effectively alleviate symptoms of dyspepsia in acid peptic diseases, while also being well-tolerated, convenient for patients, and safe.

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

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Introduction

Acid peptic diseases are prevalent in modern everyday life because to factors such as stressful work situations, irregular meal schedules, excessive consumption of processed foods, and less physical exercise. [1] They have a significant impact on the well-being and efficiency of affected individuals, as well as on the occurrence and death rates of these patients. [2] A significant portion of the population regularly consumes antacid medicines for this purpose. In recent years, there has been a significant revolution in the treatment of acid peptic diseases, with the development of very effective and safe medications such as histamine-2 receptor antagonists (H2RAs) and proton-pump inhibitors (PPIs). [2] Nevertheless, the majority of these drugs just provide alleviation for the symptoms. In addition, H2RAs quickly acquire tolerance when used repeatedly and have an

analgesic effect that may alleviate heartburn while leaving the esophagus vulnerable to acid. [3]

The short plasma half-life and the need for dosage before meals are important challenges associated with PPIs. In addition, it is believed that prolonged use of high-dose PPIs may impact the assimilation of vital substances including calcium, magnesium, and Vitamin B12. [4] Therefore, the demand for novel medications arises in the context of achieving extended symptom management that prevents symptom remission. Pomegranate (*Punica granatum*) has been widely used as a traditional treatment for acidosis, dysentery, microbiological infections, diarrhea, helminthic infections, bleeding, and respiratory diseases. [5] Ayurveda has also documented the use of pomegranate seeds, fruit peel, and fruit rind in several preparations. [6]

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

A prospective research including 50 patients was conducted at ANMMCH, GAYA, Bihar, India for one year. Prior to screening and recruiting, informed written agreement was acquired from all participants. The primary research outcomes were the assessment of symptoms related to acid peptic diseases using the Gastrointestinal Symptom Rating Scale (GSRS) scores on day 0, 15, and 29, as well as the evaluation of the taste of the formulation.

Several groups were formed using patients for the study. The first group served as the control group and was inoculated with *H. pylori* and fed a standard pellet. The second group consisted of patients who were inoculated with *H. pylori* and treated with *Punica granatum* aqueous extracts (PGAE) at two different dosages (250mg/kg and 500mg/kg). The last group consisted of patients who were inoculated with *H. pylori* and treated with the standard drug omeprazole at a dosage of 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

- 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 participants were instructed to consume a solution made by dissolving 1 sachet of PEG in 200 ml (equivalent to 1 cup) of water, twice daily after meals, for a duration of 28 days. The patients were instructed to cease consuming excessive hot and heavy meals, while also engaging in modest physical exercise. The participants were instructed to bring back the unused sachets during the follow-up session to guarantee adherence.

All successive patients visiting the outpatient departments (OPDs) at the three study locations and experiencing acid peptic diseases were assessed to see whether they met the eligibility requirements. They were briefed about the research and their entire medical history was obtained along with demographic statistics. The participants had blood examinations, namely a hemogram and liver function tests. Only those individuals with test levels falling within the normal range were contacted for recruiting.

During the recruiting process, a thorough examination of the abdomen was conducted, and the individual's vital signs, including heart rate and blood pressure, were recorded. Subsequently, baseline investigations were conducted, including bleeding time (BT), clotting time (CT), and Gastro Panel examinations. Endoscopic procedures, namely bleeding test (BT) and clotting test (CT), were performed to evaluate the indications of gastrointestinal bleeding seen in instances of peptic ulcers. The Gastro Panel comprises four specific tests: pepsinogen I (PgI), pepsinogen II (PgII), gastrin 17 (G17), and *Helicobacter pylori*

antibodies (IgG). Pepsinogens (Pgl and II) serve as indicators of the histological and functional condition of the stomach lining, specifically in relation to inflammation. G17 represents the prevailing and plentiful kind of gastrin, and its release is affected by the level of acidity in the stomach. H. pylori antibodies indicate the existence 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 reported as the mean value plus or minus the standard deviation and were evaluated using a paired t-test. The nonparametric data were reported as the median (range) and evaluated using the Wilcoxon rank-sum test. The categorical data were quantified and subjected to analysis using the 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 | 832.00±24.86 | 14.76 | 0.0001 |
| 2 | High dose | 458.42±8.52 | 41.89 | |
| 3 | Low dose | 128.42±1.28 | 84.66 | |
| 4 | Omeprazole | 622.18±12.48 | 24.56 | |

The results showed that in the Punica granatum treatment group with a dose above 500 mg/kg, Ulcer Area (mm²) was 128.42±1.28 and Ulcer Inhibition % was 84.66. In the Punica granatum treatment group with a dose of 250 mg/kg Ulcer Area (mm²) was 458.42±8.52 and Ulcer Inhibition 41.89%. In the omeprazole treatment group, Ulcer

Area (mm²) was 622.18±12.48 and Ulcer Inhibition was 24.56% while in the control group Ulcer Area (mm²) was 832.00±24.86 and Ulcer Inhibition 14.76% 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) | 416.4±0.82 |
| Total flavonoids (mg QE/g) | 19.34±31.05 |
| Total anthocyanins (mg cyanidin-3-O-glucoside /100g) | 33.37±0.26 |
| DPPH radical-scavenging activity% | 92.8±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 | 5.6 ±0.62 |
| <i>Salmonella enterica</i> | 0 | 10.0 ±1.34 |
| <i>Pseudomonas fluorescens</i> | 0 | 0 |
| <i>Yersinia enterocolitica</i> | 0 | 12.0 ±1.35 |
| Gram-positive bacteria | | |
| <i>Bacillus cereus</i> | 0 | 10.5 ±0.76 |
| <i>Listeria monocytogenes</i> | 0 | 0 |
| <i>Staphylococcus aureus</i> | 0 | 0 |
| Fungus | | |
| <i>Aspergillus flavus</i> | 0 | 3.7 ± 0.35 |
| <i>Aspergillus niger</i> | 0 | 7.3 ±0.60 |
| <i>Candida albicans</i> | 0 | 0 |

The highest zone of inhibition 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 bacteria that colonizes the intestines of 50-80% of individuals worldwide. [15] Its infection is one of the primary and essential causes for chronic bacterial infection among people. It has a high currency for all genders and all ages. According to the research, it is directly or indirectly responsible for a variety of human disorders, the most frequent 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 analytical study demonstrated that diabetes individuals had more malignant infections in the digestive tract than non-diabetic people. [20] Irregular diets impair the ordinary action of the oesophagus, stomach and duodenum. This sickness is generated by the mucosa internal digestion by stomach acid and pepsin. So, damage to stomach mucosa will happen and creates ulcer, other elements are efficient in generating gastric ulcers. [21] Gastric ulcer is a disorder of the stomach lining that has common symptoms such as vomiting, burning, dull abdominal pain, headache, weight loss, poor oral resistance, stenosis, perforation and stomach bleeding. [22]

The findings indicated that in the *Punica granatum* treatment group with a dosage above 500 mg/kg, Ulcer Area (mm²) was 128.42±1.28 and Ulcer Inhibition was 84.66%. In the group of subjects treated with *Punica granatum* at a dosage of 250 mg/kg, the Ulcer Area measured 458.42±8.52 mm², and the Ulcer Inhibition was calculated to be 41.89%. The Ulcer Area (mm²) in the omeprazole treatment group was measured to be 622.18±12.48,

with an Ulcer Inhibition of 24.56. In the control group, the Ulcer Area (mm²) was measured to be 832.00±24.86, and the Ulcer Inhibition was found to be 14.76%. The *Punica granatum* treatment groups showed a substantial Ulcer Inhibition % compared to both the omeprazole treatment group and the control group (P=0.0001). Pomegranate peel exhibited significant antioxidant activity as determined by its DPPH radical-scavenging activity percentage. The greatest zone of inhibition was seen against *Y. enterocolitica* and *S. enterica* in comparison to the other bacteria examined. The zone of inhibition against *B. cereus* was reported to be 10.5 mm, which was the second highest. The latest research indicates that the anti-ulcer action is linked to the enhanced synthesis of adherent mucus and elevated pH levels in the stomach. [23] These factors may prevent the generation of oxygen-derived free radicals and maintain the levels of MDA within a normal range. Administering aspirin to rats is an effective technique for investigating the causes of ulcers, as well as for assessing its ability to prevent or minimize stomach ulcers. [24] This approach also allows for the examination of various changes in parameters such as prostaglandins, cytokines, and nitric oxide. [25] Plants that are rich in polyphenols can help manage gastric ulcers by stimulating antioxidant activity, regulating the colonization of *H. pylori* bacteria, maintaining a balance in the regulation of prostaglandins and anti-angiogenic factors, reducing oxidative damage to the stomach lining, promoting the production of nitric oxide by endothelial nitric oxide synthase, and increasing the production of natural protective substances in the stomach lining. [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 administrated 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

PEGs were shown to be tasty, patient-friendly, safe, and effective in alleviating symptoms of dyspepsia in acid peptic diseases, according to the findings of the current investigation.

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