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THE EFFICACY OF CURCUMIN, PROKINETIC AGENTS, AND ALGINATE-BASED THERAPY AS ADJUVANT TREATMENTS FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) : A LITERATURE REVIEW

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Abstract
Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal disorder characterized by reflux of gastric contents into the esophagus, causing mucosal injury, inflammation, and reduced quality of life. Many patients still experience persistent symptoms even though they were treated with standart therapy (PPIs), highlighting the need for adjunctive therapies targeting broader pathophysiological mechanisms. This literature review aimed to evaluate the efficacy and mechanisms of curcumin, prokinetic agents, and alginate-based therapy as adjunctive treatments for GERD. A literature review was conducted using PubMed, ScienceDirect, and Google Scholar databases. Articles published within the last 10 years, available in full text, and relevant to the topic were included. Ten studies consisting of in vivo, in vitro, randomized controlled trials, clinical trials, and meta-analyses were analyzed. Curcumin acts as a promising anti-inflammatory and antioxidant through the inhibition of the NF-κB pathway and reduction of oxidative stress, potentially protecting the esophageal mucosa from reflux-induced injury. Prokinetic agents improved esophageal motility, enhanced lower esophageal sphincter pressure, and accelerated gastric emptying, contributing to symptom improvement and better quality of life. Alginate-based therapy formed a raft-like barrier that reduced postprandial reflux and preserved epithelial integrity by preventing pepsin-induced E-cadherin degradation. Curcumin, prokinetic agents, and alginate-based therapy show complementary mechanisms that may improve GERD management beyond acid suppression alone.

Keywords: *Alginate, Curcumin, Gastroesophageal Reflux Disease, Prokinetic Agents*

Abstrak
Penyakit refluks gastroesofageal (GERD) adalah gangguan gastrointestinal kronis yang ditandai dengan refluks isi lambung ke dalam kerongkongan, menyebabkan cedera mukosa, peradangan, dan penurunan kualitas hidup. Banyak pasien masih mengalami gejala yang menetap meskipun telah diobati dengan terapi standar (PPI), yang menyoroti kebutuhan akan terapi tambahan yang menargetkan mekanisme patofisiologis yang lebih luas. Tinjauan literatur ini bertujuan untuk mengevaluasi efikasi dan mekanisme kurkumin, agen prokinetik, dan terapi berbasis alginat sebagai pengobatan tambahan untuk GERD. Tinjauan literatur dilakukan menggunakan basis data PubMed, ScienceDirect, dan Google Scholar. Artikel yang diterbitkan dalam 10 tahun terakhir, tersedia dalam teks lengkap, dan relevan dengan topik tersebut disertakan. Sepuluh

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studi yang terdiri dari studi in vivo, in vitro, uji coba terkontrol secara acak, uji klinis, dan meta-analisis dianalisis. Kurkumin bertindak sebagai antiinflamasi dan antioksidan yang menjanjikan melalui penghambatan jalur NF-κB dan pengurangan stres oksidatif, berpotensi melindungi mukosa esofagus dari cedera akibat refluks. Agen prokinetik meningkatkan motilitas esofagus, meningkatkan tekanan sfingter esofagus bagian bawah, dan mempercepat pengosongan lambung, berkontribusi pada perbaikan gejala dan kualitas hidup yang lebih baik. Terapi berbasis alginat membentuk penghalang seperti rakit yang mengurangi refluks pasca makan dan menjaga integritas epitel dengan mencegah degradasi E-cadherin yang diinduksi pepsin. Kurkumin, agen prokinetik, dan terapi berbasis alginat menunjukkan mekanisme komplementer yang dapat meningkatkan manajemen GERD di luar penekanan asam saja.

Kata Kunci: Alginat, Agen Prokinetik ,Kurkumin, Penyakit Refluks Gastroesofageal

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic condition of the upper gastrointestinal tract characterized by the reflux of stomach contents into the esophagus. This condition can cause uncomfortable symptoms and potential tissue damage, including laryngitis, refractory asthma, tooth erosion, and chronic cough. GERD is dubbed "*The Billion-Person Disease*" based on data from the Global Burden of Disease (GBD) 2021, which reported a global prevalence of 825.6 million cases in 2021 an 80% increase since 1990 and predicts it will exceed 1 billion cases by 2035).(Mo et al., 2025) The pathophysiology of GERD is multifactorial. One of these factors is obesity, which increases intraabdominal pressure, thereby compromising the integrity of the gastroesophageal junction and facilitating reflux.(Mukhtar et al., 2022) Additionally, smoking can exacerbate the condition because nicotine blocks cholinergic receptors, which relax the circular muscle fibers of the lower esophageal sphincter (LES).LES dysfunction causes the anti reflux barrier to fail in containing rising stomach acid, resulting in chronic exposure of the esophageal mucosa to a mixture of stomach acid, pepsin, and bile salts.(Pharmacophore ; Almourgi et al., 2022)This chronic exposure triggers inflammation and damage to the esophageal squamous epithelium. As an adaptive response to chronic injury, metaplasia occurs, wherein the damaged squamous epithelium is replaced by columnar epithelium with intestinal characteristics (goblet cells) that are more resistant to acid.(Spechler et al., 2017) This condition is known as Barrett's esophagus. The multidimensional impact of GERD including sleep disturbances, reduced work productivity, emotional distress, and the risk of complications underscores that GERD must be viewed and managed as a serious chronic condition, not merely a mild digestive complaint.(Souza and Spechler, 2022)

Currently, the primary management of GERD relies on proton pump inhibitors (PPIs), such as omeprazole, lansoprazole, and esomeprazole, which work by suppressing gastric acid secretion in the parietal cells of the stomach. This therapy effectively heals erosive esophagitis and reduces symptoms in the majority of patients. However, this approach has substantial limitations. Up to 40% of GERD patients continue to experience chronic symptoms despite undergoing standard dose PPI therapy a condition known as refractory GERD (rGERD).(Mermelstein et al., 2018) PPIs target only the acid component, while other issues such as non acid reflux, esophageal and gastric motility disorders, the presence of postprandial acid pockets, and visceral hypersensitivity remain unaddressed. Furthermore, long term PPI use is associated with various risks, including vitamin B12 deficiency, an increased risk of Clostridium difficile infection, and impaired renal function. These limitations underscore the need for additional therapeutic approaches that target the pathophysiological mechanisms of GERD more broadly and comprehensively.(Zheng and Tao, 2025)

Various adjunctive therapeutic approaches have been developed, including curcumin, prokinetic agents, and alginate based therapy. First, alginate-based therapy offers a non systemic mechanism of action by forming a *raft* (thick gel) that floats on the surface of the stomach contents after reacting with stomach acid.(Hoad et al., 2025)This physical barrier mechanically prevents gastric contents from rising into the esophagus and has been shown to effectively reduce heartburn symptoms, particularly in patients with postprandial symptoms and in special populations such as pregnant women. Second, prokinetic agents (domperidone, metoclopramide, mosapride) focus on addressing the motility dysfunction aspect of the pathophysiology not addressed by PPIs. These medications work by increasing LES pressure, reducing the frequency of transient LES relaxations (TLESRs), and accelerating gastric emptying, thereby reducing the volume of gastric contents that could potentially reflux.(Penagini and Bravi, 2010) Third, curcumin (Curcuma longa) offers a mucosal targeted approach. Curcumin exhibits anti inflammatory and antioxidant activity through inhibition of the *NF-κB* pathway, thereby potentially protecting the esophageal mucosa from acid induced damage and aiding tissue healing. Thus, these three agents each target different components of the pathophysiology. Alginate as a physical barrier, prokinetics as a motility corrector, and curcumin as a protector and restorer of the esophageal mucosa.

Although PPIs remain the primary treatment for GERD, their limitations in addressing the full spectrum of the disease's pathophysiology have driven a paradigm shift toward a multimodal approach. Current management guidelines, including the Lyon Consensus 2.0, explicitly recommend the addition of adjuvant therapies such as alginate in patients who remain symptomatic despite receiving optimal PPI therapy. Within this framework, the combination of these three agents (alginate, prokinetics, and curcumin) offers a comprehensive and complementary strategy to PPI therapy. Alginate complements PPIs by forming a physical barrier that overcomes the limitations of PPIs in neutralizing postprandial acid pockets, thereby mechanically preventing reflux even though PPIs have reduced acid volume. Prokinetic agents compensate for the weakness of PPIs in improving motility dysfunction by strengthening the LES and accelerating gastric emptying. Meanwhile, curcumin acts as a protector and restorer of the esophageal mucosa from inflammatory damage caused by acid exposure that may still occur. These three agents are highly worthy of consideration as adjunct therapies to PPIs that can be integrated into the GERD management algorithm, particularly in patients with an inadequate response to monotherapy with PPIs. Therefore, this literature review was conducted to map existing scientific evidence, identify unanswered research gaps, and provide a theoretical foundation for the development of future adjunct therapies to PPIs.

METHOD

This study employed a literature review design, searching for scientific articles through several electronic databases, including PubMed, ScienceDirect, and Google Scholar. The search process used the keywords *Alginate, Curcumin, Gastroesophageal Reflux Disease, Prokinetic agents*. Article selection was conducted through identification, screening, adjustment to inclusion criteria, and elimination of irrelevant articles. Inclusion criteria included articles published within the last 10 years, written in Indonesian or English, available in full text, and discussing topics relevant to the research. Based on this selection process, 9 articles were identified as relevant and met the criteria for use in this study.

RESULT AND DISCUSSION

Table 1. Literature Review Table

No.	Author	Methode	Result	Conclusion
1.	Lee et al. 2021.	In vivo	Significantly decreased ROS, Perooxynitritie ($ONOO^-$), and proinflamatory protein compared to normal group with an optimal dose 200mg/kg body weight)	*Curcumin Longa Rhizomae 30% EtOH extract* suppressed excessive oxidative stress generational and inhibiting the expression of proinflammatory proteins through the MAPKs and NF-κB pathways.on acute reflux esophagitis rats.
2.	Gurlek et al. 2024.	In vivo	The rats that were given curcumin Grup III and IV increased submucosal collagen while the damage in muscularis mucosa and tunica muscularis were regressed better than other groups with an optimal dose 200mg/kg body weight	Curcumin decreased the level of esophageal tissue damage and maybe considered as a supportive treatment for acute corrosice esophagitis
3.	Samuels et al. 2023.	In vitro	Protect E-Cadherin (p value < 0.0001), ADAM-10 Cleavage and MMP were decreased compares to pepsin group	Alginate provides long-term protection against E-cadherin degradation, ADAM10 maturation, and MMP induction, suggesting that alginate may prevent the worsening of GERD severity in patients taking PPIs.
4.	Ergun et al. 2024.	In vitro	Biological mechanism related to toxicity such as peroxisome activated via PPARα, TGF-β signaling, protein pro-apoptosis and mythocondrial dysfunction were downregulated	Gaviscon which is contain sodium alginate mitigate the harmful changes against pepsin-induced dysregulation in GERD-related signaling pathways
5.	Knarr 2025.	In vitro	Alginate reacts with stomach acid and $Ca2^+$ and create floating gel layer on the surface of	Alginate are used as pharmaceutical agent for the treatment of GERD symptom

			the stomach contents.	
6.	Wang et al. 2026.	Combined in vitro and in vivo	Cytotoxicity assays confirmed an excellent biocompatibility, flow cytometry analysis demonstrated an increased proportion of cells in S phase. whereas in vivo confirmed the increased of healing and and the decreased of pore size	Alginate offers new possibilities for regenerative medicine applications in digestive tract tissue engineering and wound repair.
7.	Xi et al. 2021.	Meta-Analysis	The addition of a prokinetic agent to proton pump inhibitor (PPI) therapy results in greater improvement in GERD symptoms compared to PPI therapy alone.	The addition of a prokinetic agent to PPI therapy provide better symptom control compared to PPI monotherapy and contributes to an improvement in patients quality of life
8.	Jeon et al. 2022.	RCT	Decreased the gastroesophageal health-related quality of life scores from baseline (GERD-HRQL scores p value 0.295)	Treatment groups with esomapride demonstrated decreased GERD-HRQL scores compared to those at baseline, although this difference was not significant, suggesting a potential benefit
9.	Lakhtakia et al. 2024.	Clinical Trials	Decreased the frequency of GSAS symptoms significantly after 6 weeks (p value < 0.001)	Combination of pantoprazole and itopride exhibited a good profile and was effective in patients with symptoms of dyspepsia with gerd overlap

Effects of Curcumin on Patients with GERD

Esophageal reflux is a pathophysiological process that occurs in patients with GERD. Inflammation of esophageal epithelial cells is activated in response to inappropriate pH levels of gastric acid.(Zhang et al., 2022) This inflammation stimulates inflammatory cytokines (IL-6 and IL-8), which cause cellular changes and disrupt the key inflammatory signaling pathway, NF-κB.(Zhang et al., 2022) These

cellular changes lead to persistent cytokine production and increased the risk of esophageal cancer or pre-malignant condition characterized by the replacement of the normal squamous epithelium by a metaplastic via oxidative damage pathways.(Han and Zhang, 2022)

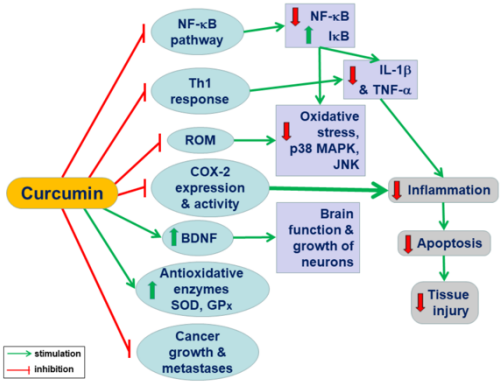

Figure 1: Curcumin Mechanism as an Anti-inflammatory and Antioxidant(Kwiecien et al., 2019b)

An in vivo study of curcumin-based therapy has been shown to prevent inflammatory cytokine expression in rat esophageal tissue.(Jin A. Lee et al., 2021) (Gurlek et al., 2024) Curcumin can effectively inhibit NF-κB activation through NF-κB inhibition, exhibiting pH-independent anti-inflammatory and anticarcinogenic effects.(Kwiecien et al., 2019) Curcumin also suppresses bile acid-induced DNA damage and promotes apoptosis by inhibiting NF-κB, thereby reducing the viability of damaged cells and activating the apoptotic pathway in malignant cells.) This facilitates the elimination of abnormal cells caused by inflammation and reduces the risk of their development into cancer.(Kwiecien et al., 2019b) of Prokinetic Agent on Patients with GERD

One crucial component of the pathophysiology of GERD is a disruption in the esophageal defense mechanisms.(Rieder et al., 2010) Gastric reflux can occur due to transient relaxation of the lower esophageal sphincter (TLESR) after meal, which is not related to lower esophageal sphincter relaxation (LESR) or secondary peristalsis.(Rieder et al., 2010) The proportion of TLESR episodes not related to LESR increases as the severity of the disease increases.(Rieder et al., 2010) This impaired motor function allows for more reflux episodes and increased acid clearance dysfunction leading to injury and contribute to permanent impairment of LES tone and esophageal peristalsis.(Rieder et al., 2010)This mechanism occur when human esophageal mucose

exposed with acid, and realeased platelet activation factor (PAF).(Rieder et al., 2010) The binding of PAF and PAF receptor induced the inhibition of neurally mediated circular muscle contraction.(Rieder et al., 2010) PAF can also activate the circular muscle of the esophagus to secrete IL-6.(Rieder et al., 2010) The muscle-derived IL-6 then leads to increased production of H_2O_2 and IL-1β; H_2O_2 and IL-1β canthemselves induce PAF production.(Rieder et al., 2010) This indicates the existence of a self-perpetuating cycle of inflammation and motility abnormalities.(Rieder et al., 2010)

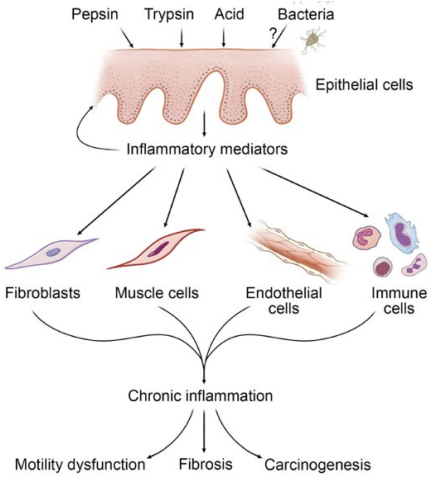

Figure 2. Mechanism of Motility Dysfunction Induced by Inflammation.(Rieder et al., 2010)

Quality of life (QoL) is commonly impaired in patients with GERD, depents the presence of esophageal lesions induced by acid exposure.(Saracco et al., 2021) The addition of a prokinetic agent as an adjuvant therapy has been reported to improve QoL in patients, as reflected by the overall scores that used to be evaluate the frequency, severity, and degree of distress has been reported to improve.(Xi et al., 2021) [20],(Lakhtakia et al., 2024) This beneficial effects may be related to the mechanism of prokinetic agents.(Ren et al., 2014) Prokinetic acts by increasing acetylcoline release from parasympathetic nerve endings which is, enhance lower esophageal sphincter pressure and improve esophageal peristalsis, esophageal acid clearance, and gastric emptying.(Futagami et al., 2010).

3.3 Alginate-based Therapy Effects on Patients With GERD.

Acid exposure to the esophageal mucosa occurs not only at the macroscopic level, but also at the cellular level. E-cadherin is the primary adhesion protein in epithelium and plays a crucial role in maintaining tissue integrity and mucosal barrier function.(Niessen, 2007) Exposure of e-cadherin to pepsin results not only in enzymatic degradation but also in regulated intramembrane proteolysis (RIP), producing specific cleavage fragments.(Lal and Caplan, 2011) RIP is an evolutionary cell signaling mechanism. Membrane proteins are regularly cleaved by sheddases at the cell surface, followed by intramembrane proteases, resulting in fragments that retain biological activity.(Lal and Caplan, 2011) These RIP fragments of E-cadherin can influence cell adhesion, resistance to apoptosis, and cell proliferation, indicating that E-cadherin damage under reflux conditions is not merely destructive but can also trigger signaling changes that contribute to barrier dysfunction and pathological changes in the epithelium.(Lal and Caplan, 2011)

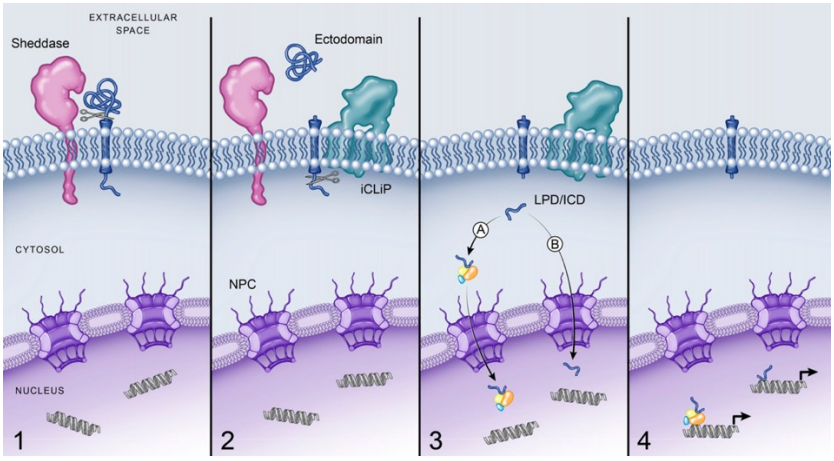

Figure 3. Signaling Mechanism of RIP(Hodges et al., 2022)

Another key approach is needed to minimize the exposure of esophagus to acidic refluxate while also preserving barrier integrity(Knarr, 2025) Alginate-based therapy represent one such strategy/ Alginates form a raft-forming anti-reflux preventing postprandial reflux, provides longterm protection against pepsin induced E-cadherin degradation and exhibit excellent mucoadhesive for preserving the barrier integrity.(Samuels et al., 2023),[16] Beyond the protective effect, alginate-based therapy

offer regenerative effect as reflected by increased cell replication during S phase(Wang et al., 2026) These synergistic effect offers new therapeutic option for better control of GERD symptoms.

CONCLUSION

GERD is a multifactorial disease involving acid exposure, motility dysfunction, epithelial barrier disruption, and chronic inflammation. PPIs, the cornerstone of therapy, have limitations in comprehensively addressing the broader pathophysiological mechanisms of GERD that contribute to persistent symptoms in most patients. This literature review demonstrates that curcumin, prokinetic agents, and alginate-based therapies each target distinct but complementary aspects of GERD pathogenesis. Curcumin exerts anti-inflammatory and antioxidant effects through inhibition of the NF-κB pathway and oxidative stress and has the potential to protect the esophageal mucosa from chronic injury. Prokinetic agents enhance esophageal and gastric motility, improve lower esophageal sphincter function, and reduce reflux episodes, thus contributing to improved symptom control and quality of life. Meanwhile, alginate-based therapies act as an anti-reflux barrier while maintaining epithelial integrity against pepsin-mediated damage, with emerging evidence suggesting additional regenerative potential. This adjunctive therapy may provide a more comprehensive therapeutic approach when combined with PPIs, particularly in patients with refractory GERD.

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