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ABOUT COVER

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The primary aim of the *World Journal of Gastrointestinal Pharmacology and Therapeutics* (*WJGPT*, *World J Gastrointest Pharmacol Ther*) is to provide scholars and readers from various fields of gastrointestinal pharmacology and therapeutics with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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MINIREVIEWS

Rebamipide in gastric mucosal protection and healing: An Asian perspective

Manish Kak

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Abstract

This review emphasizes the exemplary safety and efficacy of rebamipide in the treatment of gastric ulcers and other mucosa-related disorders, positioning it as a viable candidate for inclusion in treatment guidelines across India and globally. An in-depth literature review of rebamipide was carried out on PubMed and Google Scholar. Rebamipide has a multifaceted mechanism of action, including prostaglandin synthesis, scavenging free radicals, and enhancing mucin production, leading to enhanced mucosal protection and ulcer healing. Rebamipide serves as a highly effective and safe treatment option for gastric ulcers and gastroesophageal reflux disease. The efficacy of this drug in treating ulcers often surpasses that of routinely used agents such as pantoprazole, sucralfate, misoprostol, famotidine, lansoprazole, and esomeprazole. This superiority of rebamipide can be attributed to the low rate of adverse events associated with it and its mild side effects, contributing to its widespread adoption across Southeast Asia and Russia. This popularity extends to its application beyond gastrointestinal ailments. Notably, it has been successfully employed in the treatment of ophthalmological, oncological, and bone regeneration-related issues. Rebamipide's exemplary safety and efficacy in treating gastric ulcers and other mucosa-related disorders support its potential for inclusion in treatment guidelines, not only in India but also globally.

Key Words: Rebamipide; Peptic ulcer; Gastroesophageal reflux disease; Mucosal protection; Treatment

Core Tip: This review highlights rebamipide's superior safety and efficacy in treating gastric ulcers and mucosal disorders, making it a strong candidate for inclusion in global treatment guidelines. An extensive literature review reveals its multifaceted mechanism of action, including prostaglandin synthesis, free radical scavenging, and mucin production enhancement, leading to enhanced mucosal protection and ulcer healing. Rebamipide often surpasses other common treatments like pantoprazole and esomeprazole due to its low adverse event rate and mild side effects. Its broad application extends to ophthalmology, oncology, and bone regeneration, further underscoring its therapeutic versatility.

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INTRODUCTION

Peptic ulcer disease (PUD) is prevalent globally, particularly in developing nations like India[1]. Worldwide, PUD affects approximately four million people annually, with a 5%-10% lifetime prevalence[2]. In India, the lifetime prevalence of PUD is 11220 cases per 100000 population and is highest at 28800 cases per 100000 population, during the fifth decade of life[3]. PUD may be attributed to *Helicobacter pylori* (*H. pylori*) infections, usage of non-steroidal anti-inflammatory drugs (NSAIDs) or selective serotonin reuptake inhibitors, smoking, stress, lifestyle habits, gastric bypass surgery, or genetic predisposition[4]. Most treatments for PUD address its underlying cause, such as eliminating an *H. pylori* infection with antibiotics; minimizing or discontinuing NSAID usage; reducing acid production with proton pump inhibitors (PPIs), H2-receptor antagonists (H2RAs), and potassium-competitive acid blockers; and by promoting mucosal defence using mucoprotectants that induce prostaglandin activity (misoprostol) or those that act independently of prostaglandin activity (bismuth and sucralfate)[5].

Patients using H2RAs experience a higher recurrence rate of PUD (54.5%) than non-users (28.4%). Similarly, antibiotic use is associated with increased PUD recurrence (52.9% *vs* 27%) in antibiotic users compared with non-users, respectively [6,7]. While PPIs are the mainstay treatment for PUD, they can exacerbate small intestinal damage caused by NSAIDs. Concerns about the long-term use of PPIs, H2RAs, antacids, and vonoprazan also include interference with calcium, iron, magnesium, and vitamin B12 absorption, as well as side effects like nausea, constipation, and nasopharyngitis, and the potential for conditions such as pneumonia, *Clostridium difficile* infection, cardiovascular effects and chronic kidney failure [6].

Rebamipide, however, is better tolerated and has fewer side effects than conventional PUD treatments as it stimulates the production of prostaglandins in the gastric mucosa, enhancing both, the speed and quality of ulcer healing[8]. Additionally, it shields the gastric mucosa from the acute damage caused by NSAIDs and oxidative injuries[8]. The primary objective behind the development of this drug was to enhance the quality of ulcer healing, particularly since antisecretory drugs do not offer this benefit. Rebamipide has demonstrated both, ulcer healing and ulcer preventive qualities[8]. Further, rebamipide is more cost-effective than anti-secretory drugs like PPIs and H2RAs[9]. This article aims to comprehensively explore the molecular mechanisms, efficacy, safety, and advancements in the use of rebamipide in various gastrointestinal (GI) conditions, as well as its potential in treating other medical conditions.

An extensive and in-depth search of the literature on rebamipide was carried out on PubMed and Google Scholar using the keywords "rebamipide", "peptic ulcer", "gastroesophageal reflux disease", and "mucosal protection". Studies on the safety, efficacy, and mechanism of action of rebamipide were identified and collated for inclusion in this review.

RESULTS AND DISCUSSION

History of rebamipide

Rebamipide, developed in the 1980s, addressed the numerous challenges associated with conventional PUD treatments [10]. Rebamipide is derived from the amino acid 2(1H)-quinolinone[11] and is chemically known as (2R)-2-[(4-chlorobenzoyl) amino]-3-(2oxo-1H-quinolin-4-yl) propanoic acid, with the formula $C_{19}H_{15}ClN_2O_4$ and a molecular weight of 370.79 g/mol[12]. It is an established mucoprotective agent used for treating gastritis and PUDs[13].

Presently, rebamipide is available as 100 mg tablets under various trade names in India[14]. Although it is not sanctioned for the treatment of PUD in the United States and Europe, rebamipide is extensively used in Asia. This variance in acceptance stems from differing perspectives on ulcer healing between Western and Asian countries. While the West prioritizes rapid healing, Asian systems emphasize the quality of ulcer healing, aiming to mitigate the high recurrence rate of ulcers following the discontinuation of acid-suppressive therapy[12,15].

Pharmacokinetics and metabolism of rebamipide

Rebamipide is a white, crystalline, odourless, bitter powder available as film-coated tablets[12]. An understanding of the distinct chemical, absorptive, bioavailability, metabolic, and excretory properties of rebamipide is pivotal for informed

clinical decisions on its usage and effective therapeutic outcomes.

Absorption: It is a highly lipophilic, poorly water-soluble, and slightly acidic molecule (pK_a = 3.38) that is least soluble in an acidic medium[16,17]. As a result, rebamipide is poorly absorbed in the acidic upper GI tract, but is better absorbed in the lower GI tract, leading to two distinct peaks in its plasma concentration[11,18]. Although food intake is associated with lower absorption of rebamipide, it does not influence its bioavailability[12].

Distribution: It has a high affinity for blood proteins[11,12] and 98.4%-98.6% of the drug in the bloodstream is bound to plasma proteins[12]. Rebamipide containing radiolabelled ^{14}C, when administered orally to rats, showed that the highest drug concentrations occurred in the stomach, intestines, kidneys, and liver[19]. This distribution pattern allows for targeted ulcer treatment, expediting ulcer healing, and minimizing systemic effects. Accumulation-related toxicity was reported to be unlikely, even with multiple doses[11]. Rebamipide also accumulates in the reproductive organs[11]. Notably, a study found that in infertile men taking 900 mg of rebamipide daily for three months, rebamipide concentrations in semen surpassed those in plasma. This correlated with reduced levels of reactive oxygen species, improved sperm viability, and enhanced fertilization capability[11,20]. In women, preclinical studies showed that rebamipide is found in breast milk; therefore, rebamipide use is contraindicated in breastfeeding women[11].

Metabolism: Rebamipide undergoes minimal first-pass metabolism[11]. In the liver, rebamipide is metabolized into 6-hydroxy-rebamipide and 8-hydroxy-rebamipide compounds, primarily by the enzyme CYP3A4; other enzymes seem to play no significant role in metabolizing this drug[12].

Effect on the metabolism of other drugs: Even high concentrations of rebamipide (0.5 mM) have no significant impacts on the various cytochrome P450 subtype-mediated drug metabolism pathways[11,12]. In clinical therapy, the C_{max} level of rebamipide in human plasma after a single oral administration of 100 mg is approximately 0.6 μM, indicating minimal involvement in drug metabolism interactions[11,12]. Unlike PPIs and H2RAs, rebamipide does not affect gastric hydrochloric acid secretion, which reduces its potential impact on the absorption/bioavailability of other concurrently administered drugs[12,19].

Elimination: The blood plasma elimination half-life of rebamipide is approximately two hours. When 100 mg of rebamipide is orally administered to healthy adult males, roughly 10% of the administered dose is eliminated in urine, and the remainder is eliminated as inactive metabolites in feces[12,19].

Molecular mechanisms of the action of rebamipide

Rebamipide exerts its ulcer-healing and gastric mucosa-protective effects *via* several molecular mechanisms which are highlighted below and in Figure 1.

Gastroprotective, ulcer healing, and cytoprotective effects of rebamipide

Numerous studies have explored the gastroprotective, cytoprotective, and ulcer-healing properties of rebamipide, including its stimulation of cyclooxygenase-2 (COX-2) expression, scavenging of free radicals, suppression of neutrophil activity, and effects on cytokine production[19].

Gastroprotective effects: Rebamipide activates the extracellular signal-regulated protein kinase 1 and 2 (ERK1/2) and p38 mitogen-activated protein kinase (p38MAPK) pathways, which are crucial for the induction of COX-2 expression[19]. This increases the levels of prostaglandin E2 (PGE2), prostacyclin, and thromboxane A2, which are, in turn, vital for gastric mucosal protection and intestinal injury healing[19]. Rebamipide induces COX-2 expression through the phosphorylation and activation of 5′ adenosine monophosphate-activated protein kinase (AMPK) and acetyl-coenzyme A (CoA) carboxylase. This triggers a shift toward the anti-inflammatory nuclear factor erythroid 2-related factor 2 (NRF2) pathway from the nuclear factor kappa B (NF-κB) pathway. Acetyl-CoA carboxylase also inhibits T-cell differentiation, leading to interleukin (IL)-17 production, all of which support gastric protection[11]. Both COX-2 and PGE2 stimulate mucin secretion in the gastric mucosa, which contributes to the gastroprotective effects of rebamipide. Rebamipide also activates the AMPK, which further stimulates prostaglandin production in the gastric mucosa[21-23]. The drug also stimulates the expression of PGE2 receptor 4 and prostanoid receptors, which enhance GI motility and mucin secretion [by promoting the secretion of molecule mucin (MUC) 2 and increasing the gene expression of *MUC1* and *MUC4*][16,24,25]. In addition to all these effects, rebamipide reverses NSAID-induced intestinal injury by inhibiting the toll-like receptor 4/NF-κB pathway, which inhibits the production of the zonula-occludens (ZO-1) and claudin-1 proteins; this aids in restoring tight junctions by restoring the levels of ZO-1 and claudin-1 in the gastric mucosa[26]. Another gastroprotective effect of rebamipide is mediated through its angiogenic effects as the drug promotes angiogenesis in the gastric mucosa *via* two distinct mechanisms. The first is by upregulating the expression of the proangiogenic genes such as *vascular endothelial growth factor*, *epidermal growth factor receptor* (*EGFR*), and *fibroblast growth factor receptor-2* in gastric epithelial cells[19,27]. The second mechanism involves the direct proangiogenic effects of rebamipide on microvascular endothelial cells[27].

Ulcer healing effects: Acetic acid (AA)-induced colitis is an experimental model that resembles human ulcerative colitis (UC) across a range of histopathological characteristics[28]. In AA-induced colitis, rebamipide upregulates the expression of the silent information regulator-1/forkhead box O3a/nuclear factor NRF2 pathway and the peroxisome proliferator-activated receptor gamma cytoprotective signal, which ameliorates the effects of AA-induced colitis. Moreover, it also mitigates inflammatory signals and inflammatory cytokine secretion by suppressing the AA-induced activation of the

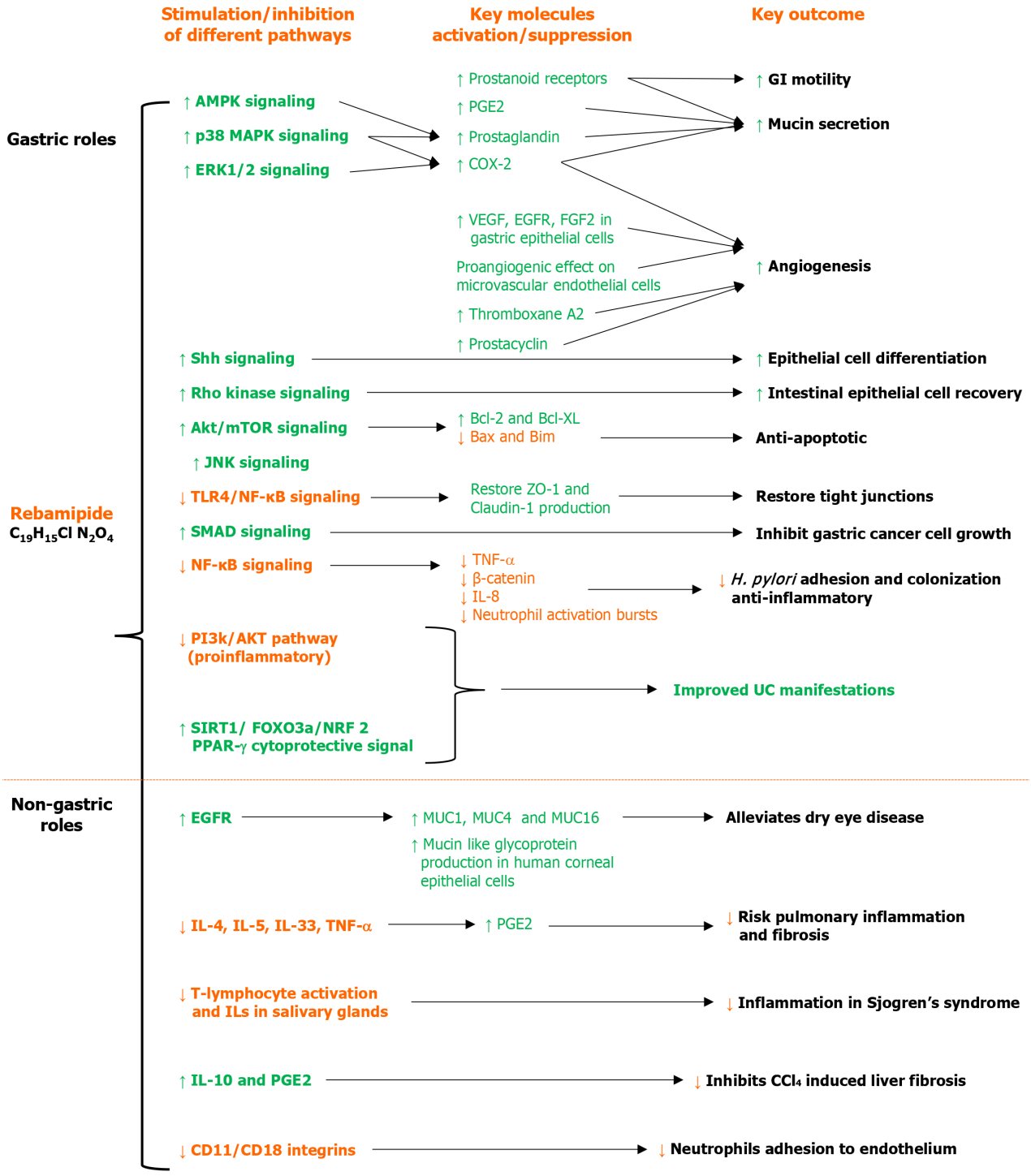

Figure 1 Molecular-level mechanisms of the action of rebamipide. AKT/mTOR: Protein kinase B/mammalian target of rapamycin; AMPK: Adenosine monophosphate-activated protein kinase; Bax: B-cell lymphoma 2 associated X; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma extra-large; Bim: B-cell lymphoma 2 interacting mediator of cell death; CCl_4: Carbon tetrachloride; CD: Cluster of differentiation; COX-2: Cyclooxygenase-2; EGFR: Epidermal growth factor receptor; ERK1/2: Extracellular signal-regulated protein kinase 1 and 2; FGF2: Fibroblast growth factor receptor-2; GI: Gastrointestinal; *H. Pylori*: *Helicobacter pylori*; IL: Interleukin; JNK: Jun N-terminal kinase; MUC: Mucin; NF-κB: Nuclear factor kappa B; PGE2: Prostaglandin E2; PI3K/AKT: Phosphoinositide 3-kinase/protein kinase B; PPAR-γ: Proliferator-activated receptor gamma; P38MAPK: P38 mitogen-activated protein kinase; Shh: Sonic hedgehog; SIRT1/FoxO3a/NRF2: Silent information regulator-1/forkhead box O3a/nuclear factor erythroid 2-related factor 2; SMAD: Suppressor of mothers against decapentaplegic; TLR4/NF-κB: Toll-like receptor 4/nuclear factor kappa B; TNF-α: Tumour necrosis factor alpha; UC: Ulcerative colitis; VEGF: Vascular endothelial growth factor; ZO-1: Zonula-occludens.

phosphoinositide 3-kinase/protein kinase B (AKT) pro-inflammatory pathway. Overall, rebamipide aids in reducing UC symptoms and healing the gastric mucosa[29]. In addition, studies have shown that rebamipide enhances intestinal cell recovery and ulcer wound healing by activating the Rho kinase pathway[19,30].

Cytoprotective/anticancer effects: During chemotherapy, rebamipide administration suppresses the cytotoxic effects of 5-fluorouracil and cisplatin by activating the ERK1/2, A kinase C-terminal domain, Jun N-terminal kinase, p38MAPK, and

mammalian target of rapamycin (mTOR) signalling pathways[19,31]. The activation of the ERK1/2 and p38MAPK signalling pathways increases mucin and COX-2 production, while the activation of the AKT/mTOR pathway increases the cellular levels of antiapoptotic factors B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma extra-large and reduces those of proapoptotic proteins Bcl-2 associated X and Bcl-2 interacting mediator of cell death[19]. It has also been shown that rebamipide triggers the suppressor of mothers against decapentaplegic (SMAD) signalling pathway, leading to the inhibition of human gastric cancer cell growth[32]. Rebamipide suppresses the induction of β-catenin (a proto-oncogene activated by *H. pylori* cytotoxin-associated protein A), which reduces the potential for tumour proliferation and metastasis [11].

Anti-H. pylori effects of rebamipide

Rebamipide has been reported to significantly increase both the short-term (ten days to two weeks) and long-term (4-12 weeks) eradication efficiency of anti-*H. pylori* therapy[33]. The drug's antagonistic effects on *H. pylori* include inhibiting bacterial adhesion to and colonization of the gastric mucosa and suppressing *H. pylori*-induced effects such as tumour necrosis factor alpha (TNF-α) production, β-catenin induction, NF-κB activation, IL-8 production, and neutrophil oxidative bursts[24,33,34]. Additionally, the urease produced by *H. pylori*, which amplifies the mucosal cytotoxicity caused by the bacterium, is inhibited by rebamipide[11]. Research also suggests that rebamipide restores the expression of sonic hedgehog (a signalling protein that plays a crucial role in epithelial cell differentiation) in the gastric mucosa of Mongolian gerbils with *H. pylori* infection; this led to the rejuvenation of the atrophied gastric mucosa in this animal model[35].

Effects of rebamipide on the cornea

Rebamipide enhances the expression of *MUC1*, *MUC4*, and *MUC16* genes through the activation of the EGFR pathway, leading to the increased production of mucin-like glycoproteins in human corneal epithelial cells[36]. Topical application of rebamipide, therefore, significantly ameliorates the symptoms related to dry eye disease and leads to notable improvements in corneal fluorescein staining, conjunctival lissamine green staining, and tear film break-up time in individuals with dry eye disease[37].

Other anti-inflammatory effects of rebamipide

Besides its ulcer-healing, cytoprotective, and anti-*H. pylori* effects, rebamipide also demonstrates anti-inflammatory properties in the lungs. It reduces the expression of inflammatory cytokines like IL-4, IL-5, IL-33, and TNF-α, while increasing PGE2 levels, which mitigates the risk of pulmonary inflammation and fibrosis[21]. Rebamipide inhibits neutrophil adhesion to the endothelium by suppressing cluster of differentiation (CD) 11, integrin subunit α-2/CD18, and integrin subunit β-2 expression[11]. It also hampers effector T-lymphocyte activation, IL production, and autoantibody generation, along with reducing nuclear factor NF-κB signalling activity in salivary glands, which relieved inflammation in mice models of Sjögren's syndrome[11]. In addition, rebamipide has been shown to halt carbon tetrachloride-induced liver fibrosis by curbing oxidative stress and inducing PGE2 and IL-10 production[11,38].

In summary, rebamipide has pleiotropic effects, which include elevating PGE2 production, increasing gastric mucus production, scavenging free radicals, inhibiting neutrophil activation, suppressing gastric mucosal inflammation, affecting apoptosis-regulating genes, and stimulating angiogenesis, all of which contribute to enhancing gastric and intestinal epithelial healing, in addition to its other effects[19].

EFFICACY OF REBAMIPIDE IN DIFFERENT GI CONDITIONS

Use of rebamipide in the management of gastric ulcers

Effectiveness against *H. pylori*: Rebamipide, when added to the classic triple regimen for *H. pylori* eradication, significantly increases the efficiency of the treatment without affecting the safety of the therapy[33]. Across three groups—one treated with omeprazole (20 mg) + amoxicillin (1000 mg) + clarithromycin (500 mg) (all medications twice a day) for ten days; another had the same regimen as the first group + rebamipide 100 mg, thrice a day, for ten days; and the third group had the same regimen as group 2, but with prolonged rebamipide administration (for twenty days)[39]. The efficacy of *H. pylori* eradication in the three groups was 82.3%, 84.4%, and 87.5%, which proved that the addition of rebamipide to the treatment regimen improved eradication rates, whether used simultaneously or for an extended period (Table 1)[11,27,33,39-48]. Additionally, patients in the third group exhibited accelerated healing of erosive and ulcerative lesions in the stomach and duodenum by the 21st and 28th days of treatment[39]. Post-*H. pylori* eradication, rebamipide can also be used to enhance gastric mucosa repair and reduce inflammation[39]. Rebamipide supplementation may also enhance *H. pylori* eradication in PPI-amoxicillin dual therapy[40]. In a randomized, double-blind, placebo-controlled study, the impact of rebamipide on gastric ulcer healing after one week of *H. pylori* eradication therapy showed that the healing rate in the rebamipide group was significantly higher than that in the placebo group (80% *vs* 66.1%, $P = 0.013$)[19].

Effectiveness in treating post-endoscopic submucosal dissection ulcers

In a study on the treatment of gastric ulcers induced by endoscopic resection, treatment with rebamipide led to superior rates and quality of ulcer healing (Table 1)[11,27,33,39-48]. Histological analysis also revealed reduced fibrosis at the ulcer site in the rebamipide group at two and four weeks post-treatment[19,42]. The addition of rebamipide to PPI therapy can also effectively treat larger ulcers and rebamipide + PPI regimens were found to be as effective as polaprezinc + PPI

Table 1 Efficacy and safety of rebamipide (alone or in combination) *vs* other drugs/treatment combinations used for the treatment of different gastrointestinal conditions

Condition	Comparison	Outcome	Adverse events	Ref.
H. pylori infection	Eradication therapy + rebamipide *vs* eradication therapy-rebamipide. Rebamipide after eradication therapy *vs* placebo after eradication therapy	Addition of rebamipide enhanced the effectiveness of *H. pylori* eradication treatment. Gastric ulcer healing after the eradication therapy was higher in the rebamipide group	No significant differences in AEs reported between the + rebamipide and rebamipide groups. The 55.2% reported AEs (diarrhea and abnormal taste sensation) in the rebamipide group and 51.7% reported AEs in the placebo group	Andreev *et al* [33], 2019. Andreev *et al* [39], 2018. Nishizawa *et al* [40], 2014
Post-endoscopic submucosal dissection ulcers	Rebamipide *vs* misoprostol	The occurrence rate of gastric ulcers was lower in the rebamipide group compared with the misoprostol group	Total severity score of GI symptoms and use of antacid were significantly lower in the rebamipide group than the misoprostol group	Kim *et al*[41], 2014
	2% rebamipide solution *vs* saline solution	Healing score was significantly higher in the rebamipide group	No AEs reported	Fujimoto *et al* [42], 2018
	Vonoprazan + rebamipide *vs* esomeprazole + rebamipide	Ulcer scar rates at week 4 were comparable across both groups	No AEs reported	Ichida *et al*[43], 2019
	Polaprezinc + pantoprazole *vs* rebamipide + pantoprazole	Ulcer healing rates were comparable across both groups	No AEs reported	Jung DH *et al* [48], 2021
	Pantoprazole/lansoprazole + rebamipide *vs* placebo	Ulcer reduction rate was higher for the pantoprazole/lansoprazole + rebamipide group	No AEs reported	Yan *et al*[44], 2019
Non-steroidal anti-inflammatory drug induced gastroenteropathy	Rebamipide + meloxicam *vs* lansoprazole + meloxicam	Fewer mucosal breaks were reported in the rebamipide + meloxicam group	Significantly fewer AEs were reported in the rebamipide + meloxicam group (31.5%) *vs* the lansoprazole + meloxicam group (65%)	Oh *et al*[45], 2022
Gastroesophageal reflux disease	Rebamipide + esomeprazole/lansoprazole *vs* esomeprazole/lansoprazole	Reductions in reflux symptoms were higher in the rebamipide group	No AEs reported	Bakulina *et al* [11], 2023
Gastritis	Rebamipide *vs* sucralfate	Reductions in GI symptoms (abdominal pain, belching, and acid reflux) and gastric mucosal inflammation were more apparent in the rebamipide group than in the sucralfate group	Rebamipide was associated with fewer AEs (specifically diarrhea)	Du *et al*[46], 2008
GI hemorrhage	Rabeprazole + rebamipide *vs* rabeprazole	Lower incidence of GI hemorrhage was noted in the rebamipide group	No significant differences seen in the occurrence of major adverse cardiac events	Jia *et al*[47], 2022
Ulcerative colitis	Rebamipide micro-enemas	Complete remission: 45%. Significant improvement: 18.2%. Slight improvement: 27.3%	No side effects reported	Tarnawski *et al* [27], 2004

AEs: Adverse effects; GI: Gastrointestinal; *H. pylori*: *Helicobacter pylori*.

regimens in healing ulcers four weeks after endoscopic submucosal dissection (ESD); furthermore, rebamipide can also be used in combination with vonoprazan, and this treatment regimen was found to be as effective as esomeprazole + rebamipide in promoting ESD ulcer healing (Table 1)[11,27,33,39-48]. Another study showed that a combination treatment of intravenous pantoprazole, oral rebamipide, and lansoprazole significantly reduced ESD ulcer size (especially for those > 35.5 mm in size) after four weeks of therapy compared to a placebo[44].

Although current first-line ulcer treatment guidelines do not include rebamipide as a therapeutic agent, it is worth noting that the extended use of antibiotics and PPIs carries various health risks, including *Clostridium difficile* infection, pneumonia, gastric cancer, bone fractures, and cognitive impairment[17,49]. Currently, there is substantial evidence to support the inclusion of rebamipide in these ulcer treatment regimens due to its multiple beneficial effects, few adverse effects (AEs), and excellent safety profile.

Use of rebamipide in treating NSAID-induced GI injuries

Several studies have shown that patients on long-term NSAID therapy have reduced incidences of GI bleeding if they are concomitantly prescribed rebamipide[50,51]. Studies have demonstrated that rebamipide can be as effective as standard treatments involving PPIs, H2-blockers, and misoprostol, and in some cases, it has even outperformed these conventional approaches for treating NSAID-induced GI injuries[50].

An evaluation of the different medications used to prevent NSAID-associated GI bleeding found that PPIs and H2 blockers were effective in preventing upper GI bleeding, while rebamipide and misoprostol were effective in preventing bleeding from all parts of the GI tract[19,51]. Therefore, rebamipide may be a potential alternative to PPIs for elderly chronic NSAID users who do not have a previous history of GI bleeding or perforation, or additional risk factors beyond age[17]. In patients on long-term NSAID therapy, rebamipide was as effective as misoprostol in preventing NSAID-induced peptic ulcers and was better tolerated than misoprostol[52]. Recently, a study utilizing the Food and Drug Administration Adverse Event Reporting System and the Japanese Adverse Event Reporting Database found that the risk of lower GI tract injury was diminished when rebamipide was combined with loxoprofen and diclofenac; this confirms its preventive effect on NSAID-induced GI tract injury[53].

A study on capsule endoscopy findings indicated that rebamipide was more effective than lansoprazole in preventing small intestine damage caused by NSAIDs (Table 1)[11,27,33,39-48]. Additionally, rebamipide has fewer side effects than lansoprazole, making it a potentially safer option for preventing NSAID-induced small intestinal damage (Table 1)[11,27,33,39-48]. When considering the potential issues of poor compliance and the AEs associated with misoprostol, rebamipide emerges as a clinically effective and safe alternative for treating NSAID-induced mucosal toxicity (Table 1)[11,27,33,39-48]. In patients aged > 60 years undergoing dual antiplatelet therapy after percutaneous coronary intervention, using a rabeprazole and rebamipide combination could decrease the risk and severity of upper GI hemorrhage[47]. Studies have also shown that rebamipide is effective in preventing small intestinal injury in those on low-dose aspirin[54].

These findings emphasize the importance of including rebamipide in gastroprotective regimes for those on NSAID therapy, especially considering its efficacy in preventing GI bleeding, UC, and gastric cancer.

Use of rebamipide in treating UC and preventing gastric cancer

Several studies have reported the anti-inflammatory effect of rebamipide enemas in addressing mild to moderate cases of distal hormone-resistant or hormone-dependent active UC as they contributed to the restoration of damaged intestinal epithelium[19]. Although the link between UC and gastric cancer is unclear, several studies have shown that UC may contribute to the occurrence of gastric cancer[55]. High-dose rebamipide administration (900 mg/day) was associated with a reduced risk of gastric cancer in patients who underwent ESD for early gastric neoplasms[51]. Rebamipide likely exerts these anticancer effects *via* its cytoprotective effects stemming from the activation of the SMAD signalling pathway (Figure 1).

Use of rebamipide in the management of gastroesophageal reflux disease

In addition to its use in treating PUD, NSAID-induced GI injuries, and UC, rebamipide is useful in the treatment of gastroesophageal reflux disease (GERD). Since immunological and inflammatory responses play a significant role in GERD development, the anti-inflammatory effects of rebamipide make it a promising option for the treatment of this disease[56].

Typically, GERD results from a disruption in oesophageal mucosal cytoprotection, which rebamipide helps to restore (Figure 1)[56]. Studies have indicated that PPI (like esomeprazole or lansoprazole) + rebamipide therapy is superior to esomeprazole/lansoprazole monotherapy in alleviating GERD symptoms[56-58]. Currently, PPIs and H2RAs are standard GERD treatments[59], and while there are no specific clinical recommendations for the use of rebamipide in GERD patients, evidence suggests that adding rebamipide to existing therapies enhances recovery and reduces GERD recurrence[56].

Use of rebamipide in treating functional dyspepsia, chronic gastritis, and carbohydrate intolerance

Apart from its use in treating major GI conditions, rebamipide is also used to alleviate conditions such as functional dyspepsia, which may be caused by disorders related to motility, dysfunction in sensory and motor functions associated with heightened sensitivity to mechanical and chemical stimuli, immune system activation, increased permeability of the lining in the upper small intestine, and disruptions in the autonomic and enteric nervous systems ; chronic gastritis, caused by *H. pylori*[60]; and carbohydrate intolerance, which are common challenges in gastroenterology[19]. In a multicentre study, 100-200 mg of rebamipide taken thrice daily, improved the quality of life of dyspeptic patients by alleviating flatulence, belching, abdominal pain, and post-meal discomfort[19,61]. Further, rebamipide positively impacted the clinical, endoscopic, and histological characteristics of chronic gastritis in PPI-refractory dyspeptic patients [19,62]. Studies have shown that rebamipide outperforms sucralfate by substantially reducing both clinical and endoscopic inflammation indicators[19,46]. Rebamipide exhibited a more potent inhibitory effect on mucosal inflammation in cases of chronic erosive gastritis when compared to sucralfate and was better tolerated than sucralfate[46].

In a recent Russian pilot study, researchers explored how rebamipide affected disaccharidase activity in 13 patients with enteropathy and impaired digestion. The primary clinical sign of the patients' condition was a reduced tolerance to food items, particularly carbohydrates, and a decline in the activity of membrane enzymes, specifically related to carbohydrates, within the mucous membrane of the small intestine[63]. Over 12-24 weeks, a daily dosage of 300 mg of rebamipide improved food tolerance, reduced flatulence, provided relief from abdominal pain, and resolved stool issues. The study showed significant increases in disaccharidase activity in the mucous membranes of the small intestine[64].

Safety, tolerability, and AEs associated with rebamipide

A meta-analysis in 2019 found no significant differences in the frequency of AEs among patients undergoing *H. pylori* eradication treatment with or without rebamipide[33]. A systematic review and meta-analysis of 15 randomized controlled trials reported that approximately 36.1% of patients reported AEs; however, no serious incidents were noted (Table 1)[11,27,33,39-48]. Adverse drug reactions to rebamipide are rare, with most side effects being mild and

manageable through dose adjustments[11].

The most commonly reported AEs are GI symptoms such as constipation, bloating, diarrhoea, and nausea[65]. Some minor changes in blood parameters, such as increased liver enzymes, blood urea nitrogen, alkaline phosphatase, leukopenia, lymphocytosis, and thrombocytopenia, have also been observed[12]. Rare AEs include hypersensitivity reactions and skin issues, which were seen in less than 1% of the patients. In the elderly population, 11 common yet non-serious AEs occurred within two to nine days of rebamipide administration; these included dyspepsia, somnolence, and edema[59]. Pulmonary AEs associated with rebamipide use are more frequently reported in elderly patients compared to younger adults[21]. However, rebamipide did not increase the risk of AEs compared to other drugs used to treat PUD and GERD such as misoprostol, pantoprazole, sucralfate, or rabeprazole (Table 1)[11,27,33,39-48] and was associated with a lower risk of pulmonary AEs compared to these drugs[21].

Advancements in rebamipide formulations

Although rebamipide is effective in reducing inflammation, enhancing mucoprotection, and accelerating ulcer healing, it has a low bioavailability due to low solubility and permeability[14]. To make rebamipide suitable for systemic use, a rebamipide prodrug, SA001, with improved systemic exposure compared to conventional rebamipide has been developed. It has a good safety profile when taken twice daily and is as effective as a thrice-daily 100 mg dose of rebamipide for treating erosive gastritis[65]. Efforts are also ongoing to develop sustained-release rebamipide tablets using various polymers[66].

Use of rebamipide for other indications

Rebamipide is an approved ophthalmic drug used to treat dry eye disease[67]. It is also effective as a mouthwash in preventing severe mucositis and stomatitis[68]. The drug is widely utilized by oral physicians and dermatologists for treating conditions like recurrent aphthous stomatitis and Behcet's syndrome[12] as it is well tolerated and can be administered conveniently. Additionally, rebamipide may influence osteoclast differentiation and the pathogenesis of temporomandibular joint osteoarthritis, offering a novel approach for the treatment of this disease[69].

Prospects in the use of rebamipide

The future of rebamipide in GI disease treatment looks promising, particularly as ongoing research explores its potential in treating conditions like irritable bowel syndrome and functional dyspepsia, and as a preventive against the development of gastric cancer[70,71]. Further studies and clinical trials will help to clarify its full potential, establish optimal dosing regimens, and assess its role in combination therapies. As a safe and effective gastroprotective agent, rebamipide could become an increasingly important part of the treatment landscape for chronic and complex GI conditions.

Rebamipide has also shown promise in preventing stenosis after oesophageal ESD[72] and as an adjuvant therapy for cancer patients[73]; it can also help reduce methotrexate-induced nephrotoxicity. Currently, trials are ongoing to investigate its use in managing conditions like gouty and rheumatoid arthritis, osteoarthritis, Sjögren's syndrome, bronchial asthma, vitiligo, atherosclerosis, and kidney and liver diseases. In traumatology, rebamipide accelerates bone regeneration, while in ophthalmology, it aids corneal epithelium regeneration and treating ocular damage[11,73,74]. Rebamipide also helps with chronic ocular graft-versus-host disease-related dry eye disease and vernal keratoconjunctivitis, offering a steroid-sparing option[75,76]. Additionally, rebamipide shows potential in treating male infertility, improving sperm health, and increasing pregnancy rates with minimal side effects[11].

CONCLUSION

In conclusion, rebamipide has emerged as a versatile and promising treatment option in Indian gastroenterology. It can be used to treat PUD, NSAID-related injuries, and various GI conditions and has an excellent efficacy, tolerance, and safety profile. Its potential also extends beyond the treatment of GI disorders, with evolving formulations and applications in fields like ophthalmology and oncology. Ongoing research continues to unveil the therapeutic potential of this drug. Overall, the diverse mechanisms of action, favourable safety profile, and evolving formulations of rebamipide position it as a versatile tool for managing not only GI-related, but also other diverse medical conditions in the Indian healthcare landscape.

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