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RESEARCH ARTICLE

THE ROLE OF GUT MICROBIOTA IN GASTROESOPHAGEAL REFLUX DISEASE: A SYSTEMATIC REVIEW

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a common digestive disorder characterized by retrograde flow of stomach contents into esophagus, leading to symptoms like heartburn and chronic cough. Worldwide prevalence of GERD varies, with lifestyle factors contributing to rising incidence. Current research indicates that gut microbiota plays a significant role in GERD pathophysiology, particularly through microbial dysbiosis and its influence on inflammation and mucosal integrity.

Aim: This systematic review aims to consolidate existing-research on relationship between gut microbiota and GERD, assess the impact of probiotics on symptom management, and identify mechanism through which microbial imbalance may affect disease progression.

Material and methods: A systematic literature search was conducted across multiple electronic databases for studies published from 2014-2024. Inclusion criteria focused on randomized-controlled-trails and cohort studies investigating gut microbiota in GERD. Total eight-studies were included, encompassing 771,198 participants. Data extraction was performed on microbiota composition, symptom assessment and probiotic interventions.

Results: Findings revealed significant difference in gut microbiota composition between GERD patient vs. healthy controls, with GERD patients showing increased levels of Proteobacteria and decreased levels of Bifidobacterium. Probiotic intervention resulted in reduction in dysbiosis prevalence (56.2% in placebo vs. 6.2% in probiotics, $P<0.001$), indicating potential therapeutic benefits. Moreover, specific taxa associated with GERD risk were identified, showcasing the complex interplay between gut microbial communities and GERD severity.

Conclusion: The review underscores intricate relationship between gut microbiota and GERD, with probiotics showing promise in symptom management. Future research must focus on large-scale studies to elucidate specific mechanism of probiotics, and explore dietary interventions to enhance therapeutic strategies for GERD management.

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Introduction:-

Gastroesophageal reflux disease (GERD) is a prevalent digestive disorder characterized by the retrograde flow of stomach and duodenal contents into the esophagus, leading to a range of symptoms that can drastically impair an individual's quality of life [1]. These symptoms typically include heartburn, acid regurgitation and chest pain, with extra-esophageal manifestations such as chronic cough and laryngitis [2]. Epidemiological studies have indicated that the global prevalence of GERD varies widely, affecting approximately 10% to 20% of populations in Western countries and 5.2% to 18.3% in various Asian nations [3]. The rising incidence of GERD is a growing concern, attributed to lifestyle factors such as obesity, smoking, and dietary habits [4].

The pathogenesis of GERD involves complex interactions between mechanical, physiological and environmental factors. Primary mechanism includes esophageal motility dysfunction, hiatal hernias, and reduced mucosal resistance, which collectively facilitates the reflux of acidic gastric contents [5]. While the traditional view focuses on chemical damage from gastric acid, current findings suggest that inflammatory processes and microbial factors may also play crucial roles in disease progression [6]. Specifically, chronic inflammation in the esophagus has been associated with the development of Barrett's esophagus (BE), a condition that can precede esophageal adenocarcinoma (EAC), with a notable risk of malignant transformation [7, 8].

The gut microbiota, a complex community of microorganisms residing in the gastrointestinal tract, has garnered attention for its potential involvement in GERD [9]. Emerging research indicates that disruptions in the gut microbiota may contribute to the pathophysiology of gastrointestinal diseases, including GERD [10]. The normal esophageal microbiome predominantly consists of gram-positive bacteria, such as Streptococcus, while GERD patients often exhibit a shift towards gram-negative anaerobes, including Bacteroidetes and Proteobacteria. This dysbiosis, characterized by altered microbial composition and function, may exacerbate inflammation and influence disease severity [11, 12].

Management of GERD typically begins with lifestyle modifications, including dietary changes and weight management [13]. When these interventions prove insufficient, proton pump inhibitors (PPIs) are commonly prescribed to suppress gastric acid production. Although PPIs are effective in alleviating symptoms for many patients, approximately 40% do not achieve adequate symptom control, necessitating ongoing treatment that may have associated risks, such as gastrointestinal infections and nutrient malabsorption [14]. These adverse effects raise concerns regarding the long-term use of PPIs and have prompted interest in alternative therapeutic strategies [15].

Probiotics, defined as live microorganisms that confer health benefits when administered in appropriate amounts, have emerged as a potential adjunctive treatment for GERD [16]. Research has demonstrated that probiotics may help restore microbial balance, enhance intestinal barrier function, and modulate immune responses, potentially alleviating GERD symptoms and reducing reliance on acid suppression therapies [17]. Studies have shown that probiotics can improve gut health in various conditions, suggesting their therapeutic potential for GERD as well [18, 19]. Despite the growing body of literature surrounding GERD and gut microbiota, significant gaps remain. Majority of studies have primarily focused on esophageal and gastric microbiomes, with limited exploration of the gut microbiota's role in GERD [20, 21]. Additionally, the interplay between microbial communities and host metabolites in the context of GERD has yet to be fully elucidated. Moreover, while probiotics have been studied in various gastrointestinal disorders, their specific effects on GERD and the underlying mechanism warrant further investigation.

The aim of this systematic review is to consolidate existing research on the relationship between gut microbiota and GERD, assess the impact of probiotics on disease management and identify potential mechanisms through which microbial imbalances may influence GERD pathophysiology. By addressing these gaps, this review seeks to provide insights that may guide future research directions and clinical practices, ultimately contributing to improved management strategies for GERD. Understanding these relationships not only has implications for clinical management but also highlights the potential for preventive strategies that could reduce the risk of progression to more severe esophageal conditions, including Barrett's esophagus and esophageal adenocarcinoma.

Material and Methods:-

PICO Question

To guide this systematic review, the formulated PICO question is: In patients diagnosed with gastroesophageal reflux disease (GERD) (Population), how does the modulation of gut microbiota through probiotic intervention (Intervention) compare to standard care or no intervention (Comparison) in improving GERD symptoms and altering microbiota composition (Outcomes)?

Search Strategy

A systematic literature search was performed for studies published between 2014 and 2024. Electronic databases, including PubMed, Web of Science, Cochrane Library, and Scopus, were searched using a combination of relevant keywords and MeSH terms. The specific search terms included "GERD," "gastroesophageal reflux," "gut microbiota," "microbiome," "dysbiosis," "probiotics," and "therapeutic modulation," connected by Boolean operators such as "AND" and "OR." Additionally, focused searches on Google Scholar and the Directory of Open Access Journals were also conducted, alongside reviewing reference lists from selected articles and pertinent meta-analysis. Only randomized controlled trials (RCTs) and cohort studies that examined the relationship between gut microbiota and GERD, including variations in microbiota composition among GERD patients compared to healthy control were included.

Eligibility Criteria

The inclusion criteria encompassed RCTs and cohort studies that investigated the role of gut microbiota in GERD pathogenesis, composition and therapeutic implications of microbiota modulation. Studies must have focused on human populations and assessed microbiota variations between individuals with GERD and healthy controls. Exclusion criteria included animal studies, case reports, clinical trials without control groups, systematic reviews, meta-analyses, and letters to the editor. Studies involving participants who had received antibiotics, probiotics, or prebiotics within two months prior to the intervention were also excluded to prevent confounding effects on microbiota composition. This strict criterion ensured that the included studies accurately represented the relationship between gut microbiota and GERD.

Study Selection

The study selection followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Initially, two independent reviewers screened titles and abstracts to identify potentially relevant studies. his two-tier screening process was critical for ensuring that only studies that met the eligibility criteria were included in the systematic review. Discrepancies between the reviewers were resolved through discussion and consensus, thereby enhancing the reliability of the study selection process.

Data Extraction and Primary Outcomes

Data extraction was performed systematically, focusing on key aspects relevant to the study objectives. Extracted data include subject characteristics (age, sex, and health status), details of study design (randomization, blinding, sample size, and probiotic strains), and specific clinical outcomes related to GERD and microbiota composition. Primary outcomes included characterization of gut microbiota in GERD patients compared to healthy controls, the identification of dysbiosis, and effects of probiotic interventions on GERD symptoms. Secondary outcomes included the assessment of therapeutic implications of microbiota modulation, including improvements in quality of life and esophageal pH levels.

Data Analysis and Quality Assessment

Data analysis for this review involved qualitative synthesis of findings to the role of gut microbiota in GERD. Descriptive statistics were employed to summarize participant demographics and study interventions, focusing on microbiota composition and variations observed between groups. For quality assessment, the Jadad scale was utilized for RCTs, while cohort studies were evaluated using the Newcastle-Ottawa scale. These assessment tools enable a thorough overall strength of the evidence (see Table 1 and 2).

Results:-

Characteristics of the included Studies

The review identified a total of 8 studies that met the eligibility criteria after screening 470 records and assessing 214 full-text articles. Of the 206 articles excluded, the reasons included literature reviews and letters to the editor (n

= 72), studies on non-GERD diseases (n = 14), various publication types (n = 12), surgical interventions (n = 27), investigations of non-probiotic products (n = 24), non-English publications (n = 39), and studies focusing on gut microbiota and GERD without pertinent outcomes (n = 18). This selection process highlights the rigorous criteria applied to ensure that only relevant and high-quality studies were included in the final analysis, culminating in a focused review on the characteristics of the included studies concerning GERD and gut microbiota (Figure 1).

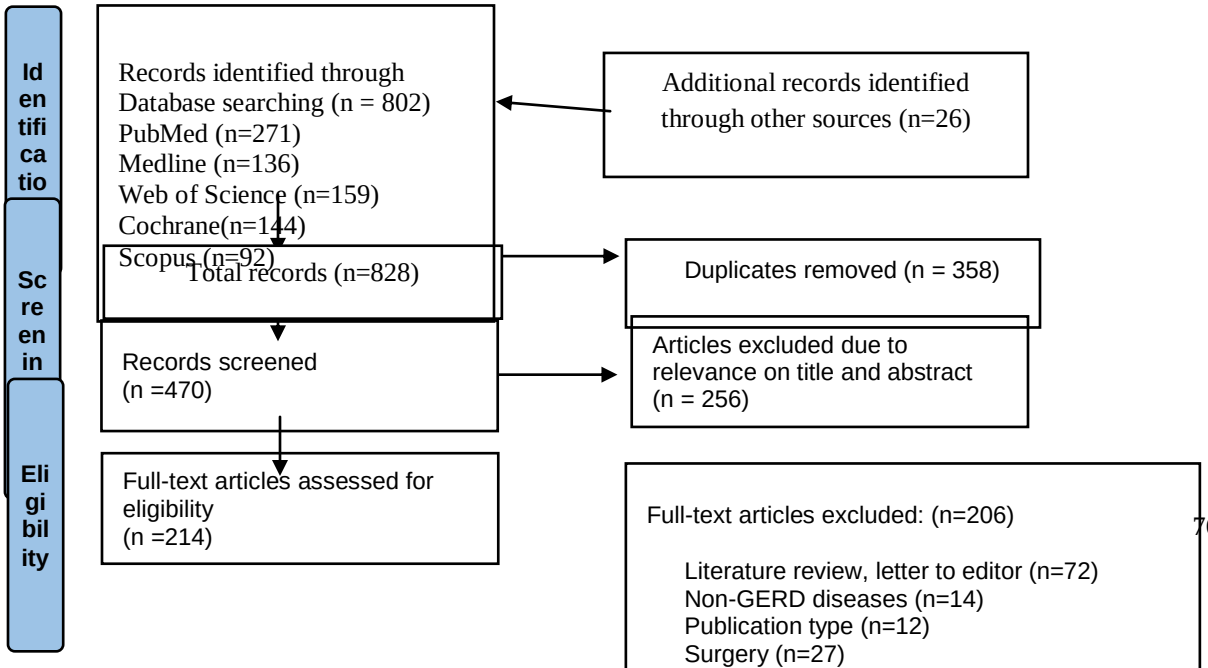
Study Participants and Baseline Characteristics

A total of 771,198 participants were included in the review with the mean age ranging from 1-18 years. The sex distribution varied, with males dominating approximately 48% to 56% across studies. Health conditions primarily included gastroesophageal reflux disease (GERD), confirmed through endoscopy and pH monitoring, with some studies also examining Barrett's esophagus. The study designs included randomized controlled trials, cohort studies, and bidirectional randomization studies reflux symptoms such as abdominal pain, bloating, and mucosal injury were assessed using various methods. The relationship between gut microbiota and GERD was investigated, revealing significant alterations in microbial diversity and composition linked to GERD. Clinical interventions primarily involved proton pump inhibitors (PPIs) and probiotics, with mean dosages of 20 mg/day for PPIs and up to 900 billion CFUs/day for probiotics. Adverse effects noted included increased dysbiosis with PPI use and gastrointestinal symptoms. Key outcomes indicated that probiotics significantly reduced dysbiosis prevalence (from 56.2% in placebo to 6.2% in probiotics, $P < 0.001$) and highlighted specific bacterial taxa associated with GERD, demonstrating both protective and risk factors in the gut microbiota (appendix table 3).

Microbiota Composition in GERD vs. Healthy Controls

The analysis of gut microbiota composition in patients with gastroesophageal reflux disease (GERD) reveals significant differences when compared to healthy controls (HC). Ye (2023) identified 834 operational taxonomic units (OTUs) through 16S rRNA and metagenomic sequencing, noting that GERD patients had 2,250 unique OTUs compared to 595 in the HC group [22]. Furthermore, a significant reduction in alpha diversity was observed in the GERD cohort, characterized by decreased Shannon and Simpson indices, and a shift in microbial community structure, highlighted by increased abundances of Proteobacteria and Bacteroidetes, alongside a reduction in Firmicutes and Actinobacteria. Key genera such as Bacteroides and Prevotella-9 were enriched in the GERD group, whereas Bifidobacterium was notably decreased. Liu (2024) further elucidated these associations using Mendelian Randomization (MR) analysis, linking specific taxa, including Tenericutes (OR: 1.11, P=0.02) and Haemophilus (OR: 1.09, P=0.02), with increased GERD risk, while taxa such as Lachnospiraceae UCG004 (OR: 0.91, P=0.03) were associated with a decreased risk [23]. Wang et al. (2024) confirmed these findings by identifying several taxa with a potential causal association with GERD, including the Family Clostridiales Vadin BB60 group, which was inversely correlated with GERD risk.

Factors influencing these microbiota variations include genetic predispositions, as evidenced by the strong F-statistics for SNPs related to gut microbiota, alongside environmental factors such as diet and antibiotic use, which may further modulate gut microbial diversity [24]. Overall, the evidence indicates that children and adults with GERD exhibit distinct microbiota composition compared to health controls, highlighting the need for further investigation into underlying mechanism and potential therapeutic interventions targeting these microbial communities.



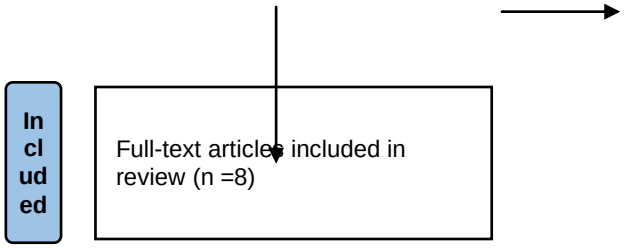


Figure 1:- PRISMA Study.

Mechanisms of Gut Microbiota in GERD Pathophysiology

The role of gut microbiota in the pathophysiology of GERD is multifaceted, influencing esophageal mucosal integrity, inflammation and reflux mechanisms. Singh et al. (2022) demonstrated that short-term proton pump inhibitor (PPI) treatment significantly alters the gut microbiota composition, increasing the abundance of families such as Leuconostacaceae and Streptococcaceae, which are associated with metabolite production that may impact mucosal health. The metabolomic analysis indicated decreases in metabolites like Uracil and L-Tryptophan, alongside increases in phenylacetic acid, suggesting that shifts in microbial metabolites could contribute to inflammation and mucosal barrier dysfunction [25]. Belei et al. (2018) reported a significant rise in small intestinal bacterial overgrowth (SIBO) prevalence in GERD patients following PPI treatment (56.2%, $P < 0.001$), linking this condition to dysbiosis and suggesting that changes in gut microbiota may compromise gastrointestinal motility and exacerbate reflux symptoms [26]. Furthermore, Shi et al. (2019) highlighted the interaction between gut and gastric microbiota, noting distinct community structures between healthy controls and GERD patients, with the latter showing decreased richness in gastric mucosal microbiota, which could affect esophageal defenses. The altered microbiota composition and its metabolic byproducts likely impact the function of the lower esophageal sphincter (LES), further increasing reflux symptoms [27]. Overall, these findings underscore the complex interplay between gut microbiota, gastric microbiota, and their collective impact on esophageal health, suggesting that dysbiosis and resultant metabolic changes may play crucial roles in GERD pathophysiology.

Therapeutic Implications of Microbiota Modulation

Recent studies highlight the therapeutic potential of microbiota modulation in managing GERD. Yang et al. (2023) identified specific bacterial families associated with GERD, revealing that higher levels of Bifidobacteriaceae and Christensenellaceae correlated negatively with GERD risk, indicating their protective roles, while Mollicutes and Rikenellaceae were positively linked to GERD risk [28]. Denease Francis et al. (2023) further demonstrated that infants treated with proton pump inhibitors (PPIs) exhibited distinct microbial profiles compared to controls, highlighting the influence of PPI treatment on gut microbiota composition [29]. Belei et al. (2018) provided compelling evidence for probiotics in mitigating the adverse effects of PPIs, showing that only 6.2% of children in probiotics group developed small intestinal bacterial overgrowth (SIBO), compared to 56.2% in the placebo group ($P< 0.001$). this highlighted that specific probiotic strain could effectively reduce GERD symptoms by maintain a healthier gut microbiome. Moreover, dietary modifications and inclusion of prebiotics may further enhance gut health, potentially improving GERD symptoms by fostering beneficial bacterial growth [26]. These outcomes collectively indicate the importance of probiotics and dietary strategies in therapeutic landscape for GERD, focusing on the need for further research into specific strains and their mechanism of action in diverse populations.

Discussion:-

This systematic review reveals significant insights into the relationship between gut microbiota and gastroesophageal reflux disease (GERD), underscoring the potential for microbiota modulation as a therapeutic strategy. The included studies consistently demonstrated distinct microbial compositions in GERD patients compared to healthy controls, with a notable reduction in bacterial diversity and shifts in specific taxa, such as increased abundances of Proteobacteria and Bacteroidetes, alongside decreased levels of Bifidobacterium. The findings also indicated that higher levels of protective bacterial families, such as Bifidobacteriaceae and Christensenellaceae, were inversely correlated with GERD risk, while Mollicutes and Rikenellaceae were associated with increased risk. Additionally, the impact of PPIs on altering gut microbiota profiles in infants was also identified, which may exacerbate GERD symptoms. The probiotics can reduce the prevalence of small intestinal bacterial overgrowth among GERD patients, with striking decrease from 56.2% in placebo group to 6.2% in those receiving probiotics ($P<0.001$). This supports the notion that specific probiotic strains can maintain a healthier gut

microbiome and potentially alleviate GERD symptoms [30]. These findings highlight intricate interplay between microbiota and GERD pathophysiology, focusing on need for continued research into targeted microbiome-based interventions to optimize treatment outcomes for individuals suffering from GERD.

A majority of the studies analyzed found significant associations between specific bacterial taxa and GERD. For instance, Li et al. (2024) observed a reduction in the phylum Actinobacteria among GERD patients, which aligns with our findings that indicated alterations in gut microbiota composition linked to GERD severity [31]. Similarly, studies by D'Souza et al. (2021) and Wang (2024) found a marked increase in Proteobacteria and Bacteroidetes levels in pediatric GERD patients, while levels of Firmicutes and Actinobacteria were notably lower, suggesting a dysbiotic state in these individuals that could exacerbate reflux symptoms [21, 32].

The mechanisms by which probiotics exert beneficial effects on GERD symptoms are multifaceted. Probiotics including Lactobacillus and Bifidobacterium species are known for their ability to modulate immune responses and produce short-chain fatty acids (SCFAs) like lactic acid which can enhance gut barrier function and reduce inflammation [33, 34]. Our study noted that 79% of comparisons included reported positive effects of probiotics on GERD-related symptoms, including regurgitation, heartburn, and abdominal discomfort. This finding echoes the result of meta-analysis by Agah et al. (2020), where supplementation with Lactobacillus gasseri LG21 resulted in significant decrease in reflux episodes and symptom severity, with frequency scores dropping from 6.2 to 4.8 after 12 weeks of treatment [35].

Moreover, the role of gastric emptying in GERD has been studied by Nakae et al. (2016) that reported that LG21 improved gastric emptying rates, which may mitigate symptoms of reflux by reducing time food remains in the stomach [36]. This finding is significant, as delayed gastric emptying is recognized contributor to GERD pathophysiology. Our study also indicated that probiotics can enhance gastric motility and possibly decrease transient lower esophageal sphincter relaxations. Another important aspect is interaction between probiotics and PPIs. Our study revealed that PPIs could enhance colonization of certain probiotic species while simultaneously leading to microbial dysbiosis. Earlier research by Kiecka et al. (2023) and Levy et al. (2020) found that prolonged PPI use altered esophageal microbiome and could contribute to increase risk of infections due to reduced gastric acidity [37, 38]. Our findings also suggest that concurrent probiotic therapy may help restore microbial balance and alleviate adverse effects linked with PPI therapy.

The pathophysiological implications of gut microbiota in GERD also extend to inflammatory responses. Studies showed that specific bacterial communities, particularly those producing SCFAs, play crucial role in maintaining intestinal homeostasis and preventing inflammatory conditions [6, 39]. Our review also aligns with research conducted by Venegas et al. (2019), which focused on inverse relationship between attendance of SCFA-producing bacteria and severity of GERD symptoms [34]. This reinforces the potential therapeutic benefits of probiotic in enhancing SCFA production and mitigating inflammation. A retrospective study by García-Santos et al (2023) evaluated various probiotic strains and their efficacy in managing GERD symptoms, highlighting that multi-strain formulations, including Lactobacillus and Bifidobacterium species, were particularly effective [40]. This supports our findings of diverse product formats utilized across studies and varied efficacy reported.

This systematic review has some limitations that should be acknowledged. First, the heterogeneity in study designs and outcomes among the included trials hindered the ability to perform a meta-analysis, limiting the robustness of our conclusions. Additionally, the varying formulations and dosages of probiotics used across studies may affect their efficacy and comparability. The small sample sizes of some studies also restrict the generalizability of findings. Moreover, the potential confounding effects of coexisting conditions, such as Helicobacter pylori infection and other gastrointestinal disorders, were not uniformly evaluated, which may influence the relationship between gut microbiota and GERD [41, 42]. Lastly, while we identified several relevant studies, the overall quantity of research specifically linking probiotic strains to GERD remains limited, indicating a need for further investigations.

Conclusion:-

In conclusion, this systematic review underscores the significant relationship between gut microbiota and GERD, revealing distinct microbial profiles associated with the condition. Notably, probiotics demonstrate a promising role in managing GERD symptoms, particularly by reducing dysbiosis and promoting beneficial microbial communities. Our findings highlight the necessity for future research focused on large-scale, well-designed studies to further elucidate the specific mechanisms through which probiotics influence GERD. Additionally, exploring dietary

interventions and their synergistic effects with probiotics could enhance therapeutic strategies. Overall, understanding the intricate interplay between gut microbiota and GERD paves the way for innovative, microbiome-based approaches to optimize patient management and prevent progression to more severe esophageal conditions.

Appendix

Tab. 1:- The quality assessment of the included studies using the JADAD scale.

Author Name & Year	Study Design	JADAD Score	Comments
Xiaolin Ye, 2023	Randomized study	3	Randomization and blinding reported, but details on withdrawals not specified.
Yuan Liu, 2024	Bidirectional two-sample randomization study	2	Randomization described, but no mention of blinding or withdrawals.
Kui Wang et al., 2024	Bidirectional Randomization study	2	Randomization present, but lacks blinding details and withdrawal information.
Gulshan Singh et al., 2022	Double-blind, parallel, placebo-controlled trial	5	Clear randomization, blinding, and handling of withdrawals well-documented.
Oana Belei et al., 2018	Prospective, randomized controlled trial	4	Randomization and blinding clearly described; withdrawals mentioned but not detailed.
Ti Yang et al., 2023	Two-sample randomization study	3	Randomization mentioned, but details on blinding and withdrawals not provided.

JADAD Scale Explanation:

- **0**: No randomization, no blinding, no description of withdrawals.
- **1-2**: Studies with randomization but lacking details on blinding and withdrawals.
- **3-4**: Studies that adequately describe randomization, blinding, and withdrawals.
- **5**: Highest quality studies with complete reporting on all aspects of the JADAD scale.

Table 1:- The quality assessment of included cohort studies using the Newcastle-Ottawa Scale (NOS).

Author Name & Year	Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)	Total Score (out of 9)	Comments
Yi-Chao Shi et al., 2019	3	1	2	6	Well-defined cohort, but no description of follow-up.
Denease Francis et al., 2023	4	2	3	9	Comprehensive reporting; strong design and clear outcomes.

Newcastle-Ottawa Scale Explanation:

- **Selection**: Up to 4 stars for clear definition of cohorts and appropriate selection criteria.
- **Comparability**: Up to 2 stars for controlling for confounding factors.
- **Outcome**: Up to 3 stars for clearly defined outcomes and appropriate follow-up.

Table 2:- Data Extraction sheet of the included studies.

Author name & year of publication	Study design	Participant characteristics	Reflux symptoms	Clinical interventions	Gut Microbiota and GERD Relationship	Adverse effects	Key finding
Xiaolin Ye, 2023 [22]	Randomized study using metagenomics and metabolomics analysis	Total Participants: 60 (30 children with GERD, 30 healthy controls) Age Range: 3 to 14 years Health Conditions: GERD confirmed by endoscopy or 24-hour esophageal pH examination	Documented gastrointestinal symptoms consistent with GERD	focus on gut microbiota analysis and metabolomic profile	Significant differences in gut microbiota diversity and composition between children with GERD and healthy controls; dominant bacteria in GERD included Proteobacteria and Bacteroidota.	Assessments for gastrointestinal symptoms were made.	- Gut microbiota diversity was significantly lower in GERD children. - Significant differences in metabolic pathways related to energy, amino acids, and lipid metabolism. - 288 different metabolites detected; changes correlated with specific bacterial levels. - Potential for targeting specific bacteria related to arachidonic acid metabolism for future GERD treatments.
Yuan Liu, 2024 [23]	Bidirectional two-sample randomization study	Total participants: 26,078 (MiBioGen: 18,340; Dutch Microbiome Project: 7,738; GERD: 602,604; BE: 56,429) Health Conditions: Included GERD and Barrett's esophagus (BE)	Phenotypic definitions included self-reporting, ICD-10/ICD-9 diagnoses, operative procedures, and use of GERD-related medication	focus on gut microbiota analysis and metabolomic profile	Identified 11 bacterial taxa and 13 metabolic pathways associated with GERD; 18 taxa and 5 pathways associated with BE.	Assessments for gastrointestinal symptoms were made; prevalence of SIBO (small intestinal bacterial overgrowth) monitored	- Established causal links between gut microbiota and GERD/BE. - Faecalibacterium prausnitzii showed suggestive impact on both GERD (OR=1.087) and BE (OR=1.388). - Weight and BMI were identified as crucial mediators. - Reverse MR indicated BE affected multiple taxa and pathways but GERD did not affect gut microbiota. - Significant associations found between gut microbiota taxa and metabolic pathways with GERD and BE risks.
Kui Wang et al., 2024 [24]	Bidirectional Randomization study	Total Participants: 97,047 (18,340 for gut microbiota, 78,707 GERD cases, 288,734 controls)	GERD symptoms include abnormal	focus on gut microbiota analysis and metabolomic profile	Genetic correlation indicating both protective and risk-related microbiota	Assessments for gastrointestinal symptoms	1. Protective microbiota: Family Clostridiales Vadin BB60, Genus Lachnospiraceae UCG004, Genus Methanobrevibacter, Phylum

		Age: 3-14 years Sex: Male 56%, female 44% Health Conditions: GERD confirmed by endoscopy or 24-hour esophageal pH examination.	esophageal acid exposure leading to symptoms and/or mucosal injury.		taxa for GERD.	were made.	Actinobacteria ($P < 0.05$). 2. Risk factors: Class Mollicutes, Genus Anaerostipes, Phylum Tenericutes ($P < 0.05$). 3. GERD influences gut microbiota, leading to dysbiosis in 13 classes post GERD onset. 4. Reliable results confirmed through sensitivity analyses for heterogeneity and pleiotropy.
Gulshan Singh et al., 2022 [25]	Double-blind, parallel, placebo-controlled trial	Total Participants: 30 Age: 18-56 years Sex: 10 males, 20 females Health Conditions: Healthy volunteers without pre-existing gastrointestinal symptoms; no antibiotic treatment or dietary restrictions	Participants were not specified to have reflux symptoms; they were healthy volunteers.	PPI (Omeprazole 20 mg/day) or placebo for 6 weeks, followed by multi-strain probiotics (900 billion CFUs/day) for 4 weeks	PPI treatment led to microbial alterations (e.g., increased abundance of Streptococcaceae) and probiotics potentially mitigate PPI-induced dysbiosis	Exclusion criteria included individuals with dietary sensitivities, Helicobacter pylori infection, pregnancy, or chronic conditions.	- PPI enhanced colonization of certain probiotics (e.g., Streptococcus thermophilus) - Probiotics suppressed PPI-induced microbial changes - Metabolomic changes observed, with certain metabolites increased post-treatment - Probiotics may be beneficial when combined with PPIs for gut microbiota health
Oana Belei et al., 2018 [26]	Prospective, randomized controlled trial	**Total Participants:** 248 children (128 with GERD, 120 controls) **Age: 1**-18 years (mean age 8 ± 2.2 years) **Sex Distribution:** Control group: 41 girls, 79 boys; Placebo group: 29 girls, 35 boys; Probiotics group: 21 girls, 43 boys **Health Conditions:** Children with GERD (diagnosed based on NASPGHAN/ESPGHAN guidelines); controls were healthy children	Assessed using a Likert scale for severity of gastrointestinal symptoms (e.g., abdominal pain, bloating, diarrhea)	12 weeks of PPI treatment (esomeprazole) Two groups: - Placebo group: PPI + placebo (64 children) - Probiotics group: PPI + Lactobacillus reuteri DSM 17938 (64 children)	Long-term PPI use was associated with dysbiosis; probiotics reduced dysbiosis prevalence significantly compared to placebo	Assessments for gastrointestinal symptoms were made; prevalence of SIBO (small intestinal bacterial overgrowth) monitored	- Dysbiosis in 56.2% of placebo group vs. 6.2% in probiotics group ($P < 0.001$) - SIBO detected in 36 (56.2%) in placebo group; only 4 (6.2%) in probiotics group - Symptoms more prevalent in placebo group (63.8% symptomatic) vs. probiotics group (0% symptomatic) - Probiotics significantly decreased dysbiosis and SIBO prevalence among children treated with PPI compared to placebo
Yi-Chao Shi et al.,	Comparative study using	**Total Participants:** 55 (40 GERD patients, 15 healthy	GERD patients had endoscopic	GERD patients classified as non-	PPI use associated with decreased	Helicobacter pylori	- PPI administration reduces bacterial diversity in gastric

2019 [27]	16S rRNA gene sequencing to analyze gastric mucosal and fecal microbiota.	controls) **Age:** 1-18 years **Sex:** male 55%, female 45% **Health Conditions:** GERD patients (with and without PPI use) and healthy controls (HCs)	evidence of esophagitis (based on the Los Angeles classification).	PPI users and PPI users (omeprazole, 40 mg/day). Users further divided into short-term (6 months) and long-term (18 months).	gastric microbial diversity; specific changes in microbial composition observed in both gastric and fecal samples.	infection, pregnancy, or chronic conditions.	microbiota. - Increased abundances of Planococcaceae, Oxalobacteraceae, and Sphingomonadaceae in PPI users. - Fecal microbiota composition differed significantly between PPI users and non-users. - Long-term PPI users had higher Ruminococcus and Methylophilus abundances. - Metabolic pathway alterations in gastric and fecal microbiomes were identified.
Ti Yang et al., 2023 [28]	Two-sample randomization study	Total Participants: 647,604 (129,080 cases of GERD and 473,524 controls) Age: 1-18 years Sex: male 48%, female 52% Health Conditions: GERD defined using ICD codes, physician diagnosis, and adjudication	GERD symptoms assessed via physician diagnosis and ICD codes	focus on gut microbiota analysis and metabolomic profile	Analysis of 196 bacterial traits using genetic instruments; identified associations between gut microbiota and GERD	individuals with dietary sensitivities, Helicobacter pylori infection, pregnancy, or chronic conditions.	8 bacterial taxa associated with GERD (4 risk factors, 4 protective factors) - Protective Factors: Bifidobacteriaceae (P = 0.026), Bifidobacteriales (P = 0.002), Christensenellaceae (P = 0.000), Odoribacter (P = 0.024) - Risk Factors: Mollicutes (P = 0.003), Tenericutes (P = 0.003), Rikenellaceae (P = 0.015), Prevotella 9 (P = 0.013) - No reverse causal relationship found between GERD and gut microbiota
Denease Francis et al., 2023 [29]	Cohort study conducted at Stony Brook Hospital from February 2016 to June 2019	Total Participants 76 recruited, 60 enrolled (29 with reflux, 29 controls) Age: 2 weeks to 6 months Sex: Reflux infants: 46.7% male; Control infants: 58.6% male Health Conditions: Infants with symptomatic gastroesophageal reflux and healthy controls	Clinically diagnosed gastroesophageal reflux	Proton pump inhibitors (PPI) therapy for reflux infants, duration ≥ 4 weeks prior to enrollment	PPI exposure linked to altered gut microbiota profiles; reflux infants showed increased diversity and richness	Assessments for gastrointestinal symptoms were made; prevalence of SIBO (small intestinal bacterial overgrowth) monitored	- Significant differences in α- and β-diversity between reflux infants and controls - Increased Firmicutes in reflux infants - Control group dominated by Bifidobacterium - Duration of PPI exposure correlated with microbiome diversity and abundance

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