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Review

Hyaluronic acid and chondroitin sulfate-based medical devices: formulations, esophageal mucosal protection, and their place in the management of GERD

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***Abstract*:** Gastroesophageal reflux disease (GERD) remains a challenging condition, even in the third millennium. For much of the past century, Schwartz's dictum—"No acid, no ulcer"—has shaped our approach to acid-related diseases, making acid suppression the cornerstone of therapy. Proton pump inhibitors (PPIs) are widely regarded as the standard treatment for GERD. However, they provide only symptomatic relief and do not address the underlying disease. Moreover, nearly 50% of patients experience limited or no response to PPIs in clinical practice. Recent advances in understanding GERD's pathophysiology, particularly the role of impaired mucosal integrity, have led to innovative therapeutic strategies. Among these, medical devices designed to prevent reflux or coat the esophageal mucosa and form a stable protective barrier represent a significant breakthrough. Esophageal mucosal protection is emerging as a promising approach, especially for patients who do not respond adequately to PPIs. While mucosal-protective agents such as sucralfate and irsogladine have long been available, their formulations have not been well-suited for esophageal protection. The rapid transit time of liquids through the esophagus (typically just a few seconds, even in a supine position) limits the duration of contact between active ingredients and the mucosa. However, hyaluronic acid and chondroitin sulfate-based medical devices have revolutionized the field by enabling active ingredients to adhere to the esophageal lining, ensuring prolonged contact and enhanced protection. Further advancements have led to the development of three distinct formulations (Esoxx™ One, Esoxx Defence, and Esoxx Protection), incorporating additional components, that is, Poloxamer 407, aluminum hydroxide, or natural remedies such as *Aloe vera* and honey. Each of these formulations offers unique physicochemical properties tailored to address both typical and atypical GERD symptoms. By leveraging the novel therapeutic approach of mucosal protection, these innovations aim to improve treatment outcomes and enhance patients' overall quality of life.

Plain language summary

Medical devices with esophageal mucosal protective activity for the management of GERD

Gastro-esophageal reflux disease (GERD), a condition where stomach acid or food flows back into the esophagus, is highly prevalent in the Western world and strongly impairs quality of life. It can cause symptoms like heartburn (a burning feeling in your chest), regurgitation (feeling like food is coming back up), and sometimes even coughing or a sore throat. GERD is still a tough condition to manage, even today. For many years, doctors have focused on reducing stomach acid to treat GERD, with proton pump inhibitors (PPIs) being the standard treatment. However, PPIs only help with the symptoms and don't tackle

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the root cause of the disease. Additionally, about half of patients don't experience enough relief from PPIs. New research into the causes of GERD has led to the development of new treatments, especially those designed to protect the lining of the esophagus. These treatments aim to prevent acid from damaging the esophagus or to create a protective barrier around it. Recently introduced medical devices containing hyaluronic acid (HA) and chondroitin sulfate (CS) that stick to the esophagus offer good protection of the esophageal mucosa, ultimately aiming to provide better results and a better quality of life for patients.

Keywords: GERD, NERD, LPR, diagnosis, treatment, PPIs, mucosal protection, hyaluronic acid, chondroitin sulphate, medical devices

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Introduction

Gastroesophageal reflux disease (GERD) is a common and chronic condition, affecting 10%–30% of the Western population.[1] This condition is characterized by the reflux of gastric contents into the esophagus, leading to symptoms and/or mucosal damage, as well as potential complications.[2–4] The pathogenesis of GERD is multifactorial, involving an interplay of anatomical, physiological, and lifestyle factors.[2,4] Recent studies have emphasized two key contributors in the onset of GERD symptoms: impairment of esophageal epithelial barrier and neuro-immune modulation, which may lead to increased reflux hypersensitivity or hyperalgesia.[5–7]

Given the multifactorial nature of GERD pathogenesis, management strategies must be similarly multifaceted.[8–10] Current pharmacologic approaches to address this clinically challenging condition are limited. Reflux inhibitors represent a promise unfulfilled, effective prokinetics are lacking and antidepressants, despite being effective in selected patients, give rise to adverse events in up to 32% of patients.[11–14] Antisecretory drugs (H_2-receptor antagonists, H_2RAs, and proton pump inhibitors (PPIs) remain therefore the mainstay of medical treatment for GERD. They act indirectly by reducing the amount and concentration of gastric secretion available for reflux, thus lessening the aggressive power of the refluxed material.[15,16] PPIs also reduce the size of the acid pocket and increase the pH (from 1 to 4) of its content.[17] The clinical efficacy of these drugs has been clearly shown in many studies and the superiority of PPIs over H_2RAs has been established beyond doubt.[18] The greater pharmacodynamic effect of PPIs depends on their ability to block the final step in the production of acid, regardless the secretory stimulus. Moreover, PPIs are relatively more effective during the daytime than the nighttime and this leads to a better control of post-prandial reflux events[18] and represent therefore the standard of care.[18–20]

While PPIs remain the cornerstone of GERD treatment,[18–20] they come with limitations.[8,21–25] The effectiveness of PPI therapy in patients with esophageal symptoms ranges from 40% to 80% but—compared to those with typical GERD manifestations—is less pronounced in subjects with extraesophageal symptoms.[3,26] Studies have shown that 50% of patients with atypical GERD symptoms do not respond to 8–12 weeks of PPI therapy, and 15% show only a partial response.[25,27,28] Consequently, there is growing interest in the development and utilization of novel treatments (be they drugs or medical devices) as add-on or alternative medications to traditional pharmacotherapy.[8,29,30] In particular, medical devices offer the potential for topical therapy, reduced use of systemic therapies and, likely, improved patient outcomes.

Furthermore, mucosal lesions caused by GERD may be treated with PPI therapy in combination with other active substances or devices with the aim of enhancing their healing effect and bolstering esophageal mucosal defenses.[31–33] These devices exert mucosal defensive action by creating a film over the esophageal mucosa and acting as a mechanical barrier against the noxious components of the refluxate.[31–33] Each product, based on its specific formulation, may be tailored for patients with different clinical characteristics and natural history.[32] Some studies have indeed

shown that adding alginate-containing formulations to PPI therapy increases the response rate in patients with nonerosive reflux disease (NERD) as well as those with laryngopharyngeal reflux (LPR, for review see Scarpignato et al.[30]). Furthermore, mucosal protectants (such as antacids, alginates, and sucralfate) have been shown to be more effective than placebo in treating mild reflux symptoms and offer a viable alternative to acid suppression in this patient population.[34] A Class III medical device, Poliprotect™, has recently been introduced to the market. It consists of a polysaccharide fraction derived from *Aloe vera*, *Malva sylvestris*, and *Althea officinalis*, along with a flavonoid fraction from *Glycyrrhiza glabra* and *Matricaria recutita*. This device, known for its long-lasting mucoadhesive properties, has been shown to reduce esophageal mucosal damage induced by an acid-pepsin-bile solution.[35] A recent randomized controlled trial evaluated the efficacy and safety of Poliprotect (administered five times a day for the first 2 weeks, followed by on-demand use) compared to omeprazole in alleviating heartburn and epigastric pain or burning. The study found that Poliprotect was non-inferior to standard-dose omeprazole in relieving symptoms of heartburn and epigastric burning in patients without erosive esophagitis (EE) or gastroduodenal lesions.[36] It is worth mentioning that the comparison was made with omeprazole 20 mg, a relatively low dose that exhibits considerable inter-individual variability.[37]

An innovative development in the treatment of acid-related diseases, including GERD, is the introduction of H^+,K^+-ATPase inhibitors, known as potassium-competitive acid blockers (P-CABs). These drugs block the K^+ exchange channel of the proton pump, leading to fast, competitive, and reversible inhibition of acid secretion. P-CABs provide a rapid and more significant increase in intra-gastric pH compared to delayed-release PPIs, while maintaining similar or even stronger antisecretory effects.[38] The duration of their action depends on the drug's half-life. In the treatment of severe reflux esophagitis (C&D according to the Los Angeles classification), vonoprazan (the first P-CAB) has shown superiority over PPIs. However, the benefits of P-CABs for NERD and extra-esophageal manifestations of GERD have yet to be fully established.[39]

Over the past decade, several investigations have highlighted the role of medical devices containing hyaluronic acid (HA) and chondroitin sulfate (CS), with or without an antacid component, in the treatment of GERD. In experiments, performed on a 3D reconstructed human esophageal epithelium, formulations combining HA and CS have demonstrated a barrier-protective effect, improving esophageal epithelial integrity thus preventing the transepithelial penetration of small, toxic, and acidic molecules from the lumen.[40] This *topical* protective effect arises from their ability to adhere to esophageal mucosa and form a long-lasting protective film over the epithelial layer.[40]

The aim of this paper is to outline the complexities of GERD spectrum and provide a rationale for incorporating the recently developed medical devices into the therapeutic armamentarium. By recognizing the diversity and overlap of GERD subtypes, and evaluating the efficacy and tolerability profile of these devices, clinicians can better tailor treatment strategies to address the specific needs of each patient, ultimately enhancing the quality of life for individuals living with this chronic and challenging condition.

Epidemiology of GERD

The prevalence of GERD has progressively increased over the past few decades. However, the occurrence of gastroesophageal reflux symptoms varies significantly across countries, even when similar definitions are applied. According to the latest review,[41] GERD prevalence estimates range from 18.1% to 27.8% in North America, 8.8% to 25.9% in Europe, 2.5% to 7.8% in East Asia, 8.7% to 33.1% in the Middle East, 11.6% in Australia, and 23.0% in South America. When considering only studies that used a weekly frequency of heartburn or regurgitation to define GERD, a recent meta-analysis reported a pooled prevalence of 13.3%.[1] GERD prevalence was notably higher in individuals aged 50 or older, smokers, NSAID users, and those who were obese, although these associations were relatively modest.

A prospective European study, the ProGERD study, found that 32.8% of patients with heartburn also experienced extra-esophageal symptoms. The prevalence was higher among those with erosive reflux disease (34.9%) compared to those with NERD (30.5%).[42] The most common GERD-associated disorders included chest pain

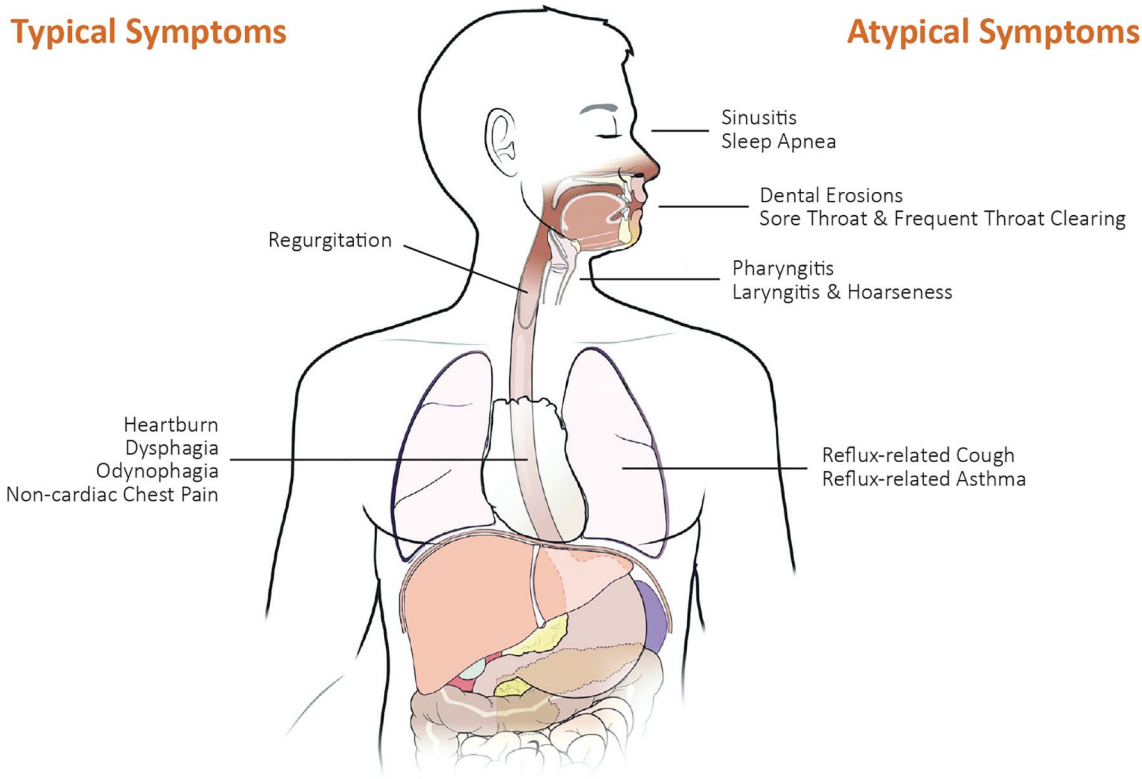

Figure 1. Clinical presentation of gastroesophageal reflux disease: typical and atypical symptoms.

(14.5%), chronic cough (13%), laryngeal disorders (10.4%), and asthma (4.8%).[42] However, this study only considered patients with concomitant heartburn, leaving out those who experienced only extra-esophageal symptoms. As a result, determining the prevalence of extra-esophageal symptoms in GERD patients without typical symptoms is more difficult, as diagnosing these cases is challenging. It is likely that the true prevalence of extra-digestive GERD is higher than previously estimated. For example, the incidence of LPR in published studies ranges from 5% to 30% (for review see Stabenau and Johnston[43]). However, due to the absence of a gold standard for diagnosing LPR, accurately assessing its prevalence and incidence remains problematic. In particular, some symptoms like chronic cough and wheezing have a significantly lower likelihood of direct reflux etiology compared with typical symptoms.[44] The complex pathophysiology of LPR and atypical GERD, which extends beyond gastroesophageal reflux to include autonomic nerve dysfunction and neural hypersensitivity, further complicates the issue.[45]

The clinical spectrum of GERD

GERD is a heterogeneous condition with a diverse and wide spectrum of symptoms and reflux profiles.[4] The frequency of clinical manifestations can vary from occasional episodes to daily symptoms.[46] GERD presents with a broad spectrum of symptoms that are typically classified into two categories: typical symptoms (such as heartburn, regurgitation, and non-cardiac chest pain) and atypical or extra-esophageal symptoms (Figure 1).[46] Extra-esophageal GERD encompasses a variety of conditions.[26] Pulmonary manifestations include asthma, bronchitis, microaspiration, and pulmonary fibrosis.[47] Ear, nose, and throat (ENT) symptoms comprise hoarseness, chronic cough, laryngitis. GERD may contribute to extraesophageal syndromes through either direct or indirect mechanisms.[48–50] Specifically, damage may result from the direct exposure of gastric acid to the mucosa of the tracheobronchial tree, laryngopharynx (including the vocal cords), middle ear, and nasal sinuses, or from the macro- and micro-aspiration of refluxed gastroduodenal contents.[48]

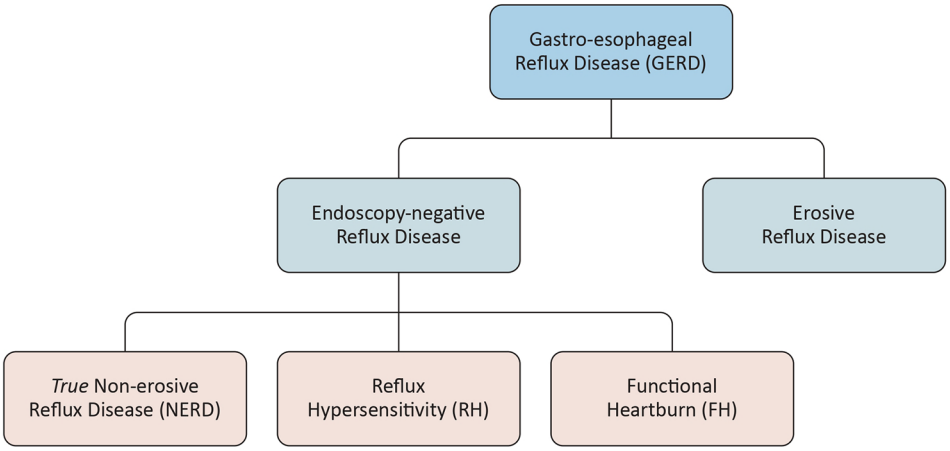

Figure 2. Phenotypic varieties of gastroesophageal reflux disease. In clinical practice, overlap between subgroups is possible.

NERD is the more common phenotype of GERD, accounting for 70%–80% of cases. It includes patients who experience typical symptoms but show no macroscopic mucosal damage at endoscopy.[51] In contrast, 20%–30% of patients may show esophageal erosions during endoscopy or develop complications such as Barrett Esophagus or esophageal stenosis.[52]

In clinical practice, GERD is empirically diagnosed based on typical esophageal symptoms and positive response to acid suppression.[53,54] However, some GERD patients may present with atypical symptoms, which can be extraesophageal or mixed in nature.[55] When refluxate reaches the proximal esophagus or even the laryngopharynx, it can lead to a condition known as LPR syndrome.[45,56] The larynx is significantly sensitive to acid and pepsin than the esophagus, with even a few reflux episodes being sufficient to cause substantial inflammation and damage to the epithelial lining.[57] Unlike the esophageal mucosa, this damage is often irreversible.[58] An Italian study found that both patients with erosive and non-erosive reflux disease experience at least one extra-esophageal symptom, particularly laryngeal symptoms, with similar prevalence rates (72% vs 79%, respectively).[59]

A comprehensive diagnosis of GERD typically involves a combination of clinical evaluation, response to acid suppression therapy, endoscopy, and functional tests such as pH-impedance monitoring.[44,54,60,61] When the evidence for GERD remains inconclusive, high-resolution manometry and advanced impedance metrics can provide clinicians with a more accurate diagnosis.[62–66] This approach is particularly useful for patients with persistent symptoms (both typical and atypical), who show no evidence of esophageal mucosal damage, especially when a trial of acid suppression has been ineffective.[25,67,68] Patients with endoscopy-negative reflux disease represent indeed a heterogeneous population, including those with true NERD, reflux hypersensitivity (RH), or functional heartburn (FH).[51] Only patients in whom acid is the primary trigger for symptom can benefit from acid suppression therapy.[54]

This diagnostic approach uncovers a broad phenotypic spectrum of GERD, ranging from endoscopy-negative reflux disease to EE (Figure 2).[4,69,70] Esophagitis refers to inflammation of the distal esophageal mucosa, which, if left untreated, can progress to erosions or ulcers. Esophageal erosions are the most common consequence of esophageal injury.[71]

The use of pH-impedance monitoring has revealed a high prevalence of esophageal functional disorders in patients with endoscopy-negative reflux disease.[4,51] In addition to *true* NERD (presence of symptoms and abnormal pH-impedance recording), RH is characterized by esophageal symptoms in the absence of clear structural, inflammatory, or functional abnormalities. Although the underlying mechanisms for esophageal hypersensitivity remain unclear, RH patients typically experience more frequently

weakly acidic reflux events, heightened sensitivity compared to those with FH, and a greater incidence of proximal reflux, factors that may contribute to their symptoms.[72,73] Notably, functional disorders such as functional dyspepsia and irritable bowel syndrome are more frequently associated with FH than with other phenotypes of non-erosive reflux disease.[74,75]

Patient journey in GERD

The "patient's journey" refers to the full experience a patient undergoes, starting from the recognition of symptoms or a health issue, through diagnosis, treatment, and ongoing management, and extending to follow-up care and long-term recovery or adaptation. It encompasses all interactions with healthcare providers, medical systems, and services, addressing both the physical and emotional aspects of the healthcare process.[76] This concept is often used to analyze and improve the overall patient experience, outcomes, and healthcare delivery. By understanding how patients navigate the healthcare system, the goal is to optimize their experiences, enhancing both health outcomes and patient satisfaction.[77,78]

GERD is a complex condition with a wide range of clinical manifestations and varying levels of severity. Treating GERD requires a personalized approach, tailored to the individual patient's symptoms, disease severity, and response to therapy.[28,79,80] Serious complications, including EE, Barrett's esophagus, and esophageal cancer, underscore the importance of effective management.[52]

General practitioners, as frontline healthcare providers, play a crucial role in managing GERD.[10] However, for more complex cases, the expertise of gastroenterologists and other specialists is essential. Collaborative care across multiple medical disciplines is necessary to address the diverse and multifaceted nature of the condition.[81] In clinical practice, gastroenterologists typically assess symptoms and medical history and may perform an upper gastrointestinal (GI) endoscopy when indicated to confirm a GERD diagnosis.[82] In patients with macroscopically normal esophageal mucosa, additional functional tests are needed to differentiate between true NERD, RH, or FH. Notably, pH-impedance monitoring can quantify both acid and non-acid reflux, while also correlating symptoms with reflux events.[44,65,83,84] Measuring baseline impedance is particularly informative, as it provides insight into mucosal integrity, enabling a comprehensive evaluation of the patient's condition.[84–86] Esophageal mucosal impedance can also be measured during endoscopy using specially designed catheters that pass through the operative channel.[87,88] However, this technique is typically available only at referral centers.

Patients presenting with chronic cough, laryngitis, and upper airway symptoms suggestive of GERD are often referred to an ENT specialist. After a thorough evaluation, the specialist may suspect extraesophageal GERD and recommend further diagnostic testing, which may include a consultation with a gastroenterologist.[26,56,66,89] In this context, the ENT specialist plays a key role in assessing and managing the impact of GERD on both the upper respiratory and digestive systems, providing valuable insights that allow a more comprehensive and coordinated treatment approach for GERD.

In conclusion, categorizing GERD patients into distinct phenotypic groups can help personalize treatment strategies, leading to more effective management. However, GERD therapy remains challenging, as acid suppression (even with co-medications) is not always sufficient. A significant proportion of GERD patients (20%–40%)[25,82,90] continue to experience symptoms despite medical treatment. In such cases, alternative therapies or mucosal protectants, either alone or in combination with acid suppressants, may achieve symptom relief and promote mucosal healing.[32,78]

HA and CS-based medical devices

The recent advances in understanding the pathophysiology of GERD, particularly the role of impaired mucosal integrity, have driven the development of novel medical devices designed to prevent reflux or coat the esophageal mucosa and form a stable protective film.[73,84,91–95] These devices can be broadly classified into two main categories[8]:

- *Raft-forming, alginate-based preparations*, which create a mechanical barrier against reflux and primarily act in the stomach.

- *Mucosal protectants*, such as HA and CS-based formulations, which primarily exert their effects in the esophagus.

Both types of medical devices are generally well tolerated, with mucosal protectants typically being more palatable. However, a key concern with these devices is the bioavailability of the active ingredients (namely HA and CS) at the level of the esophageal mucosa. The short transit time of liquids through the esophagus (typically less than 16 s, even in a supine position)[96] limits the duration of contact between the active ingredients and the mucosa.

To address this challenge, viscous liquid formulations that adhere to and coat the mucosal surface are used. These formulations not only help limit the contact of refluxed acid and pepsin with the epithelial cells[97] but also serve as a vehicle to deliver drugs locally within the esophagus.[98] In response to these considerations, bioadhesive formulations have been developed to prolong their contact with the mucosal lining.

Esoxx™ One

A Class III medical device, Esoxx™ One (Alfasigma, Bologna, Italy), was specifically designed and developed.[99,100] It is composed of a 1:2.5 ratio mixture of low molecular weight (80–100 kDa) HA and low molecular weight CS (10–20 kDa), dispersed in a bioadhesive carrier (Poloxamer 407). This combination forms a macromolecular complex that coats the esophageal mucosa, acting as a mechanical barrier to protect against the harmful components of refluxate.

Esoxx One is composed of two well-recognized physiological substances. One of them, HA, is a biologically active compound widely present in the body, playing a crucial role in cellular regulation through its interaction with specific receptors.[101] As a versatile glycosaminoglycan, it is a fundamental component of most extracellular matrices and is involved in essential physiological functions such as tissue regeneration, wound healing, morphogenesis, and structural organization of the matrix.[102] The biological significance of HA largely stems from its hydrophilic and hydrodynamic characteristics, which enable it to retain water and provide structural support. Hydrogels, which consist of cross-linked hydrophilic polymers, utilize these properties to act as scaffolds for tissue repair and regeneration, gradually breaking down through enzymatic degradation once healing is complete.[101] Moreover, the molecular weight of HA determines its effect on angiogenesis. The low molecular weight form promotes the development of new blood vessels and triggers a signaling cascade that drives endothelial cell growth and migration. Conversely, the native high molecular weight version inhibits angiogenesis, preventing blood vessel formation.[101] Topical applications of HA have been widely used to manage recurrent aphthous ulcers in the oral mucosa[103,104] providing rapid symptom relief. This therapeutic effect is likely enhanced by its dose-dependent anti-inflammatory properties, which further contribute to its effectiveness.[105]

CS is a naturally occurring glycosaminoglycan found within the extracellular matrix that surrounds cells. It is particularly abundant in cartilage, skin, blood vessels, ligaments, and tendons, where it plays a crucial role as a key component of proteoglycans.[106] Research indicates that CS contributes to various biological processes, including inflammation regulation, cell proliferation, differentiation, migration, tissue development, organ formation, wound healing, and even responses to infections.[107] These functions stem from its ability to interact with a diverse range of molecules, such as matrix components, growth factors, protease inhibitors, cytokines, chemokines, and adhesion molecules, through both specific and non-specific saccharide domains along its chains.[107] Additionally, this compound possesses immune-modulatory,[108] anti-inflammatory,[107,108] and antioxidant[109] properties. Beyond these broad interactions, CS can also bind selectively to bioactive molecules like pepsin. Studies have demonstrated that it can reduce peptic activity in both in vitro[110] and in vivo[111,112] settings. Historically, it has even been explored as a potential treatment for peptic ulcers.[113]

Poloxamer 407, composed of ethylene oxide and propylene oxide blocks, is a hydrophilic, nonionic surfactant known for its thermo-reversible properties, making it highly valuable in drug formulation. At room temperature, it remains in a fluid state, facilitating easy administration, while at body temperature, it transitions into a gel-like form, enabling sustained release of pharmaceutical compounds.[114] Formulations incorporating Poloxamer 407 have been shown to improve the

solubility of drugs with low water solubility and provide extended-release profiles in various pharmaceutical applications.[115] Additionally, its adhesive properties enhance the retention time of active agents within the gastrointestinal tract. Studies using an optical fiber spectrofluorimetric method in mice have demonstrated strong adhesion to the esophagus, allowing for effective drug diffusion into the mucosal lining.[114]

In accordance with European Council Directive 93/42/EEC,[116] the National Health Institute in Rome has designated this bioadhesive formulation as a class III medical device, intended for human use in the treatment or relief of diseases. Generally, medical devices in this category function through physical mechanisms, such as mechanical action, serving as a protective barrier, or providing structural support or replacement for organs and bodily functions.

This medical device was studied in in vitro and ex vivo models to evaluate its filming and barrier protective activity.

The mucoadhesive properties of Esoxx One were assessed for its ability to adhere to a partially purified mucin layer type II from pig stomach. The formulation remained attached to a 12% (w/w) mucin layer, even when the support was rotated 90° or when the film was rinsed with water to simulate washout during swallowing.[117]

The rheological behavior was evaluated using the amplitude sweep technique. The flow curves showed that Esoxx One exhibited a Newtonian-like behavior, with viscosity remaining unaffected by mechanical stress.[117] This characteristic suggests that the product could stay attached to the esophageal surface during ingestion, despite the mechanical stresses that typically reduce the viscosity of liquid formulations. In the rheological comparison, the formulation demonstrated the ability to interact with mucin, as evidenced by a rheological synergy. Specifically, the viscosity of the formulation/mucin mixture was higher than the sum of the viscosities of the individual components (formulation and pure mucin). This synergy points to a strong interaction between the liquid formulation and mucin, implying bioadhesive behavior with mucin, the primary component of the esophageal lining.[117]

The film-forming and barrier effects of this medical device were studied using a 3D reconstructed human esophageal epithelium model. This model is developed after 5 days of air-lifted culture of the K510 human epithelial cell line (derived from squamous cell carcinoma) in a chemically defined medium, and it fully replicates the morphology of the esophageal epithelium.[118] The film-forming capacity was evaluated by tracking the kinetics of transepithelial caffeine passage, while the barrier function was assessed by measuring transepithelial electrical resistance (TEER) and lucifer yellow (LY) permeability as markers of paracellular passage.[40,117,119,120] Compared to placebo (an identical formulation without the functional ingredients, i.e., HA and CS), caffeine passage after 15 min was significantly reduced, with this difference persisting at both 1 and 2 h. TEER remained unchanged after application of Esoxx One, indicating preserved barrier integrity, while LY permeability was reduced by both the formulation and placebo, suggesting a decrease in intercellular gaps or a strengthening of cell–cell junctions.[120]

The mucosal protective effects of Esoxx One were further evaluated by measuring the expression of the tight junction protein, claudin-4, and the back diffusion of H^+ ions. Exposure of tissue to 0.1 M HCl or simulated gastric fluid (SGF) led to a significant reduction in claudin-4 expression (by 90% and 50%, respectively). However, pre-treatment with Esoxx One completely prevented this decline in expression. As a result, the back diffusion of H^+ ions following HCl or SGF application was significantly reduced by the mucoadhesive formulation, as indicated by pH measurements taken from both the apical and basolateral surfaces. These findings suggest that the reduction in H^+ ion back diffusion is due to the preservation of mucosal integrity, as reflected by the maintenance of tight junction protein expression, rather than a direct neutralizing effect of Esoxx One. Notably, the acid-neutralizing capacity (ANC) of the formulation was minimal, measuring only 3.73 ± 0.18 mEq.[120]

An ex vivo experimental study using a swine model demonstrated that perfusing the esophageal lumen with Esoxx One prevents the increase in mucosal permeability and tissue damage induced by acid and/or pepsin.[121] Building on these findings, two double-blind,

placebo-controlled studies showed that short-term treatment with Esoxx One provides significant and rapid symptom relief in patients with GERD.[122,123]

In the first study, 52% of patients in the Esoxx One group achieved complete symptom relief, compared to only 10% in the placebo group ($p < 0.01$). Furthermore, the time to complete symptom relief was significantly shorter in the Esoxx One group (38 min) compared to the placebo group (65 min).[122] In the subsequent randomized, double-blind, placebo-controlled, two-way crossover study, 20 patients with endoscopy-negative reflux disease, who had symptoms unresponsive to antisecretory treatment were given one spoon of Esoxx One four times daily (away from meals, with a double dose before bedtime). After just 2 weeks of treatment, there was a marked and statistically significant reduction in the total Symptom Severity Index score, as well as in the individual scores for heartburn and regurgitation.[123] The substantial reduction in regurgitation episodes is particularly relevant, given that regurgitation tends to be less responsive to acid suppression than heartburn in GERD patients.[124] This suggests that persistent regurgitation may be a contributing factor to incomplete treatment response.

Several underlying mechanisms contribute to the failure of PPI treatment. They include patient-related (e.g., lack of compliance), physician-related (e.g., misdiagnosis), and drug-related (e.g., short duration of action) mechanisms.[125,126] Currently, the most effective approach to deal with PPI-refractory reflux disease is making a precise diagnosis, by adding a functional evaluation (e.g., high-resolution manometry and pH-impedance recording) to upper GI endoscopy. Including biopsy (and subsequent histological examination) of the "*macroscopically-normal*" mucosa during endoscopic examination can help to identify microscopic mucosal damage.[127,128] Microscopic esophagitis has proven to be a reliable diagnostic marker, distinguishing FH from GERD, and could help guide more appropriate treatment.[91] However, these methods, while effective, are time-consuming and costly, making them impractical for routine clinical practice.

An alternative, simpler approach could involve combination therapy, where drugs with different mechanisms of action are added to PPIs. Until very recently, only alginate-containing formulations[129,130]—given as *add-on* medications—proved to be capable of improving symptom control in endoscopy-negative patients. For those with motility-related symptoms, such as nausea, postprandial fullness, and early satiety, a trial with prokinetics may be warranted.[131] A recent meta-analysis confirmed that combining prokinetics with PPIs is more effective than PPIs alone in managing GERD.[132] However, safety issues and the dichotomy between symptoms and delayed gastric emptying in the prokinetic effect (where drugs can improve symptoms without accelerating emptying rate or vice-versa or affect neither)[133] make this treatment option challenging and unpredictable. In contrast, adding mucosal protectants, which are both effective and safe, to PPIs could offer a promising alternative.

To test this hypothesis, a double-blind, placebo-controlled trial evaluated the efficacy and safety of Esoxx One in combination with acid suppression, compared to acid suppression alone, in patients with endoscopy-negative reflux disease.[134] This design was chosen to reflect real-world clinical practice outside referral centers, where advanced diagnostic tools are not typically available. The results of this study demonstrated that adding Esoxx One (administered 1 h after each meal and at bedtime for 14 consecutive days) to acid suppression led to significantly higher symptom relief in GERD patients compared to acid suppression alone. Both primary and secondary endpoints were achieved in a larger proportion of patients. Additionally, the combination therapy was well-tolerated, with the total number of adverse events comparable to that in the placebo group.[134] The synergistic effect of Esoxx One with PPIs observed in this study suggests that adding mucosal protection to acid suppression may benefit a broader group of NERD patients, providing both symptom relief and improved health-related quality of life, and potentially reducing the incidence of treatment failures. While PPIs are effective in providing symptom relief *over time* in both erosive and non-erosive disease, as shown in studies comparing PPIs with P-CABs[135,136] this combination therapy may achieve in 2 weeks the same symptom relief that PPIs typically provide in 4 weeks. For patients seeking quicker symptom relief, this time-dependent therapeutic advantage could be particularly valuable.

Following a case report suggesting that adding Esoxx One to intensive acid suppression accelerates the healing of severe esophagitis,[137] a randomized clinical trial was conducted to evaluate the effects of combining mucosal protection with PPIs in patients with C and D esophagitis.[31] After 4 weeks, 100% of patients in the combined treatment group showed a downgrading of mucosal lesions, compared to 80% in the PPI-only group ($p < 0.01$). Additionally, the proportion of patients experiencing symptom relief, including heartburn, retrosternal pain, odynophagia, and dysphagia, was significantly higher in those receiving both mucosal protection and acid suppression.[31] Notably, in this study, the standard PPI dose was used (while a double dose is often prescribed for severe esophagitis), and the treatment duration was only 4 weeks, rather than the typical 8–12 weeks.[138,139]

During endoscopy, biopsy samples were collected and analyzed by immunohistochemistry to quantify the expression of Ki67 (a marker of cell proliferation), as well as claudin-1 and claudin-4. As expected, Ki67 expression was elevated, and tight junction proteins were reduced in the erosive mucosa of the esophagus. After therapy, Ki67 expression decreased, while levels of claudin-1 and claudin-4 increased. Notably, in tissues from patients treated with Esoxx One in combination with PPIs, these changes were significantly more pronounced, indicating a more complete restoration of mucosal integrity.[31]

A meta-analysis of three studies involving 181 patients with erosive GERD, published in Russian, assessed the efficacy of combination therapy. All studies followed a uniform design, with primary endpoints including complete epithelialization of esophageal erosions and full resolution of heartburn, measured 28 days after starting therapy. The results showed that combination therapy with Esoxx One (10 mL, four times daily) and pantoprazole (40 mg daily) was significantly more effective than monotherapy for healing of esophageal erosions at 28 days (Relative Risk (RR): 1.267, 95% CI: 1.082–1.483, $p = 0.003$). However, there was no significant difference between the groups in terms of complete resolution of heartburn on day 28 (RR: 1.638, 95% CI: 0.660–4.067, $p = 0.287$).[140]

In addition to its effectiveness in reflux esophagitis, Esoxx One was also found to be efficacious in radiation-induced esophagitis, a common complication and dose-limiting factor in oncologic treatments. In an open-label study, 41 patients undergoing radio- or radio-chemotherapy for lung, gastric, or esophageal cancer received the medical device either as a standalone treatment or in combination with supportive therapy (antacids, antisecretory compounds, anti-inflammatory drugs, opioids). In the combination group, Esoxx One was administered either concurrently with supportive drugs or as an adjuvant treatment following inadequate response to the supportive therapy. Symptom relief was substantial in nearly all patients, allowing 95% of them to successfully complete their oncologic treatment.[141]

In addition to typical GERD symptoms, extra-esophageal manifestations can also benefit from esophageal mucosal protection. In a Polish open-label study, 51 patients with LPR symptoms, such as throat clearing, hoarseness, and cough after eating or while lying down, and laryngoscopic signs, including redness, vocal fold edema, and posterior commissure hypertrophy, were evaluated.[142] The Reflux Symptom Index (RSI) and Reflux Finding Score (RFS) were assessed before and after 2 weeks of treatment with Esoxx One, in combination with PPIs. While patients were not completely symptom-free, a significant reduction in symptoms was observed across the entire patient population. After treatment, the RFS fell below the diagnostic threshold for LPR. Compared to baseline, 98% of patients showed substantial improvement in laryngeal lesions.[142] While these promising results are encouraging, they should be confirmed in larger, well-designed clinical trials.

Although originally developed for *esophageal* mucosal protection, coating of the gastric mucosa is inevitable following esophageal emptying, making its efficacy for gastric complaints unsurprising. In a retrospective, double-blind, randomized placebo-controlled study, the effects of Esoxx One were evaluated in patients with endoscopy-confirmed gastritis.[143] The study assessed symptoms (upper abdominal pain/discomfort, measured by the visual analog scale (VAS)) and mucosal lesions (blood oozing, hyperemia, and edema) before and after therapy. Compared to placebo, the treatment group showed a significant reduction in VAS pain after 5 weeks of therapy ($p < 0.001$). Additionally, 68% of patients exhibited endoscopic healing of

mucosal lesions, while 24% showed moderate improvement. The improvement in mucosal lesions was consistent with the reduction in dyspeptic symptoms.[143] While these findings suggest potential for expanding the clinical use of Esoxx One beyond esophageal conditions, caution is warranted in interpreting the results, as the study lacked appropriate histological characterization of gastritis and testing for *Helicobacter pylori* infection.

Esoxx™ Defence

The success of mucosal protection combined with acid suppression has led to the development of a modified medical device, Esoxx Defence, which incorporates a buffering agent. Among the available antacids, aluminum hydroxide is one of the most effective, rapidly neutralizing gastric acid (ANC: 29 mEq/15 mL) and increasing intragastric pH.[144] The ratio between the active ingredients of the medical device is 1:20:40 for CS, HA, and aluminum hydroxide, respectively. This antacid also exhibits pH-dependent binding and inactivation of pepsin, as well as bile-binding capacity comparable to that of colestyramine.[144,145] These pharmacological properties counterbalance two key aggressive factors of the refluxate (i.e., gastric acid and pepsin), which can damage not only the esophageal mucosa but also the upper airways.[57,146,147] Furthermore, aluminum hydroxide exerts site- and cyto-protective effects through the synthesis and release of endogenous prostaglandins.[148] When administered to GERD patients, antacids reduce esophageal acid exposure and are effective in providing symptom relief for both occasional heartburn and short-term treatment.[145,149] Due to its poor absorption, aluminum hydroxide is more suitable for long-term treatment compared to PPIs. While PPIs are very effective, they are not without adverse effects, some of which are plausible and predictable while others are rare and idiosyncratic.[19,150,151] Although much of the evidence linking PPI use to serious long-term conditions is weak, with very low odd ratios,[89,152] the potential risks associated with this drug class cannot be ignored. In contrast, aluminum hydroxide, being short-acting and poorly absorbed, avoids the hypergastrinemia[153] and disruption of gut microbiota[154,155] commonly seen with PPIs.

To leverage the physiological esophageal clearing mechanism of salivary secretion,[156] a melt-in-mouth tablet formulation was chosen. This type of tablet differs from other fast-dissolving forms, such as orodispersible tablets. While orodispersible tablets disintegrate into smaller particles upon contact with saliva, melt-in-mouth tablets dissolve or melt more smoothly into a liquid form.

This type of formulation offers several advantages[157,158]:

- **No need for water:** Melt-in-mouth tablets dissolve without the need for water, making them convenient for patients who may have difficulty swallowing pills or for those on the go.
- **Rapid dissolution:** Since the tablet dissolves quickly in the mouth, the drug is immediately topically available, leading to a quick onset of action.
- **Ease of administration:** Particularly beneficial for pediatric and geriatric populations, or individuals with dysphagia, as these tablets dissolve quickly in the mouth.
- **Portability and convenience:** Patients who struggle with swallowing regular tablets or capsules may be more likely to adhere to their medication regimen when using melt-in-mouth formulations, even while traveling.

The potential of Esoxx Defence to restore impaired mucosal integrity in GERD was evaluated in 32 patients with EE greater than Los Angeles grade B.[159] Baseline mucosal impedance, a marker of mucosal integrity, was measured at the distal (3 cm), mid (9 cm), and proximal (15 cm) esophagus before and after 2 weeks of therapy with this medical device. Patients were randomized in a 1:1 ratio to receive either Esoxx Defence (six tablets per day, taken after each meal, mid-morning, mid-afternoon, and at bedtime) or an oral antacid or alginate (as needed) for 14 ± 2 days. Secondary outcomes included symptom relief, palatability, safety, and tolerability. While baseline impedance was similar between groups, after treatment significant improvements in distal, mid, and proximal esophageal impedance were observed only in the Esoxx Defence group. The medical device demonstrated favorable results in terms of symptom relief, palatability, safety, and tolerability.[159]

In the same cohort of patients from the study, the authors conducted a thorough symptom

evaluation using the Reflux Disease Questionnaire (RDQ) and assessed health-related quality of life (HRQL) through the GERD-HQRL questionnaire. Initially, mean RDQ and GERD-HQRL values were similar between the groups. However, after treatment, a significant reduction in scores was observed only in the patients treated with Esoxx Defence.[160] These findings suggest that 2 weeks of therapy with the medical device can effectively improve both GERD-related symptoms and quality of life in patients with severe esophagitis.

Alginate-containing formulations are among the most widely used over-the-counter treatments for GERD, typically providing quick and effective symptom relief.[145,149] However, this is not always the case. To evaluate the effectiveness of Esoxx Defence in GERD patients who have a poor response to alginates, an open-label study was conducted with 40 patients, 22 of whom were on stable PPI therapy.[161] The primary endpoint was the reduction in weekly heartburn episodes, while secondary endpoints included GERD-related symptoms, patient satisfaction, and safety. The GERD Impact Scale (GIS) questionnaire was administered at baseline and again after 7 and 14 days of treatment. Results showed a significant ($p < 0.0001$) and progressive decrease in both the number of days with heartburn episodes and the GIS score compared to baseline, with improvements observed during both the first and second weeks of treatment. The reductions in heartburn episodes and GIS scores were similar in patients both on and off PPI therapy. The treatment was safe, well-tolerated, and received high patient satisfaction, with 46.2% rating it as "very good" and 43.6% as "good."[161] These results suggest that Esoxx Defence can overcome the refractoriness to other GERD medications, often observed in clinical practice.

Extra-esophageal manifestations of GERD pose significant diagnostic and therapeutic challenges, often proving refractory to PPIs, even when combined with additional medications. A randomized trial was conducted to assess the effectiveness of *Esoxx Defence* in alleviating atypical GERD symptoms, such as hoarseness, cough, throat clearing, sore throat, voice changes, globus sensation, and postnasal drip.[162] Patients in the trial were given *Esoxx Defence* in addition to omeprazole (40 mg daily), or omeprazole alone for 6 weeks. After this period, responders to the combination therapy were randomized to either continue *Esoxx Defence* alone or receive no further medication. Results showed a progressive decrease in the RSI for both groups, with patients receiving the combination treatment showing a greater reduction (7.9 ± 7.0) compared to those on omeprazole alone (12.3 ± 8.9). The difference however did not reach statistical significance. Nevertheless, a statistically significant improvement was observed for certain individual RSI items in the *Esoxx Defence* plus omeprazole group. For patients who responded to combination therapy, the RSI score further decreased under continued treatment, while patients without any therapy did not experience any improvement.[162] These findings suggest that combining *Esoxx Defence* with acid suppression may offer a rational approach to managing extra-esophageal GERD symptoms. Despite the promising results, the study's main limitation lies in its patient selection process, which was based solely on symptoms rather than objective measures of reflux and extra-esophageal manifestations. This, combined with the potential for a type II error (due to lack of statistical significance), underscores the need for a larger, more rigorous clinical trial to confirm these preliminary findings.

Burning mouth syndrome (BMS) is a condition characterized by a chronic, often unexplained sensation of burning or discomfort in the mouth, without visible oral abnormalities. The sensation can affect the tongue, lips, gums, or roof of the mouth. It's considered a complex disorder with multiple possible etiologies, and it can significantly impact the quality of life.[163] Treatment of BMS is challenging due to its complex and often multifactorial nature, the primary goal being symptom relief.[164] BMS and GERD are distinct conditions, but they can be interconnected in certain cases. While there is no definitive causal link between the two, both research and clinical experience suggest that extra-esophageal manifestations of GERD, particularly LPR, may contribute to or exacerbate BMS symptoms.[165,166] When stomach acid reaches the mouth, it can irritate the oral mucosa, leading to discomfort, a burning sensation, or dryness. This acid exposure may also affect the tongue and palate, causing a burning feeling, especially in individuals who are already susceptible to BMS. In some instances, the acidic exposure may disrupt the protective mechanisms of the oral tissues, increasing their sensitivity.[165,166]

In a study of 81 patients with BMS, 76 (93.8%) reported experiencing multiple pharyngeal reflux events during hypopharyngeal-esophageal pH-impedance monitoring. Thirty-two of these patients had both LPR and GERD.[165] In another large study involving 500 patients with established GERD, 11.2% identified BMS as their *primary* symptom, a prevalence comparable to that of chronic cough and pharyngitis.[167] Additionally, BMS was present in 124 patients with both typical and atypical GERD symptoms. Of these, 82 patients were treated for 3 months with Esoxx Defence (a tablet taken three times daily, after breakfast, after lunch, and at bedtime). Among them, 31.7% reported slight improvement, while 28% experienced almost complete remission of oral symptoms.[167] While these results may not appear particularly striking, they are still noteworthy, especially considering the difficulty in treating BMS, which is often refractory to most therapies.

Esoxx™ Protection

The clinical evidence presented above clearly shows that HS and CS-based formulations (with or without antacids) are highly effective in treating both erosive and non-erosive reflux disease. However, while Esoxx One and Esoxx Defence provide clinically significant symptom relief, they are not fully effective in addressing the extra-esophageal manifestations of GERD, including LPR and BMS.

The esophagus harbors a diverse microbial community, with Gram-positive bacteria (mainly Streptococcus) being more common in healthy individuals, while Gram-negative bacteria are more prevalent in those with GERD or Barrett's esophagus.[22,168,169] Gram-negative bacteria release lipopolysaccharides, which can activate the Toll-like receptors 4 (TLR4) and nuclear factor kappa B (NF-κB) pathways, triggering an increase in pro-inflammatory cytokine production.[168] In patients with acute reflux esophagitis, inflammation of the esophagus is predominantly characterized by T-lymphocytes, with papillary and basal cell hyperplasia occurring before surface cell erosion.[170] These observations suggest that reflux-induced inflammation may be driven by cytokines rather than by direct acid-induced chemical injury.[171] Additionally, refluxed acid and bile help stabilize hypoxia-inducible factor-2α (a key transcription factor that plays a critical role in cellular and systemic responses to hypoxia) in esophageal epithelial cells. This stabilization enhances the production of pro-inflammatory cytokines, attracting T-lymphocytes and other immune cells that contribute to esophageal damage.[171] These observations point to a potential link between esophageal dysbiosis and inflammation.

Oxidative stress refers to the imbalance between reactive oxygen species (ROS) and the body's ability to neutralize them with antioxidants. In both GERD and LPR, the oxidative stress plays a central role in mucosal tissue damage to mucosal tissues and symptom development.[172] Preclinical studies have shown that exposure to gastric refluxate induces ROS production as a response to chemical insults. These ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, can damage cellular components such as lipids, proteins, and DNA, leading to cell death, inflammation, and tissue remodeling.[172] Under normal conditions, the body's antioxidant enzymes (such as superoxide dismutase (SOD), glutathione peroxidase, and catalase) neutralize ROS.[173] However, chronic reflux exposure can impair this defense system, resulting in sustained oxidative damage. In children with reflux disease, the severity of EE has been shown to correlate with the intensity of oxidative stress, with a linear relationship between tissue SOD levels and the De Meester score.[174] In patients with LPR, low blood levels of antioxidant enzymes and elevated oxidative stress have also been reported.[175] Additionally, reduced levels of nitric oxide metabolites in exhaled breath concentrate of children with LPR further suggest an increased oxidative stress in the airways.[176]

Given these pathophysiological insights, targeting both inflammation and oxidative stress mechanisms in digestive and extra-digestive GERD could offer promising new strategies for managing this chronic and challenging condition. While, anti-inflammatory drugs, whether steroidal or non-steroidal, are highly effective, they are systemic medications (not permitted as ingredients of medical devices[116]) and came with significant adverse events.[177] To address inflammation and oxidative stress more safely, a new medical device, namely, Esoxx Protection, has been developed specifically for extra-esophageal manifestations of reflux disease and airway protection. This formulation incorporates *Aloe vera* and honey to further enhance therapeutic outcomes.

Aloe vera, a succulent plant widely known for its therapeutic properties, is often used in traditional medicine for various ailments. Its pharmacological properties are primarily attributed to its bioactive compounds, which include polysaccharides, glycoproteins, anthraquinones, saponins, and enzymes. *Aloe vera* displays a wide range of pharmacological effects,[178] many of which could be relevant in the treatment of GERD:

- Anti-inflammatory effect, mainly due to the polysaccharide acemannan.
- Antioxidant activity, attributed to its content in vitamin C, vitamin E, and beta-carotene.
- Mucosal protective thanks to the mucilage content present in the gel and to aloin (an anthraquinone compound) and barbaloin, which enhance mucosal integrity. These anthraquinone glycosides also display a laxative action provided they are given (and absorbed) in sufficient amount to stimulate bowel motility and reduce colonic water absorption.
- Demulcent properties (i.e., it forms a protective film) that may help soothe and protect the irritated lining of the esophagus.
- Wound-healing properties, due to stimulation of growth factor and collagen, which also might contribute to healing of esophageal damage.
- Antimicrobial (antibacterial, antifungal, and antiviral) activity.
- An acid buffering capacity has been also reported.

In a pilot, controlled trial, 79 patients with GERD symptoms referred for upper GI endoscopy were randomized to receive one of three treatments: *Aloe vera* syrup (standardized to 5.0 mg of polysaccharide per mL) at a dose of 10 mL per day, omeprazole (20 mg daily), or ranitidine (150 mg twice daily) for 4 weeks. The frequency of heartburn, regurgitation, belching, dysphagia, nausea, vomiting, and flatulence was assessed at 2 and 4 weeks. *Aloe vera* significantly reduced all symptoms except vomiting, with efficacy comparable to that of omeprazole and ranitidine.[179]

Honey has been used for medicinal purposes for centuries, particularly in the treatment of gastrointestinal conditions.[180] It contains a range of beneficial compounds, including small amounts of proteins, enzymes, amino acids, minerals, trace elements, vitamins, aroma compounds, and polyphenols.[181] Current research suggests that darker honeys (such as buckwheat, heather, and honeydew) and multifloral varieties tend to have more pronounced therapeutic properties than lighter or unifloral honeys. The pharmacological properties of honey, including anti-inflammatory, antioxidant, antimicrobial, and soothing effects, make it an effective remedy for conditions like GERD and LPR.[182]

Honey reduces intracellular ROS generation and helps restore intracellular glutathione levels.[183] It may also reduce inflammation by inhibiting the production of nitric oxide and prostaglandin E_2.[184] Honey contributes to the management of GERD symptoms by coating the esophagus and stomach lining, thereby preventing the upward flow of food and gastric juice. Furthermore, honey may stimulate tissue regeneration in the lower esophageal sphincter, helping to reduce the likelihood of acid reflux.[185] Honey can be used alongside conventional therapies in treating reflux esophagitis.[186]

Similar to *Aloe vera*, honey acts as a natural demulcent, forming a protective coating over mucous membranes. When consumed, honey coats the lining of the throat and esophagus, providing a soothing layer that helps alleviate the burning and irritation commonly associated with acid reflux. The thick, viscous texture of honey not only reduces discomfort in the throat but also helps alleviate irritation in the larynx and vocal cords, which is often seen in individuals with LPR. This protective action can also help calm a persistent cough and reduce hoarseness.[187] Additionally, honey is a natural humectant, meaning it attracts and retains moisture. For individuals with LPR, dry throat and irritated mucous membranes are common symptoms of reflux. Honey's ability to hydrate the throat can offer relief from dryness and promote healing.[187]

A recent, randomized, placebo-controlled trial investigated the effects of Manuka honey, which originates from New Zealand or Australia, in patients with GERD. Manuka honey is known for its high antioxidant capacity, attributed to its significant content of polyphenols, particularly flavonoids, phenolic acids,[179] and methylglyoxal, a compound found in trace amount in other honeys.[180] The study included 35 GERD patients, all of whom had heartburn or dyspeptic symptoms and were referred from General Practitioners. Participants were given Manuka honey (5 g three

times daily) or placebo in addition to PPIs for a duration of 4 weeks. After 2 weeks of treatment, 86.7% of patients in the Manuka honey group experienced symptom improvement, compared to only 26.7% in the placebo group. At the 4-week, symptom improvement was seen in 100% of the Manuka group versus 40% in the placebo group. Additionally, 73.3% of those in the Manuka group showed a downgrading of mucosal lesions on endoscopy, while only 33.3% of placebo-treated patients showed similar improvements.[181] It is important to note that, due to the variability in composition among different types of honey, the results of this study may not be directly applicable to other honey varieties. Nonetheless, the findings are promising and highlight the potential of honey, either on its own or in combination with other active ingredients, to address some unmet needs in GERD treatment.

The film-forming effect of Esoxx Protection was evaluated and compared to Esoxx One using a 3D reconstructed human esophageal epithelium model, as described above. This was done by measuring the kinetics of transepithelial caffeine passage.[119] Both devices showed a significant reduction in caffeine permeation at 1 and 2 h, compared to the negative control. After 1 h, Esoxx Protection demonstrated a significantly lower caffeine permeation rate (0.19% caffeine/min) than Esoxx One (0.30% caffeine/min, $p < 0.0001$). By 2 h, however, the permeation rates between the two devices were comparable.[119] The LY flux data at 15 min supported the caffeine permeation results. While Esoxx Protection (11.0%, $p < 0.05$) significantly reduced LY flux compared to the untreated control (15.8%), Esoxx One (14.9%, NS) did not show a significant reduction.[119] These findings suggest that Esoxx Protection reduces intercellular gaps or strengthens cell–cell junctions.

Demonstrating the potential synergy of combining *Aloe vera* and honey with HA and CS is challenging due to the unique properties of these two natural remedies. However, a clinical study in patients with LPR is currently underway to explore the therapeutic advantages of this combination (Esoxx Protection).

Discussion

GERD continues to be a challenging and difficult-to-treat condition even in the third millennium. Current pharmacologic treatments offer limited solutions. Reflux inhibitors, while promising, remain largely ineffective, and effective prokinetics are still lacking. Although antidepressants may benefit select patients, they are associated with adverse events in up to 32% of cases.[11–14] As a consequence, antisecretory drugs (H_2RAs and PPIs) remain the cornerstone of medical management for GERD. These drugs work indirectly by reducing the volume and concentration of gastric secretions available for reflux, thereby diminishing the harmful effects of the refluxed material.[15,16] The clinical efficacy of PPIs has been well-established in numerous studies, with their superiority over H_2RAs firmly demonstrated.[18]

As previously discussed, PPI-refractory reflux disease—both erosive and non-erosive—does exist.[24,25,188–190] Current pharmacologic options for managing PPI-refractory GERD are also limited. These include switching to a PPI with less dependence on the CYP2C19 enzyme, adding an H_2RA at night, using alginate-based formulations, or, as a last resort, trialing a gamma-aminobutyric acid agonist like baclofen. In cases where hypersensitivity or anxiety is suspected, neuromodulation with antidepressants may be beneficial for PPI non-responders.[25,28,188] Although research does not strongly support the routine use of prokinetic therapies for GERD, their addition could be worthwhile in patients with concurrent motility-related symptoms or established gastroparesis.[131]

Recent experimental and clinical studies have revealed that—in patients with GERD—esophageal mucosal integrity is impaired and that this feature represents a hallmark of the disease.[191,192] This understanding of GERD pathophysiology has led to the development of a new therapeutic approach: esophageal mucosal protection. While drugs with mucosal protective activities, such as sucralfate and irsogladine (the latter not marketed in Europe) have long been available, the current formulations were not suitable for esophageal protection.[8] The HA and CS-based medical devices have been advanced in the field since they allow the active ingredients to adhere to the esophageal mucosa, effectively coating the esophageal lining and providing a sufficient contact time with the esophageal mucosa.

A thorough review of the literature shows that the efficacy of PPIs in treating extra-digestive GERD

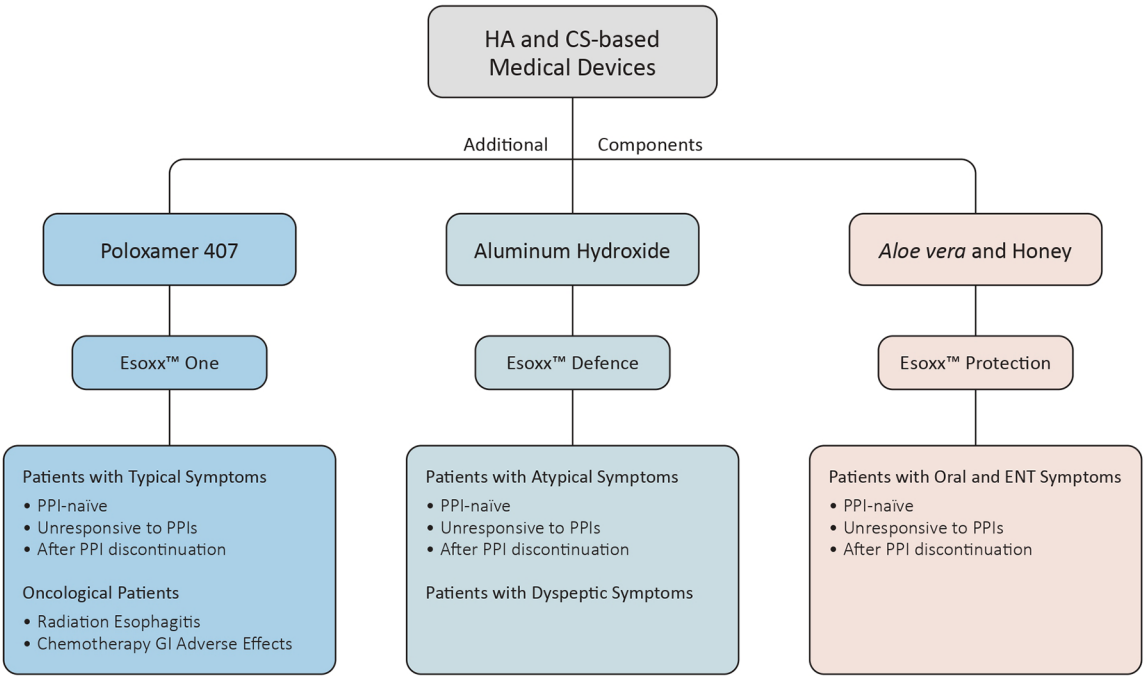

Figure 3. Medical devices with esophageal mucosal protective activity. Formulations and suggested therapeutic use in patients with gastroesophageal reflux disease.

is less consistent compared to their effectiveness in patients with typical symptoms.[3] In extra-digestive GERD, the complexity of patient presentations is often matched by the challenge of diagnosing reflux as the underlying cause of their symptoms. Diagnostic tools such as upper GI endoscopy and pH-impedance monitoring are limited by poor sensitivity, while laryngoscopy suffers from poor specificity in identifying reflux in this patient population.[193] An empirical trial of PPIs may be an appropriate initial approach for both diagnosing and managing potential extra-digestive symptoms linked to reflux. However, symptom resolution often requires higher PPI doses and longer treatment durations than those typically used for conventional GERD.[194] It is important to note that while PPI therapy and twice-daily dosing for extra-digestive GERD are not officially approved indications, they are nonetheless recommended by both gastroenterology[195,196] and other specialty guidelines.[197–199]

Several drugs, including prokinetics[200–202] and N-acetylcysteine,[203] have been tested as *add-on* treatments, but their results have been inconsistent. In contrast, mucosal protectants appear to be a more promising option for improving treatment efficacy in these patients.

The Esoxx One and Esoxx Defence medical devices are especially suitable for patients unresponsive to PPI therapy or for those with extra-esophageal manifestations of reflux disease. In addition to being used in combination with PPIs, these devices can be used alone in mild cases of GERD or after discontinuing acid suppression with the hope to maintain remission and prevent recurrence. The Esoxx Protection, including *Aloe vera* and honey, appears more suitable for patients with oral and/or ENT manifestations of GERD, such as cough, throat clearing, hoarseness, and sore throat (Figure 3).

Conclusion

A personalized treatment strategy tailored to each patient's specific phenotype is essential for effective GERD management. While PPIs remain the cornerstone of therapy, combining acid suppression with mucosal protection—especially in PPI-resistant cases—emerges as a promising approach. The use of HA- and CS-based medical devices,

each with its unique composition and therapeutic activities, holds the potential for more effective management of both typical GERD symptoms and extra-esophageal manifestations. This comprehensive approach could significantly improve treatment outcomes and enhance patients' overall quality of life.

Declarations

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Not applicable.

Consent for publication

Not applicable.

Author contributions

Carmelo Scarpignato: Conceptualization; Writing – original draft; Writing – review & editing.

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Competing interests

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References

1. Eusebi LH, Ratnakumaran R, Yuan Y, et al. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. *Gut* 2018; 67: 430–440.
2. Savarino E, Bredenoord AJ, Fox M, et al. Advances in the physiological assessment and diagnosis of GERD. *Nat Rev Gastroenterol Hepatol* 2018; 15: 323.
3. Scarpignato C and Gatta L. Acid suppression for management of gastroesophageal reflux disease:

benefits and risks. In: Morice AH and Dettmar PW (eds.) *Reflux aspiration and lung disease*. Cham: Springer International Publishing, 2018, pp.269–291.

4. Savarino V, Marabotto E, Zentilin P, et al. Pathophysiology, diagnosis, and pharmacological treatment of gastro-esophageal reflux disease. *Exp Rev Clin Pharmacol* 2020; 13: 437–449.
5. Ustaoglu A, Nguyen A, Spechler S, et al. Mucosal pathogenesis in gastro-esophageal reflux disease. *Neurogastroenterol Motil* 2020; 32: e14022.
6. Ribolsi M, Gyawali CP, Savarino E, et al. Correlation between reflux burden, peristaltic function, and mucosal integrity in GERD patients. *Neurogastroenterol Motil* 2020; 32: e13752.
7. Ustaoglu A and Woodland P. Sensory phenotype of the oesophageal mucosa in gastro-oesophageal reflux disease. *Int J Mol Sci* 2023; 24: 2502.
8. Scarpignato C, Hongo M, Wu JCY, et al. Pharmacologic treatment of GERD: where we are now, and where are we going? *Ann N Y Acad Sci* 2020; 1482: 193–212.
9. Visaggi P, Bertin L, Pasta A, et al. Pharmacological management of gastro-esophageal reflux disease: state of the art in 2024. *Expert Opin Pharmacother* 2024; 25: 2077–2088.
10. Hungin APS, Scarpignato C, Keefer L, et al. Review article: rethinking the "ladder" approach to reflux-like symptom management in the era of PPI "resistance"—a multidisciplinary perspective. *Aliment Pharmacol Ther* 2022; 55: 1492–1500.
11. Kahrilas PJ and Boeckxstaens G. Failure of reflux inhibitors in clinical trials: bad drugs or wrong patients? *Gut* 2012; 61: 1501–1509.
12. Looijer-van Langen M and Veldhuyzen van Zanten S. Does the evidence show that prokinetic agents are effective in healing esophagitis and improving symptoms of GERD? *Open Med* 2007; 1: e181–e183.
13. Weijenborg PW, de Schepper HS, Smout AJ, et al. Effects of antidepressants in patients with functional esophageal disorders or gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol* 2015; 13: 251–259.
14. Ford AC, Quigley EM, Lacy BE, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol* 2014; 109: 1350–1365.
15. Galmiche JP, Letessier E and Scarpignato C. Treatment of gastro-oesophageal reflux disease in adults. *Br Med J* 1998; 316: 1720–1723.
16. Scarpignato C, Pelosini I and Di Mario F. Acid suppression therapy: where do we go from here? *Dig Dis* 2006; 24: 11–46.
17. Kahrilas PJ, McColl K, Fox M, et al. The acid pocket: a target for treatment in reflux disease? *Am J Gastroenterol* 2013; 108: 1058–1064.
18. Savarino V, Di Mario F and Scarpignato C. Proton pump inhibitors in GORD. An overview of their pharmacology, efficacy and safety. *Pharmacol Res* 2009; 59: 135–153.
19. Scarpignato C, Gatta L, Zullo A, et al. Effective and safe proton pump inhibitor therapy in acid-related diseases—a position paper addressing benefits and potential harms of acid suppression. *BMC Med* 2016; 14: 179.
20. Barberio B, Visaggi P, Savarino E, et al. Comparison of acid-lowering drugs for endoscopy negative reflux disease: systematic review and network meta-analysis. *Neurogastroenterol Motil* 2023; 35: e14469.
21. Scarpignato C and Hunt RH. Proton pump inhibitors: the beginning of the end or the end of the beginning? *Curr Opin Pharmacol* 2008; 8: 677–684.
22. Hunt RH and Scarpignato C. Potent acid suppression with PPIs and P-CABs: what's new? *Curr Treatment Options Gastroenterol* 2018; 16: 570–590.
23. Savarino V, Marabotto E, Furnari M, et al. Latest insights into the hot question of proton pump inhibitor safety—a narrative review. *Dig Liv Dis* 2020; 52: 842–852.
24. Rettura F, Bronzini F, Campigotto M, et al. Refractory gastroesophageal reflux disease: a management update. *Front Med (Lausanne)* 2021; 8: 765061.
25. Zerbib F, Bredenoord AJ, Fass R, et al. ESNM/ANMS consensus paper: diagnosis and management of refractory gastro-esophageal reflux disease. *Neurogastroenterol Motil* 2021; 33: e14075.
26. Ghisa M, Della Coletta M, Barbuscio I, et al. Updates in the field of non-esophageal gastroesophageal reflux disorder. *Exp Rev Gastroenterol Hepatol* 2019; 13: 827–838.
27. Yadlapati R, Pandolfino JE, Lidder AK, et al. Oropharyngeal ph testing does not predict response to proton pump inhibitor therapy in patients with laryngeal symptoms. *Am J Gastroenterol* 2016; 111: 1517–1524.

28. Yadlapati R, Gyawali CP and Pandolfino JE. AGA Clinical Practice Update on the personalized approach to the evaluation and management of GERD: expert review. *Clin Gastroenterol Hepatol* 2022; 20: 984–994.
29. Savarino E, Zentilin P, Marabotto E, et al. Drugs for improving esophageal mucosa defense: where are we now and where are we going? *Ann Gastroenterol* 2017; 30: 585–591.
30. Scarpignato C, Sloan JA, Wang DH, et al. Gastrointestinal pharmacology: practical tips for the esophagologist. *Ann N Y Acad Sci* 2020; 1481: 90–107.
31. Bordin DS, Livzan MA, Mozgovoi SI, et al. The mucosal protection in the treatment of erosive reflux esophagitis: mechanisms for restoring epithelial permeability. A Randomized Clinical Trial. *J Gastrointestin Liver Dis* 2024; 33: 455–462.
32. Savarino V, Visaggi P, Marabotto E, et al. Topical protection of esophageal mucosa as a new treatment of GERD. *J Clin Gastroenterol* 2025; 59(3): 197–205
33. Samuels TL, Yan K, Patel N, et al. Alginates for protection against pepsin-acid induced aerodigestive epithelial barrier disruption. *Laryngoscope* 2022; 132: 2327–2334.
34. Surdea-Blaga T, Bancila I, Dobru D, et al. Mucosal protective compounds in the treatment of gastroesophageal reflux disease. A position paper based on Evidence of the Romanian Society of Neurogastroenterology. *J Gastrointestin Liver Dis* 2016; 25: 537–546.
35. Khalil M, Perniola V, Lanza E, et al. Poliprotect®, a medical device made of substances, potently protects the human esophageal mucosa challenged by multiple agents: evidence from in vitro and ex vivo electrophysiological models. *Int J Mol Sci* 2025; 26: 791.
36. Corazziari ES, Gasbarrini A, D'Alba L, et al. Poliprotect vs omeprazole in the relief of heartburn, epigastric pain, and burning in patients without erosive esophagitis and gastroduodenal lesions: a randomized, controlled trial. *Am J Gastroenterol* 2023; 118: 2014–2024.
37. Sharma BK, Walt RP, Pounder RE, et al. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. *Gut* 1984; 25: 957–964.
38. Scarpignato C and Hunt RH. The potential role of potassium-competitive acid blockers in the treatment of gastroesophageal reflux disease. *Curr Opin Gastroenterol* 2019; 35: 344–355.
39. Scarpignato C and Hunt RH. Potassium-competitive acid blockers: current clinical use and future developments. *Curr Gastroenterol Rep* 2024; 26: 273–293.
40. Pellegatta G, Spadaccini M, Lamonaca L, et al. Evaluation of human esophageal epithelium permeability in presence of different formulations containing hyaluronic acid and chondroitin sulphate. *Med Devices (Auckl)* 2020; 13: 57–66.
41. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014; 63: 871–880.
42. Jaspersen D, Kulig M, Labenz J, et al. Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. *Aliment Pharmacol Ther* 2003; 17: 1515–1520.
43. Stabenau K and Johnston N. How I approach laryngopharyngoesophageal reflux (LPR). *Curr Gastroenterol Rep* 2021; 23: 27.
44. Barrett CM, Patel D and Vaezi MF. Laryngopharyngeal reflux and atypical gastroesophageal reflux disease. *Gastrointest Endosc Clin N Am* 2020; 30: 361–376.
45. Savarino E, Marabotto E, Bodini G, et al. Epidemiology and natural history of gastroesophageal reflux disease. *Minerva Gastroenterol* 2017; 63: 175–183.
46. Gyawali CP, Yadlapati R, Fass R, et al. Updates to the modern diagnosis of GERD: Lyon consensus 2.0. *Gut* 2024; 73: 361–371.
47. Savarino E, Carbone R, Marabotto E, et al. Gastro-oesophageal reflux and gastric aspiration in idiopathic pulmonary fibrosis patients. *Eur Respir J* 2013; 42: 1322–1331.
48. Wong RK, Hanson DG, Waring PJ, et al. ENT manifestations of gastroesophageal reflux. *Am J Gastroenterol* 2000; 95(Suppl. 8): S15–S22.
49. Krause AJ and Yadlapati R. Review article: diagnosis and management of laryngopharyngeal reflux. *Aliment Pharmacol Ther* 2024; 59: 616–631.
50. Martinucci I, de Bortoli N, Savarino E, et al. Optimal treatment of laryngopharyngeal reflux disease. *Ther Adv Chron Dis* 2013; 4: 287–301.
51. Savarino E, Zentilin P and Savarino V. NERD: an umbrella term including heterogeneous subpopulations. *Nat Rev Gastroenterol Hepatol* 2013; 10: 371–380.

52. Savarino E, de Bortoli N, De Cassan C, et al. The natural history of gastro-esophageal reflux disease: a comprehensive review. *Dis Esophagus* 2017; 30: 1–9.

53. Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2022; 117: 27–56.

54. Scarpignato C. Poor effectiveness of proton pump inhibitors in non-erosive reflux disease: the truth in the end! *Neurogastroenterol Motil* 2012; 24: 697–704.

55. Richter JE and Rubenstein JH. Presentation and epidemiology of gastroesophageal reflux disease. *Gastroenterology* 2018; 154: 267–276.

56. Lechien JR, Vaezi MF, Chan WW, et al. The Dubai definition and diagnostic criteria of laryngopharyngeal reflux: the IFOS consensus. *Laryngoscope* 2024; 134: 1614–1624.

57. Samuels TL and Johnston N. Pepsin in gastroesophageal and extraesophageal reflux: molecular pathophysiology and diagnostic utility. *Curr Opin Otolaryngol Head Neck Surg* 2020; 28: 401–409.

58. Barry DW and Vaezi MF. Laryngopharyngeal reflux: more questions than answers. *Cleve Clin J Med* 2010; 77: 327–334.

59. Dore MP, Pedroni A, Pes GM, et al. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. *Dig Dis Sci* 2007; 52: 463–468.

60. Gyawali CP, Tutuian R, Zerbib F, et al. Value of pH-impedance monitoring while on twice-daily proton pump inhibitor therapy to identify need for escalation of reflux management. *Gastroenterology* 2021; 161: 1412–1422.

61. Siboni S, Sozzi M, Kristo I, et al. The Milan score: a novel manometric tool for a more efficient diagnosis of gastro-esophageal reflux disease. *EUG J* 2024; 12: 552–561.

62. Ribolsi M, Savarino E, Rogers B, et al. High-resolution manometry determinants of refractoriness of reflux symptoms to proton pump inhibitor therapy. *J Neurogastroenterol Motil* 2020; 26: 447–454.

63. Ribolsi M, Savarino E, Rogers B, et al. Patients with definite and inconclusive evidence of reflux according to lyon consensus display similar motility and esophagogastric junction characteristics. *J Neurogastroenterol Motil* 2021; 27: 565–573.

64. Ribolsi M, Frazzoni M, Marabotto E, et al. Novel impedance-pH parameters are associated with proton pump inhibitor response in patients with inconclusive diagnosis of gastro-oesophageal reflux disease according to Lyon Consensus. *Aliment Pharmacol Ther* 2021; 54: 412–418.

65. Frazzoni L, Frazzoni M, De Bortoli N, et al. Application of Lyon Consensus criteria for GORD diagnosis: evaluation of conventional and new impedance-pH parameters. *Gut* 2022; 71: 1062–1067.

66. Calabrese F, Pasta A, Bodini G, et al. Applying Lyon consensus criteria in the work-up of patients with extra-oesophageal symptoms—a multicentre retrospective study. *Aliment Pharmacol Ther* 2024; 59: 1134–1143.

67. Marabotto E, Savarino V, Ghisa M, et al. Advancements in the use of 24-hour impedance-pH monitoring for GERD diagnosis. *Curr Opin Pharmacol* 2022; 65: 102264.

68. Frazzoni M, Frazzoni L, Ribolsi M, et al. Applying Lyon Consensus criteria in the work-up of patients with proton pump inhibitory-refractory heartburn. *Aliment Pharmacol Ther* 2022; 55: 1423–1430.

69. Park CH, Seo SI, Kim JS, et al. Treatment of non-erosive reflux disease and dynamics of the esophageal microbiome: a prospective multicenter study. *Sci Rep* 2020; 10: 15154.

70. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101: 1900–1920.

71. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; 45: 172–180.

72. Savarino E, Zentilin P, Tutuian R, et al. Impedance-pH reflux patterns can differentiate non-erosive reflux disease from functional heartburn patients. *J Gastroenterol* 2012; 47: 159–168.

73. Savarino V, Marabotto E, Zentilin P, et al. Esophageal reflux hypersensitivity: non-GERD or still GERD? *Dig Liver Dis* 2020; 52: 1413–1420.

74. Savarino E, Pohl D, Zentilin P, et al. Functional heartburn has more in common with functional dyspepsia than with non-erosive reflux disease. *Gut* 2009; 58: 1185–1191.

75. de Bortoli N, Frazzoni L, Savarino EV, et al. Functional heartburn overlaps with irritable bowel syndrome more often than gerd. *Am J Gastroenterol* 2016; 111: 1711–1717.

76. Bolz-Johnson M, Meek J and Hoogerbrugge N. “Patient Journeys”: improving care by patient

involvement. *Eur J Hum Genet* 2020; 28: 141–143.

77. Davies EL, Bulto LN, Walsh A, et al. Reporting and conducting patient journey mapping research in healthcare: a scoping review. *J Adv Nurs* 2023; 79: 83–100.
78. Pasta A, Pelizzaro F, Marabotto E, et al. Patient journey in gastroesophageal reflux disease: real-world perspectives from Italian gastroenterologists, primary care physicians, and ENT specialists. *Ther Adv Gastroenterol* 2024; 17: 17562848241239590.
79. Yadlapati R and Pandolfino JE. Personalized approach in the work-up and management of gastroesophageal reflux disease. *Gastrointest Endosc Clin N Am* 2020; 30: 227–238.
80. Marabotto E, Pasta A, Calabrese F, et al. The clinical spectrum of gastroesophageal reflux disease: facts and fictions. *Visc Med* 2024; 40: 242–249.
81. Yadlapati R, Dakhoul L, Pandolfino JE, et al. The quality of care for gastroesophageal reflux disease. *Dig Dis Sci* 2017; 62: 569–576.
82. Savarino V, Marabotto E, Zentilin P, et al. Pharmacological management of gastro-esophageal reflux disease: an update of the state-of-the-art. *Drug Des Devel Ther* 2021; 15: 1609–1621.
83. Roman S, Gyawali CP, Savarino E, et al. Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. *Neurogastroenterol Motil* 2017; 29: 1–15.
84. Savarino E, Marabotto E and Savarino V. Recent insights on functional heartburn and reflux hypersensitivity. *Curr Opin iGastroenterol* 2022; 38: 417–422.
85. Visaggi P, Mariani L, Svizzero FB, et al. Clinical use of mean nocturnal baseline impedance and post-reflux swallow-induced peristaltic wave index for the diagnosis of gastro-esophageal reflux disease. *Esophagus* 2022; 19: 525–534.
86. Rengarajan A, Savarino E, Della Coletta M, et al. Mean nocturnal baseline impedance correlates with symptom outcome when acid exposure time is inconclusive on esophageal reflux monitoring. *Clin Gastroenterol Hepatol* 2020; 18: 589–595.
87. Patel DA, Higginbotham T, Slaughter JC, et al. Development and validation of a mucosal impedance contour analysis system to distinguish esophageal disorders. *Gastroenterology* 2019; 156: 1617–1626.e1611.
88. Ates F, Yuksel ES, Higginbotham T, et al. Mucosal impedance discriminates GERD from non-GERD conditions. *Gastroenterology* 2015; 148: 334–343.
89. Ahmed TF, Khandwala F, Abelson TI, et al. Chronic laryngitis associated with gastroesophageal reflux: prospective assessment of differences in practice patterns between gastroenterologists and ENT physicians. *Am J Gastroenterol* 2006; 101: 470–478.
90. Kahrilas PJ, Savarino E, Anastasiou F, et al. The tapestry of reflux syndromes: translating new insight into clinical practice. *Br J Gen Pract* 2021; 71: 470–473.
91. Savarino E, Zentilin P, Mastracci L, et al. Microscopic esophagitis distinguishes patients with non-erosive reflux disease from those with functional heartburn. *J Gastroenterol* 2013; 48: 473–482.
92. Martinucci I, de Bortoli N, Savarino E, et al. Esophageal baseline impedance levels in patients with pathophysiological characteristics of functional heartburn. *Neurogastroenterol Motil* 2014; 26: 546–555.
93. de Bortoli N, Martinucci I, Savarino E, et al. Association between baseline impedance values and response proton pump inhibitors in patients with heartburn. *Clin Gastroenterol Hepatol* 2015; 13: 1082–1088.
94. Giuliano E, Paolino D, Fresta M, et al. Mucosal applications of poloxamer 407-based hydrogels: an overview. *Pharmaceutics* 2018; 10: 159.
95. Ribolsi M, Frazzoni M, Marchetti L, et al. Proximal esophageal impedance baseline increases the yield of impedance-pH monitoring for GERD diagnosis and is associated with heartburn response to PPI. *Neurogastroenterol Motil* 2023; 35: e14612.
96. Blackshaw LA, Bordin DS, Brock C, et al. Pharmacologic treatments for esophageal disorders. *Ann N Y Acad Sci* 2014; 1325: 23–39.
97. Tang M, Dettmar P and Batchelor H. Bioadhesive oesophageal bandages: protection against acid and pepsin injury. *Int J Pharm* 2005; 292: 169–177.
98. Batchelor HK, Tang M, Dettmar PW, et al. Feasibility of a bioadhesive drug delivery system targeted to oesophageal tissue. *Eur J Pharm Biopharm* 2004; 57: 295–298.
99. Pizzoni A. *Glycosaminoglycan oral use and compositions*. Report No. European Patent 2 581 090 A1, 2013.

100. Pizzoni A. *Glycosaminoglycan oral use and composition*. Report No. US Patent 2014/0107064 A1, 2014.

101. Gaffney J, Matou-Nasri S, Grau-Olivares M, et al. Therapeutic applications of hyaluronan. *Mol Biosyst* 2010; 6: 437–443.

102. Volpi N, Schiller J, Stern R, et al. Role, metabolism, chemical modifications and applications of hyaluronan. *Curr Med Chem* 2009; 16: 1718–1745.

103. Nolan A, Baillie C, Badminton J, et al. The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration. *J Oral Pathol Med* 2006; 35: 461–465.

104. Kapoor P, Sachdeva S and Sachdeva S. Topical hyaluronic acid in the management of oral ulcers. *Indian J Dermatol* 2011; 56: 300–302.

105. Ialenti A and Di Rosa M. Hyaluronic acid modulates acute and chronic inflammation. *Agents Actions* 1994; 43: 44–47.

106. Lauder RM. Chondroitin sulphate: a complex molecule with potential impacts on a wide range of biological systems. *Complement Ther Med* 2009; 17: 56–62.

107. Volpi N. Anti-inflammatory activity of chondroitin sulphate: new functions from an old natural macromolecule. *Inflammopharmacology* 2011; 19: 299–306.

108. du Souich P, Garcia AG, Verges J, et al. Immunomodulatory and anti-inflammatory effects of chondroitin sulphate. *J Cell Mol Med* 2009; 13: 1451–1463.

109. Campo GM, Avenoso A, Campo S, et al. Chondroitin sulphate: antioxidant properties and beneficial effects. *Mini Rev Med Chem* 2006; 6: 1311–1320.

110. Bonfils S, Dubrasquet M and Lambling A. The inhibition of peptic proteolysis by various polysaccharides [in French]. *Rev Fr Etud Clin Biol* 1960; 5: 71–74.

111. Galzigna L and Previerocoletti MA. Action of sodium chondroitin sulfate on the enzymatic activity of pepsin [in Italian]. *Gazz Med Ital* 1965; 124: 65–67.

112. Lenzi G, Rapino P and Ferri S. On the behavior of gastric hydrochloric and peptic activity after administration of sodium chondroitin sulfate [in Italian]. *Min Med* 1963; 54: 3421–3424.

113. Baldini E and Tincani GP. Treatment of gastroduodenal ulcer with sodium chondroitin sulfate [in Italian]. *Min Gastroenterol* 1963; 9: 25–29.

114. Dumortier G, Grossiord JL, Agnely F, et al. A review of poloxamer 407 pharmaceutical and pharmacological characteristics. *Pharm Res* 2006; 23: 2709–2728.

115. Ramya Dev D, Sandhya P and Vedha Hari BN. Poloxamer: a novel functional molecule for drug delivery and gene therapy. *J Pharm Sci Res* 2013; 5: 159–165.

116. European Parliament. Council Directive 93/42/EEC concerning medical devices, https://eur-lexeuropaeu/legal-content/EN/TXT/PDF/?uri=CELEX:31993L0042&from=IT(1993, accessed 9 April 2025).

117. Pecora TMG, Ragazzo B, Bertin W, et al. Rheological behavior of a new mucoadhesive oral formulation based on sodium chondroitin sulfate, xyloglucan and glycerol. *J Funct Biomater* 2021; 12: 28.

118. Whelan KA, Muir AB and Nakagawa H. Esophageal 3D culture systems as modeling tools in esophageal epithelial pathobiology and personalized medicine. *Cell Mol Gastroenterol Hepatol* 2018; 5: 461–478.

119. Ceriotti L, Buratti P, Corazziari ES, et al. Protective mechanisms of liquid formulations for gastro-oesophageal reflux disease in a human reconstructed oesophageal epithelium model. *Med Devices (Auckl)* 2022; 15: 143–152.

120. Scarpignato C, Buratti P, Meloni M, et al. Protective effects of Esoxx™ One, a hyaluronic acid-chondroitin sulphate based mucoadhesive formulation on 3D reconstructed human esophageal epithelium. *Gastroenterology* 2022; 162(Suppl. 1): S1–S2.

121. Di Simone MP, Baldi F, Vasina V, et al. Barrier effect of Esoxx™ on esophageal mucosal damage: experimental study on ex-vivo swine model. *Clin Exp Gastroenterol* 2012; 5: 103–107.

122. Palmieri B, Corbascio D, Capone S, et al. Preliminary clinical experience with a new natural compound in the treatment of oesophagitis and gastritis: symptomatic effect. *Trends Med* 2009; 9: 219–225.

123. Palmieri B, Merighi A, Corbascio D, et al. Fixed combination of hyaluronic acid and chondroitin-sulphate oral formulation in a randomized double blind, placebo controlled study for the treatment of symptoms in patients with non-erosive gastroesophageal reflux. *Eur Rev Med Pharmacol Sci* 2013; 17: 3272–3278.

124. Kahrilas PJ, Howden CW and Hughes N. Response of regurgitation to proton pump inhibitor therapy in clinical trials

of gastroesophageal reflux disease. *Am J Gastroenterol* 2011; 106: 1419–1425.

125. Bredenoord AJ and Smout AJ. Refractory gastrooesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2008; 20: 217–223.

126. Fass R and Sifrim D. Management of heartburn not responding to proton pump inhibitors. *Gut* 2009; 58: 295–309.

127. Furnari M, Zentilin P, Mastracci L, et al. Esophageal biopsies in the management of GERD: complementary tool for many but not for all. *Hum Pathol* 2014; 45: 2512–2513. 20140816.

128. Zentilin P, Savarino V, Mastracci L, et al. Reassessment of the diagnostic value of histology in patients with GERD, using multiple biopsy sites and an appropriate control group. *Am J Gastroenterol* 2005; 100: 2299–2306.

129. Manabe N, Haruma K, Ito M, et al. Efficacy of adding sodium alginate to omeprazole in patients with nonerosive reflux disease: a randomized clinical trial. *Dis Esophagus* 2012; 25: 373–380.

130. Reimer C, Lodrup AB, Smith G, et al. Randomised clinical trial: alginate (Gaviscon Advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. *Aliment Pharmacol Ther* 2016; 43: 899–909.

131. Savarino EV, Barberio B, Scarpignato C, et al. Italian guidelines for the diagnosis and management of gastro-esophageal reflux disease: joint consensus from the italian societies of: gastroenterology and endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), AND General Medicine (SIMG). *Dig Liv Dis* 2025; in press.

132. Jung DH, Huh CW, Lee SK, et al. A systematic review and meta-analysis of randomized control trials: combination treatment with proton pump inhibitor plus prokinetic for gastroesophageal reflux disease. *J Neurogastroenterol Motil* 2021; 27: 165–175.

133. Bor S, Kalkan İ H, Savarino E, et al. Prokinetics-safety and efficacy: the European Society of Neurogastroenterology and Motility/ the American Neurogastroenterology and Motility Society expert review. *Neurogastroenterol Motil* 2024; 36: e14774.

134. Savarino V, Pace F, Scarpignato C, et al. Randomised clinical trial: mucosal protection combined with acid suppression in the treatment of non-erosive reflux disease—efficacy of Esoxx, a hyaluronic acid-chondroitin sulphate based bioadhesive formulation. *Aliment Pharmacol Ther* 2017; 45: 631–642.

135. Kahrilas PJ, Dent J, Lauritsen K, et al. A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis. *Clin Gastroenterol Hepatol* 2007; 5: 1385–1391.

136. Dent J, Kahrilas PJ, Hatlebakk J, et al. A randomized, comparative trial of a potassium-competitive acid blocker (AZD0865) and esomeprazole for the treatment of patients with nonerosive reflux disease. *Am J Gastroenterol* 2008; 103: 20–26.

137. Pietrzak AM. Esoxx™ added to standard therapy accelerates the healing of esophagitis. *Prz Gastroenterol* 2023; 18: 350–352.

138. Donnellan C, Sharma N, Preston C, et al. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *Cochrane Database Syst Rev* 2005: CD003245.

139. Bredenoord AJ, Pandolfino JE and Smout AJ. Gastro-oesophageal reflux disease. *Lancet* 2013; 381: 1933–1942.

140. Bordin DS, Andreev DN and Maev IV. Efficacy of esophagus protection in complex treatment of erosive gastroesophageal reflux disease: a systematic review and meta-analysis of controlled trials [in Russian]. *Ter Arkh* 2023; 94: 1407–1412.

141. Carrasco E, López-Campos F, Sastre-Callego S, et al. How efficacious is Ziverel™ for symptomatic relief of acute radiation-induced esophagitis? retrospective study of patients receiving oncologic treatment. *Cancer Ther Oncol Int J* 2017; 7: 555724.

142. Chmielecka-Rutkowska J, Tomasik B and Pietruszewska W. The role of oral formulation of hyaluronic acid and chondroitin sulphate for the treatment of the patients with laryngopharyngeal reflux. *Otolaryngol Pol* 2019; 73: 38–49.

143. Iannitti T, Morales-Medina JC, Merighi A, et al. A hyaluronic acid- and chondroitin sulfate-based medical device improves gastritis pain, discomfort, and endoscopic features. *Drug Deliv Transl Res* 2018; 8: 994–999.

144. Maton PN and Burton ME. Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use. *Drugs* 1999; 57: 855–870.

145. Scarpignato C and Galmiche JP. Antacids and alginates in the treatment of gastroesophageal reflux disease: how do they work and how much are they clinically useful? *Front Gastrointestin Res* 1992; 20: 153–181.

146. Bardhan KD, Strugala V and Dettmar PW. Reflux revisited: advancing the role of pepsin. *Int J Otolaryngol* 2012; 2012: 646901.

147. Tack J. Review article: role of pepsin and bile in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005; 22(Suppl. 1): 48–54.

148. Scarpignato C. Antaci protection of the gastric mucosa: an overview. In: Cheli R (ed.) *Gastric protection*. New York: Raven Press, 1988, pp.253–270.

149. Tran T, Lowry AM and El-Serag HB. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. *Aliment Pharmacol Ther* 2007; 25: 143–153.

150. Savarino E, Marabotto E, Zentilin P, et al. A safety review of proton pump inhibitors to treat acid-related digestive diseases. *Expert Opin Drug Saf* 2018; 17: 785–794.

151. Freedberg DE, Kim LS and Yang YX. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the american gastroenterological association. *Gastroenterology* 2017; 152: 706–715.

152. Vaezi MF, Yang YX and Howden CW. Complications of proton pump inhibitor therapy. *Gastroenterology* 2017; 153: 35–48.

153. Lee L, Ramos-Alvarez I, Ito T, et al. Insights into effects/risks of chronic hypergastrinemia and lifelong PPI treatment in man based on studies of patients with Zollinger-Ellison Syndrome. *Int J Mol Sci* 2019; 20: 5128.

154. Macke L, Schulz C, Koletzko L, et al. Systematic review: the effects of proton pump inhibitors on the microbiome of the digestive tract-evidence from next-generation sequencing studies. *Aliment Pharmacol Ther* 2020; 51: 505–526.

155. Fossmark R and Olaisen M. Changes in the gastrointestinal microbiota induced by proton pump inhibitors—a review of findings from experimental trials. *Microorganisms* 2024; 12: 1110.

156. Orr WC, Chen CL and Sloan S. The role of age and salivation in acid clearance in symptomatic patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2001; 15: 1385–1388.

157. Parkash V, Maan S, Deepika, et al. Fast disintegrating tablets: opportunity in drug delivery system. *J Adv Pharm Technol Res* 2011; 2: 223–235.

158. Slavkova M and Breitkreutz J. Orodispersible drug formulations for children and elderly. *Eur J Pharm Sci* 2015; 75: 2–9.

159. Savarino EV, Ghisa M, Della Coletta M, et al. Fixed combination of hyaluronic acid, chondroitin sulphate and aluminum hydroxyde restores esophageal mucosal integrity in patients with proved gastroesophageal reflux disease—a randomized, controlled, pathophysiological and clinical study. *UEG J* 2019; 7(Suppl.): 986A.

160. Savarino EV, Marinelli C, Lorenzon G, et al. Fixed combination of hyaluroic acid, chindroitin sulfate and aluminum hydroxide improved reflux symptoms and quality of life in patients qith proven gastroesophageal reflux disease—a randomized, controlled, pathophysiological and clinical study. *UEG J* 2019; 7(Suppl.): 987A.

161. Boarino V, Raguzzi I, Marocchi M, et al. Symptomatic response to GERDOFF™ in patients with gastro-esophageal reflux disease and poor response to alginates: an exploratory, post-market, open-label study. *Turk J Gastroenterol* 2020; 31: 466–473.

162. Pellegatta G, Mangiavillano B, Semeraro R, et al. The effect of hyaluronic acid and chondroitin sulphate-based medical device combined with acid suppression in the treatment of atypical symptoms in gastroesophageal reflux disease. *J Clin Med* 2022; 11: 1890.

163. Khawaja SN, Alaswaiti OF and Scrivani SJ. Burning mouth syndrome. *Dent Clin North Am* 2023; 67: 49–60.

164. Thakkar J and Dym H. Management of burning mouth syndrome. *Dent Clin North Am* 2024; 68: 113–119.

165. Lechien JR, Hans S, De Marrez LG, et al. Prevalence and features of laryngopharyngeal reflux in patients with primary burning mouth syndrome. *Laryngoscope* 2021; 131: E2627–E2633.

166. Li L, Wu S, Noma N, et al. Relationship between burning mouth disorder and gastroesophageal reflux disease: a scoping review. *Oral Dis* 2024; 30: 3600–3609.

167. Russo M, Crafa P, Franceschi M, et al. Burning mouth syndrome and reflux disease: relationship and clinical implications. *Acta Biomed* 2022; 93: e2022329.

168. Hunt RH and Yaghoobi M. The esophageal and gastric microbiome in health and disease. *Gastroenterol Clin North Am* 2017; 46: 121–141.

169. Corning B, Copland AP and Frye JW. The esophageal microbiome in health and disease. *Curr Gastroenterol Rep* 2018; 20: 39.

170. Dunbar KB, Agoston AT, Odze RD, et al. Association of acute gastroesophageal reflux disease with esophageal histologic changes. *JAMA* 2016; 315: 2104–2112.

171. Souza RF, Bayeh L, Spechler SJ, et al. A new paradigm for GERD pathogenesis. Not acid injury, but cytokine-mediated inflammation driven by HIF-2α: a potential role for targeting HIF-2α to prevent and treat reflux esophagitis. *Curr Opin Pharmacol* 2017; 37: 93–99.

172. Yoshida N. Inflammation and oxidative stress in gastroesophageal reflux disease. *J Clin Biochem Nutr* 2007; 40: 13–23.

173. Elsayed Azab A, A Adwas A, Ibrahim Elsayed AS, et al. Oxidative stress and antioxidant mechanisms in human body. *J Appl Biotechnol Bioeng* 2019; 6: 43–47.

174. Deng Y, Pan L and Qian W. Associations between the severity of reflux esophagitis in children and changes in oxidative stress, serum inflammation, vasoactive intestinal peptide and motilin. *Exp Ther Med* 2019; 18: 3509–3513.

175. Bulut F, Tetiker AT, Çelikkol A, et al. Low antioxidant enzyme levels and oxidative stress in laryngopharyngeal reflux (LPR) patients. *J Voice* 2023; 37: 924–931.

176. Soyer T, Soyer OU, Birben E, et al. Pepsin levels and oxidative stress markers in exhaled breath condensate of patients with gastroesophageal reflux disease. *J Pediatr Surg* 2013; 48: 2247–2250.

177. Aronson JK. *Meyler's side effects of analgesics and anti-inflammatory drugs*. Amsterdam: Elsevier, 2009.

178. Gao Y, Kuok KI, Jin Y, et al. Biomedical applications of *Aloe vera*. *Crit Rev Food Sci Nutr* 2019; 59(Suppl. 1): S244–S256.

179. Panahi Y, Khedmat H, Valizadegan G, et al. Efficacy and safety of *Aloe vera* syrup for the treatment of gastroesophageal reflux disease: a pilot randomized positive-controlled trial. *J Tradit Chin Med* 2015; 35: 632–636.

180. Eteraf-Oskouei T and Najafi M. Traditional and modern uses of natural honey in human diseases: a review. *Iran J Basic Med Sci* 2013; 16: 731–742.

181. Bogdanov S, Jurendic T, Sieber R, et al. Honey for nutrition and health: a review. *J Am Coll Nutr* 2008; 27: 677–689.

182. Math MV, Khadkikar RM and Kattimani YR. Honey—a nutrient with medicinal property in reflux. *Indian J Med Res* 2013; 138: 1020–1021.

183. Kassim M, Achoui M, Mansor M, et al. The inhibitory effects of Gelam honey and its extracts on nitric oxide and prostaglandin E_2 in inflammatory tissues. *Fitoterapia* 2010; 81: 1196–1201.

184. Pasupuleti VR, Sammugam L, Ramesh N, et al. Honey, propolis, and royal jelly: a comprehensive review of their biological actions and health benefits. *Oxid Med Cell Longev* 2017; 2017: 1259510.

185. Fratellone PM, Tsimis F and Fratellone G. Apitherapy products for medicinal use. *J Altern Complement Med* 2016; 22: 1020–1022.

186. Ahmed N, Sutcliffe A and Tipper C. Feasibility study: honey for treatment of cough in children. *Pediatr Rep* 2013; 5: 31–34.

187. Kuitunen I and Renko M. Honey for acute cough in children—a systematic review. *Eur J Pediatr* 2023; 182: 3949–3956.

188. Yadlapati R, Vaezi MF, Vela MF, et al. Management options for patients with GERD and persistent symptoms on proton pump inhibitors: recommendations from an expert panel. *Am J Gastroenterol* 2018; 113: 980–986.

189. Hungin APS, Molloy-Bland M and Scarpignato C. Revisiting Montreal: new insights into symptoms and their causes, and implications for the future of GERD. *Am J Gastroenterol* 2019; 114: 414–421.

190. Roman S and Mion F. Refractory GERD, beyond proton pump inhibitors. *Curr Opin Pharmacol* 2018; 43: 99–103.

191. Farré R. Pathophysiology of gastro-esophageal reflux disease: a role for mucosa integrity? *Neurogastroenterol Motil* 2013; 25: 783–799.

192. Gyawali CP, Sonu I, Becker L, et al. The esophageal mucosal barrier in health and disease: mucosal pathophysiology and protective mechanisms. *Ann N Y Acad Sci* 2020; 1482: 49–60.

193. Vaezi MF. Benefit of acid-suppressive therapy in chronic laryngitis: the devil is in the details. *Clin Gastroenterol Hepatol* 2010; 8: 741–742.

194. Khalil HS. The diagnosis and management of globus: a perspective from the United Kingdom.

Curr Opin Otolaryngol Head Neck Surg 2008; 16: 516–520.

195. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology* 2008; 135: 1392–1413.

196. Katz PO, Gerson LB and Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; 108: 308–328.

197. Koufman JA, Aviv JE, Casiano RR, et al. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. *Otolaryngol Head Neck Surg* 2002; 127: 32–35.

198. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129(Suppl. 1): 80s–94s.

199. Altman KW, Prufer N and Vaezi MF. A review of clinical practice guidelines for reflux disease: toward creating a clinical protocol for the otolaryngologist. *Laryngoscope* 2011; 121: 717–723.

200. Ezzat WF, Fawaz SA, Fathey H, et al. Virtue of adding prokinetics to proton pump inhibitors in the treatment of laryngopharyngeal reflux disease: prospective study. *J Otolaryngol Head Neck Surg* 2011; 40: 350–356.

201. Chun BJ and Lee DS. The effect of itopride combined with lansoprazole in patients with laryngopharyngeal reflux disease. *Eur Arch Otorhinolaryngol* 2013; 270: 1385–1390.

202. Poe RH and Kallay MC. Chronic cough and gastroesophageal reflux disease: experience with specific therapy for diagnosis and treatment. *Chest* 2003; 123: 679–684.

203. Dabirmoghaddam P, Amali A, Motiee Langroudi M, et al. The effect of N-acetyl cysteine on laryngopharyngeal reflux. *Acta Med Iran* 2013; 51: 757–764.