An expert opinion on antacids: A review of its pharmacological properties and therapeutic efficacy [version 1; peer review: awaiting peer review]

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**Abstract**

Acidity caused by common gastric conditions such as non-ulcer dyspepsia, duodenal ulcer, gastric ulcer, stress gastritis, gastroesophageal reflux disease (GERD), pancreatic insufficiency, bile acid-mediated diarrhea, biliary reflux, and constipation can be treated by administration of potent and efficacious acid suppressant (anti-secretory) agents such as antacids, histamine H₂ receptor blockers, and proton pump inhibitors (PPIs). Antacids provide symptomatic relief from hyperacidity as well as other associated conditions by neutralizing the gastric acid directly, thereby raising the gastric pH, attenuating the pepsin activity, restoring acid-base balance, and increasing prostaglandin and bicarbonate secretion. The effectiveness of antacids is determined by its acid neutralizing capacity (ANC) and buffering capacity. Antacids containing a combination of aluminum hydroxide, magnesium hydroxide, and other ingredients such as those present in Digene showed better therapeutic efficacy even at low dosage with fewer side effects, persistent increase in gastric pH, faster and longer duration of pain relief, and fast relief from gas. Various clinical studies suggest that to obtain fast symptomatic relief, the treating physician can utilize antacids with the highest neutralizing capacities like Digene.

**Keywords**

antacids, acidity, gastroesophageal reflux disease, gastrointestinal disorders, acid reflux, aluminum hydroxide, magnesium hydroxide, simethicone, magnesium silicate
Introduction
Gastrointestinal (GI) disorders vary in prevalence and severity, from typical short-term occurrences of dyspepsia (indigestion), to more harmful and severe chronic disorders. Endogenous factors like leukotrienes, pro-inflammatory cytokines, acid, pepsin, activated neutrophils, histamine, reflux bile, proapoptotic proteins, ischemia, reactive oxygen species, and exogenous factors, like non-steroidal anti-inflammatory drugs (NSAIDs) and stress, attack the gastric mucosa, causing damage and ulceration.1

Acid reflux is a symptom of gastroesophageal reflux disease (GERD), which can be mild or severe depending upon its occurrence (Mayo Clinic). In 2020, the global prevalence of GERD was 14%, and in Asia it was 13%.2 Healthcare expenditure for GI disorders was estimated to be approximately $135.9 billion in the year 2015 and that for acid suppressing drugs was found to be $60 billion in the last five years.3 Acid reflux is also one of the causes of perforated peptic ulcers, which occur in around 2–10% of all patients with peptic ulcer disease. The mortality rate is approximately 10–40% depending on age, presence of comorbidities, and diagnostic and treatment delay.4

Gastric disorders have a negative impact on quality of life and can cause work impairment and higher health-related costs. GI disorders may also lead to social withdrawal in some patients due to fear of recurrence of symptoms.5 Common gastric conditions, such as gastric ulcer, GERD, duodenal ulcer, non-ulcer dyspepsia, constipation, stress gastritis, biliary reflux, pancreatic insufficiency, and bile acid-mediated diarrhea, can usually be treated by administration of efficacious and potent acid suppressant (anti-secretory) agents, such as proton pump inhibitors (PPIs), histamine H2 receptor blockers and, antacids.6

Antacids are weak bases that can reduce the acidity of gastric contents and lead to symptomatic pain relief.7 The main therapeutic benefit of antacid is their quick onset of action, which allows them to relieve gastrointestinal discomfort in minutes. This review explores the literature evidence and expert opinion the pharmacological features and therapeutic efficacy (fast and sustained action with a low risk of adverse effects) of antacids.

Antacids and their properties
Antacids are a group of drugs that have been on the market for years. In the 19th century, the popularity of antacids grew, and they were used for the treatment of various gastric disorders. Antacids are a combination of various salts of magnesium, calcium, or aluminum8 that provide symptomatic relief from hyperacidity as well as other associated conditions by neutralizing the gastric acid directly, thereby, raising the gastric pH, attenuating pepsin activity, restoring acid-base balance, and increasing bicarbonate and prostaglandin secretion. Antacids act by neutralizing the acid in the stomach, thereby preventing the acid from reaching the duodenum. The therapeutic objectives of antacids include relieving pylorospasm, alleviating pain, and avoiding digestion and corrosion caused by acid chyme. Though the mechanism of neutralization of the acid varies depending on the salts comprising the antacid formulations, the end goal is stomach acid neutralization.

Antacid components and their pharmacokinetic and pharmacodynamic properties
Table 1 presents the components of various antacids and their pharmacokinetic and pharmacodynamic properties.

Table 1. Antacids and their features.

<table>
<thead>
<tr>
<th>Antacid</th>
<th>ANC</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide</td>
<td>29</td>
<td>Modest</td>
<td>Low systemic absorption</td>
<td>Heartburn, GERD, peptic ulcer, stress ulcer</td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td>35</td>
<td>High</td>
<td>Low systemic absorption, efficacious antacid</td>
<td>Peptic ulcer, gastritis, esophagitis, acid reflux, peptic ulcer, indigestion, heartburn</td>
</tr>
<tr>
<td>Magnesium silicate</td>
<td>Low</td>
<td>Non-absorbable antacid</td>
<td>High doses cause hypomagnesaemia; less water soluble</td>
<td>Heartburn, constipation, indigestion</td>
</tr>
<tr>
<td>Simethicone</td>
<td>-</td>
<td>Effective even without absorption by the body</td>
<td>Gas production in the GI tract is not reduced</td>
<td>Peptic ulcer, dyspepsia, gaseous distention, post-operative and irritable colon</td>
</tr>
</tbody>
</table>

ANC, acid neutralizing capacity; GERD, gastroesophageal reflux disease; GI, gastrointestinal.
Aluminum hydroxide
Aluminum hydroxide, an inorganic salt, is one of the compounds of the many aluminum salts. It is used in antacid formulations mostly in combination with magnesium or calcium salts, but very rarely alone. Aluminum hydroxide is absorbed in very small quantities by the digestive tract, and approximately 17–30% of the formed aluminum chloride is absorbed (DrugBank Online). Aluminum hydroxide acts by dissociating into Al$^{3+}$ and OH$^{-}$ in the stomach. The free hydroxide group binds to the free proton in the stomach producing water and insoluble aluminum salts, mostly Al(OH)$_3$.

This proton binding increases the overall pH of the stomach (less acidic), thereby reducing indigestion. The resulting aluminum salt is excreted via feces. Antacids containing aluminum salts can be used by pregnant women and also during labor for aspiration prophylaxis although none of the studies have reported it, but aluminum is found to be endogenous to breast milk and can be taken by breastfeeding women too.

Magnesium hydroxide
Magnesium hydroxide is also called milk of magnesia. It can be used as a laxative and as an antacid; however, its dose may vary depending upon the condition to be treated. It is used as an antacid for temporary relief of heartburn, sour stomach, upset stomach, or acid indigestion. Magnesium hydroxide acts by neutralization of gastric acids. The hydroxide ions combine with protons of the hydrochloric acid formed by the parietal cells in the stomach resulting in the formation of magnesium chloride and water (International Foundation for Gastrointestinal Disorders). Slow absorption of magnesium hydroxide from the small intestine is observed, which ranges from 15–50%. After absorption, it is rapidly excreted in the urine and the unabsorbed drug is excreted in the saliva and feces. Individuals with renal failure can be at a high risk of hypermagnesemia as the kidney has a major role in drug clearance (DrugBank Online).

Magnesium silicate
Magnesium silicate is a mixture of magnesium oxide and silicon. It is considered as magnesium salt of silicic acid. In the pharmaceutical industry, it finds its use in a variety of different formulations where it is either used as a dietary supplement or in antacid and antacid preparations, in antifungal topical agents, as a component of antiepileptic drugs, and in the treatment of acne. It acts as an astringent and neutralizing agent. Oral administration leads to rapid neutralization in the stomach forming silicon dioxide and magnesium chloride, and some of the magnesium is absorbed from the modified portion. Due to its low absorption, the pharmacokinetic properties of magnesium silicate are considered as irrelevant. Daily administration of more than 50 mEq magnesium can lead to hypermagnesemia (DrugBank Online).

Simethicone
Simethicone is an antifoaming agent, which is used to reduce gas in the gastrointestinal tract for the management and treatment of flatulence. It is considered pharmacologically inert and acts locally. As it is not absorbed from the digestive tract, it does not interfere with nutrient absorption or with gastric secretion. As it is not absorbed by the body, it is excreted in the feces unchanged and is hence considered safe. It can be used to relieve symptoms in gastric conditions such as peptic ulcer, dyspepsia, irritable colon, and post-operative gaseous distention. It is used as a self-medication to relieve symptoms such as gas, including pressure, upper digestive tract bloating, stuffed feeling, or fullness. It acts by decreasing the surface tension of gas bubbles in the GI tract, thereby leading to coalescence and dispersion of the gas bubbles and their removal from the GI tract via belching or flatulence. Simethicone causes accumulation of gas bubbles that can pass more easily through the upper GI or lower GI opening. However, simethicone does not reduce the actual production of gas in the GI tract. It can be compounded with other antacids such as aluminum hydroxide, magnesium hydroxide, or magnesium silicate. Not many adverse effects are reported, except for nausea and mild diarrhea.

Clinical evidence on efficacy of various antacids
The effectiveness of antacids is solely determined by the individual’s acid neutralizing capacity (ANC). ANC is one of the most well-known in vitro parameters reflecting the in vivo efficacy of antacids. There is a lot of clinical evidence that suggests formulations having a higher ANC provide better symptomatic relief, are more efficacious, and have a faster onset of action. Several in vitro studies have compared ingredients of different formulations for their antacid activity. All of them have reported that formulations having aluminum hydroxide, magnesium hydroxide, and simethicone have high ANCs, which consequently makes them more efficacious, better at providing symptomatic relief, and achieve quicker onset of action compared with other antacids. An in vitro study suggested that there was no correlation between pH and ANC in antacids with higher pH. A study comparing the results of preliminary antacid test (PAT), the pH ANC, acid neutralizing potential (ANP), and buffering capacity of two marketed formulations like F1 [Digene Ultra Fizz] and F2 [a standard, commercially available product] showed that Digene Ultra Fizz had a higher pH of acid-antacid solution (F1, 8.20±0.02 vs. F2, 6.53±0.01), better neutralizing capacity (F1, 46.89±0.6 vs. F2, 30.12±1.3 mEq/dosage), and 2.7 times higher ANP (F1, 245 mins vs. F2, 90 min) than F2. Overall, the study concluded that Digene had higher antacid and buffering properties than F2 when tested in vitro.
When seven commonly prescribed antacids containing oxethazaine suspensions were evaluated in in vitro studies, similar results were observed: formulations having higher ANC were more efficacious. The reference antacid formulation of Digecaine was highly efficacious, having an ANC of 29.0 mEq and relative effectiveness was 100.13 Furthermore, an in vivo study comparing four different antacids on the basis of their ANC, bile salt binding capacity, cost, and patient acceptance reported a significant difference in ANC, bile acid binding capacity, and cost of these formulations. The four formulations included were almasilate or aluminum magnesium silicate (A); dimethicone aluminum hydroxide + magnesium oxide (B); sodium bicarbonate + sodium alginate (C); and aluminum hydroxide + magnesium hydroxide (D). The antacid containing dimethicone had the highest ANC and bile acid binding capacity. The final takeaway of the study was that in order to achieve maximum compliance with antacid therapy, patients should be allowed to choose from a range of preparations.14

Formulations such as Dioval with composition of aluminum and magnesium hydroxide were found to have ANC values of 26.28±0.05 by pH meter method and 26.17±0.18 by titration method, which were the highest among all formulations tested. Among solid formulations, ANC was highest for Riflux Forte: 25.77±0.06 by pH meter method and 25.73±0.17 by titration method. A higher magnesium hydroxide concentration was noted in both of these formulations as compared with other antacids. Hence, it was concluded that for an acute and faster symptomatic relief from dyspepsia, antacids having a higher concentration of magnesium hydroxide are helpful.15 The results of the dynamic and static tests conducted on hydrotalcite 500 mg and other antacids like algeldrate magnesium hydroxide, magnesium/calcium carbonate, magaldrate, almasilate, and calcium carbonate confirmed that a suitable ANC is reflected by rapid onset and longer duration of action with higher buffering capacity. Hydrotalcite had the best binding potential to taurodeoxycholic acid as confirmed by the bile acid binding capacity test. Rossett-Rice (RR) test reported that hydrotalcite at a dose of 1,000 mg kept the pH level above 3 for 76.9 min. These pharmacochemical properties make hydrotalcite a more favorable antacid as compared with the others.15 Furthermore, a Canadian study that tested 23 liquid and 18 tablet antacids found highest ANCs in the concentrated liquid antacids (Mylanta-2 Extra Strength, Amphojel 500, Gelusil Extra Strength, Maelox TC, and Divolv Ex). The treatment of peptic ulcer requires high-dose antacid therapy, and liquid antacids with a high or an intermediate-high ANC are the recommended agents.16 A double blind trial showed that antacid gels like Mucaine in combination with oxethazaine are effective in relieving the symptoms of heartburn in pregnant women (27 out of 31 cases obtained complete relief).17 On similar lines, another double blind comparative study demonstrated that treatment with Mucaine and Mucaine without oxethazaine were more effective than placebo during late pregnancy for the relief of heartburn.15 On evaluation of efficacy of simethicone in patients with functional dyspepsia, significantly better symptom control was observed by simethicone and cisapride in patients with functional dyspepsia after 2, 4, and 8 weeks of treatment. Out of the two, simethicone showed superior prokinetic properties than cisapride in the first 2 weeks of treatment.19 Table 2 summarizes the in vitro evidence on the efficacy.

Management of GERD with antacids

Clinical presentations of GERD range from a variety of symptoms like heartburn, regurgitation, and acid reflux. Suppression of this acid reflux has remained the foundation of pharmacological therapy for treating GERD.20 Although PPIs are still the first-line of treatment for GERD, recent literature has raised concerns about their adverse events and has precipitated doubts about the safety of long-term use of PPIs, thereby aggravating concerns over overprescribing of PPIs.21 According to experts, GERD treatment often requires a symptom-based approach at the inception of the treatment. This is usually followed by a pathogenesis-based approach, during which the symptomatic response to acid suppressant therapy validates the role of acid reflux. The symptoms that do not respond to acid suppression verify the role of other factors.21 The treatment for managing acid reflux in GERD is usually split up into three prominent therapeutic levels (self-care, primary care, and secondary care), with precise recommendations being available at each care level. Majority of patients having symptoms of acid reflux are usually controlled at the level of self-care and primary care.22 At this level, due to the involved stomach acid-related pathologies, PPIs are considered as the mainstay therapy for most of them but these agents take a longer duration to work, sometimes longer than the H2 blockers as well. Furthermore, newer clinical studies have highlighted the ineffectiveness of PPIs in treating some patients with PPI-refractory GERD.23 Antacids and alginate-antacids are known to provide intermittent and rapid symptom relief at the self-care and primary care level.22 A meta-analysis conducted in 2007 reported that over-the-counter medications showed effectiveness in providing relief from acid reflux symptoms of GERD, and antacids and alginate-antacids effectively improved postprandial gastric symptoms.24 Antacids or alginate-antacids have demonstrated a prominent place in treatment of all levels of GERD, independently and in combination with acid suppressive therapies (H2 blockers and PPIs).25 Treatment with alginate-antacids reportedly reduces the damage caused due to pepsin and bile acid injury by formation of raft-like structures.26 Across all levels of management, defining symptoms is critical for deciding the treatment pattern and the course of action to be taken.
**Table 2. Summary of preclinical and clinical evidence on efficacy of various antacids.**

<table>
<thead>
<tr>
<th>Author, year (ref.)</th>
<th>Type of study</th>
<th>Study characteristics</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhawal and Barve, 2019</td>
<td><em>In vitro</em></td>
<td>Comparison of 13 formulations with respect to ANC, PAT, and ANP</td>
<td>Antacid properties of Digene products (F5, F7, and F13) were better</td>
</tr>
<tr>
<td>Jakaria et al., 2015</td>
<td><em>In vitro</em></td>
<td>Comparison of the activity of five different commercial antacids containing oxethazaine</td>
<td>Non-systemic antacid having dried aluminum hydroxide gel, magnesium hydroxide, and simethicone had the greatest efficacy</td>
</tr>
<tr>
<td>Bhoir and Bhagwat, 2013</td>
<td><em>In vitro</em></td>
<td>Comparison of relative effectiveness of seven different commercial antacids containing oxethazaine</td>
<td>Digecaine, an anesthetic antacid had the highest ANC amongst the marketed antacids tested</td>
</tr>
<tr>
<td>Jacyna et al., 1984</td>
<td><em>In vitro</em></td>
<td>Comparison of four antacids: Malinal, Asilone, Gaviscon, and Maalox to determine patients' acceptance for these therapies</td>
<td>Preference for antacid by patients was determined by factors like taste, smell, texture, age, and sex</td>
</tr>
<tr>
<td>Jagadesh et al., 2015</td>
<td><em>In vitro</em></td>
<td>Comparison of the ANC of six different liquid and six solid tablet formulations</td>
<td>Diovol and Riflux Forte have highest ANCs among all liquid and solid formulations, respectively. Both of these have highest concentration of magnesium hydroxide among others</td>
</tr>
<tr>
<td>Miederer et al., 2003</td>
<td><em>In vitro</em></td>
<td>Comparison of hydrotalcite and other preparations of antacids for acid neutralization and bile acid binding capacities</td>
<td>Hydrotalcite and some other antacids like almasilate, magaldrate and others showed favorable ANC. Also, hydrotalcite had the highest binding potential to bile acids</td>
</tr>
<tr>
<td>MacCara et al., 1985</td>
<td><em>In vitro</em></td>
<td>Comparison of ANCs of 23 liquid and 18 tablet antacids</td>
<td>Highest ANCs were found in the concentrated liquid antacids and as the treatment of peptic ulcer disease requires high-dose antacid therapy, liquid antacids with a high or an intermediate-high ANC are the recommended agents</td>
</tr>
<tr>
<td>Carne, 1964</td>
<td>Double-blind trial (n=36)</td>
<td>Comparison of Mucaine and an identical antacid gel containing aluminum and magnesium hydroxide, but no topical anesthetic in heartburn during pregnancy</td>
<td>Mucaine showed a significant improvement over simple antacid therapy for the treatment of heartburn in pregnancy</td>
</tr>
<tr>
<td>Kovacs et al., 1990</td>
<td>Double-blind parallel trial (n=50)</td>
<td>Comparison of the efficacy of Mucaine and Mucaine without oxethazaine vs. placebo</td>
<td>Two active treatments were more effective than placebo for the relief of heartburn, but there was no statistically significant difference between groups for the relief of nausea and regurgitation</td>
</tr>
<tr>
<td>Holtmann et al., 2002</td>
<td>Double-dummy, randomized placebo-controlled trial (n=185)</td>
<td>Comparison of the efficacy of simethicone, the prokinetic cisapride, and placebo</td>
<td>Simethicone and cisapride were significantly better than placebo for symptom control like nausea, bloating, reflux, and pain and satiety</td>
</tr>
</tbody>
</table>

ANC, acid neutralizing capacity; ANP, acid neutralizing potential; PAT, preliminary antacid test.

**Self-care**

Popular expert opinion favors the use of low-dose PPIs in treating acid reflux in GERD patients at the self-care level. However, the speed of action and onset of symptom relief is one of the most important factors in determining the choice of therapy. Therefore, antacids or alginate-antacids, which offer the most rapid symptom relief can be used ‘as required’. Evidence suggests that antacids or alginate-antacids offer more rapid symptom relief when compared with alternative...
treatments and could thus be used in combination with acid suppressants. If patients present with alarming symptoms, they are strongly recommended to consult a primary care physician for referral to a specialist.6,27–29

**Primary care**

It has been noticed that PPI or a combination of PPI and alginate-antacid therapy may potentially be more beneficial than acid suppressive therapy alone at the primary care level.22 Expert panelists recommend the use of antacids or alginate-antacids for symptomatic primary care patients with reflux or with ongoing symptoms that are not completely controlled with acid suppressants.6,27–29

**Secondary care**

Secondary-care level specialists are committed to dealing with more complicated cases of patients who are partially or completely unresponsive to treatment. Therefore, accurate diagnosis and prognosis are important in deciding a suitable strategy for long-term treatment. PPI therapy can be complemented with adjuvant therapy (oxethazaine-antacid/alginate-antacid) at the secondary care level.6,27–29

**Expert opinion on antacids**

Considering the wide array of antacid components used in the various commercially available antacid formulations, understanding the therapeutic effect of these components and their clinical use is important. It is observed that hyperacidity is common in Indian clinical practice with an average duration of 2–4 weeks depending on patient profile. Common symptoms of hyperacidity are distension, belching, sour taste, bitter mouth, bloating, flatulence, localized/diffuse pain radiating to back/chest (heartburn), burning ache, regurgitation (e.g., GERD), vomiting, nausea, and indigestion. The treatment approach includes lifestyle management, dietary modifications, and pharmacotherapy with antacid combinations/H2 receptor antagonists. Consistent with literature, we observed aluminum hydroxide to be a slow-acting agent, but it has a longer duration of action mainly due to its mechanism of action where it dissociates into Al3+ and OH- and the freed hydroxide groups bind to free protons producing water and insoluble aluminum salts. This proton binding makes the overall pH of the stomach basic thereby, reducing the symptoms. Aluminum hydroxide can also prevent diarrheal complications caused due to magnesium salts when given as a combination therapy. We concur with the evidence from literature and clinical studies that magnesium salts are fast acting and thereby provide quick relief; however, they have a shorter duration of action mainly due to their pharmacological properties. Aluminum hydroxide also has a laxative property that counteracts the aluminum hydroxide side effects, thereby providing an added advantage with combinations. Therefore, most of the antacid formulations such as Digene, Gelusil, and Gaviscon contain magnesium and aluminum salts. It has been observed that many antacid preparations contain simethicone, which gives effective relief from gas. The reason behind the gas production could be the antacid itself considering that antacids work on stomach acid and can cause flatulence. Simethicone acts by decreasing the surface tension of gas bubbles in the GI tract and facilitates their expulsion. It has a short and quick duration of action as it is generally given as needed, and it has a wide therapeutic index as it is not systemically absorbed.

We recommend that addition of sodium carboxymethyl cellulose (CMC) to an antacid formulation is an added advantage because it can successfully treat majority of the chronic constipation cases caused due to antacid therapy. Gut motility is disturbed mainly due to antacid cations causing constipation in patients under antacid treatment.30 These cations affect the smooth muscle of the gut and enteric nervous system and cause the release of gastrointestinal hormones. Additionally, antacid cations also alter the physicochemical properties of intraluminal contents. Cations formed on treatment with aluminum inhibit the motor activity of the stomach and intestine leading to constipation. Hence, most of the antacid formulations contain laxatives such as sodium CMC.30 Its mucin-like coating action is an added advantage as it interacts with the stomach and intestinal mucin layer, thereby increasing the residence of the formulation and its bioavailability.31

Antacid combinations are considered as an effective way in certain recalcitrant conditions. Antacids elicit their mechanism of action via neutralization of the stomach acid by the chemical entities in the antacids, which are bases (alkalis), thereby making the stomach content less corrosive and gentle. Antacids, such as Digene, contain components that are highly efficacious and are found to reduce symptoms of acidity, thereby making them a treatment of choice in clinical practice.

**Conclusions**

Antacids containing a combination of aluminum hydroxide, magnesium hydroxide, and other ingredients showed significant clinical results in vitro, thus reviving the confidence levels of clinicians to use these antacids across all types of GI disorders. Though PPIs have long been the treatment of choice for most gastric disorders, we recommended antacids as a complement to PPIs in the management of acidity due to GI conditions because of their enhanced therapeutic efficacy with longer duration of action, low dosage requirement, favorable side-effect profile, persistent maintenance of gastric pH, faster onset of action compared with other combinations. We believe that antacids with simethicone help in faster...
reduction of gas and those with laxatives like sodium CMC reduce or counteract constipation. The capacity of different antacids and their formulations to neutralize acid varies. The ANC of a formulation with higher magnesium hydroxide content is generally greater than that of other formulations. Real world and prospective studies evaluating the role of antacids suggest that to get faster symptomatic relief the treating physician can utilize antacids with a higher neutralizing capacity. Hence, it can be concluded that incorporation of antacid alone or in combination in the treatment strategy for GI disorders is favorable. However further studies are recommended.

Data availability
Underlying data
No data are associated with this article.

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References


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