

# Sweeteners and the Gut: A Systematic Review of Synthetic Versus Natural Impacts on Gut Microbial Diversity

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## **Abstract**

Synthetic and natural sweeteners are widely consumed, yet their effects on gut microbiota diversity and host metabolism remain contested. This systematic review synthesized evidence from ten studies, including human trials, animal models, and in vitro experiments, to evaluate microbial and metabolic outcomes associated with sweetener exposure in healthy adults. Synthetic sweeteners such as sucralose and neotame were consistently associated with reduced alpha diversity, enrichment of pro-inflammatory taxa, and impaired glucose tolerance. In contrast, natural sweeteners including steviol glycosides, erythritol, rebaudioside A, and xylitol preserved microbial richness and promoted short-chain fatty acid (SCFA) production. The findings support the hypothesis that synthetic sweeteners negatively affect microbial diversity, whereas natural sweeteners preserve or enhance microbial resilience.

Interpretation of results was complicated by heterogeneity in dosage, duration, and delivery methods, underscoring the need for standardized protocols. Professional organizations such as the Academy of Nutrition and Dietetics and the U.S. Food Drug Administration affirm the

safety of approved nonnutritive sweeteners within established intake levels, while federal agencies emphasize the importance of long-term research into microbiota outcomes. Collectively, the evidence supports cautious use of synthetic sweeteners and highlights natural alternatives as potential microbiota-supportive options. Practitioners should apply individualized recommendations, balancing organizational guidance with patient-specific needs.

**Keywords:** synthetic sweeteners, natural sweeteners, gut microbiota, microbial diversity, dysbiosis, short-chain fatty acids

## 1. Introduction

### 1.1 Introduce the Problem

Interest in sweeteners has increased substantially over the past decade due to concerns about sugar intake, metabolic health, and evolving dietary preferences (Garcia et al., 2022; Hetta et al., 2025; Chattopadhyay et al., 2014). Artificial sweeteners such as sucralose, saccharin, acesulfame-K, neotame, and aspartame are widely incorporated into beverages, processed foods, and medications due to their low or zero caloric content (Lee et al., 2024; Kroger et al., 2006). However, emerging evidence suggests the compounds may disrupt gut microbial diversity and promote dysbiosis by reducing beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* (Lee et al., 2024; Kidangathazhe et al., 2025; Suez et al., 2022).

The gut microbiota plays a central role in metabolic, immune, and gastrointestinal health, and its composition is highly responsive to dietary inputs (Hetta et al., 2025; Suez et al., 2022; Garcia et al., 2022). Sweeteners, both synthetic and natural, can influence microbial fermentation, short-chain fatty acid (SCFA) synthesis, and mucosal integrity, with downstream effects on host metabolism and inflammation (Lee et al., 2024). Clarifying their role in gut microbial ecology is essential for guiding evidence-based dietary recommendations and public health policy.

### 1.2 Explore Importance of the Problem

Natural sweeteners such as Stevia, monk fruit, agave nectar, coconut sugar, honey, and maple syrup are often perceived as more wholesome alternatives. Nonnutritive natural sweeteners including steviol glycosides, erythritol, rebaudioside A, and xylitol have demonstrated neutral or beneficial effects on gut microbiota, such as increased *Bifidobacteria* and *Akkermansia* and preservation of microbial diversity (Garcia et al., 2022; Kidangathazhe et al., 2025). These effects may be linked to enhanced SCFA production and reduced inflammatory signaling (Ruiz-Ojeda et al., 2019).

In contrast, synthetic sweeteners have been associated with enrichment of potentially pathogenic taxa such as *Enterobacteriaceae* and reduction of beneficial groups like *Lachnospiraceae* (Kidangathazhe et al., 2025). Studies have employed diverse models, including human trials, animal studies, and in vitro fermentation systems, each offering distinct insights but also contributing to heterogeneity in findings (Ruiz-Ojeda et al., 2019). This review builds on prior work by integrating microbial and metabolic outcomes across

study designs.

### *1.3 Describe Relevant Scholarship*

Previous research has examined the effects of both synthetic and natural sweeteners on gut microbiota composition, microbial diversity, and metabolic outcomes. Synthetic sweeteners such as sucralose, saccharin, acesulfame-K, and neotame have been associated with reduced microbial diversity, enrichment of pro-inflammatory taxa, and alterations in glucose tolerance in both human and animal studies (Lee et al., 2024; Méndez-García et al., 2022; Suez et al., 2022). These findings suggest that synthetic sweeteners may disrupt microbial stability, although results vary depending on dosage, duration, and study design. For example, some studies report significant microbial shifts, while others find minimal or no changes, particularly with saccharin (Serrano et al., 2021).

In contrast, natural sweeteners such as steviol glycosides, erythritol, rebaudioside A, and xylitol have demonstrated neutral or beneficial effects on gut microbiota. Studies have reported preservation of microbial richness, increases in beneficial taxa such as *Bifidobacteria* and *Akkermansia*, and enhanced short-chain fatty acid production (Garcia et al., 2022; Mahalak et al., 2020; Kidangathazhe et al., 2025). These outcomes suggest natural sweeteners may support microbial stability and metabolic resilience.

Despite growing interest, the literature remains heterogeneous, with variability in study populations, sweetener types, intervention durations, and analytical methods. Prior reviews have often focused on individual sweeteners or isolated outcomes, leaving a gap in comprehensive comparisons across synthetic and natural sweetener classes. This systematic review addresses that gap by integrating microbial and metabolic findings across human, animal, and in vitro models.

### *1.4 State Hypotheses and Their Correspondence to Research Design*

The primary hypothesis guiding this review is synthetic sweeteners negatively affect gut microbiota diversity and metabolic outcomes, whereas natural sweeteners preserve or enhance microbial richness and metabolic resilience. Secondary objectives include evaluating heterogeneity across study designs and identifying gaps for future research.

This systematic review follows PRISMA guidelines and employs structured article selection, risk of bias assessment, and synthesis of microbial and metabolic endpoints. This design permits inference regarding consistent patterns across diverse models and highlights areas where evidence remains inconclusive.

## **2. Method**

### *2.1 Search Strategy*

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines (Page et al., 2021). A structured protocol was developed in advance to ensure methodological transparency and reproducibility. The review aimed to identify and synthesize peer-reviewed studies examining

the effects of synthetic sweeteners compared to natural sweeteners on gut microbiota composition and diversity in healthy adults. The protocol was registered with PROSPERO (CRD420251088766).

A comprehensive literature search was conducted between June 2025 and August 2025 using PubMed, ScienceDirect, Google Scholar, and University of Houston Library search tools. The search strategy combined controlled vocabulary (MeSH terms) with key words related to population, intervention, and outcomes. (see **Table 1**). Boolean operators (AND, OR) were used to refine results, and filters were applied to identify articles published between 2015 and 2025. A 10-year window was selected to capture both foundational mechanistic studies and contemporary clinical trials, as research on sweeteners and gut microbiota has expanded substantially over the past decade.

Table 1. MeSH and Key Terms for Database Searching

Key Words MeSH Terms to describe the population	Key Words MeSH Terms to describe the intervention	Key Words MeSH Terms to describe the outcome
Healthy Humans	Artificial sweeteners	Microbiome
Adult AND Men	Saccharin	Diversity
Adult AND Women	Sucralose	Intestinal flora
	Xylitol	Human gut microbiota
	Natural Sugar	Intestinal microbiome
		Gut diversity

## 2.2 Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria aligned with the research question (see **Table 2**). Eligible studies were original, peer-reviewed research articles involving human clinical trials, animal models, and in-vitro experiments that compared synthetic sweeteners (e.g. sucralose, saccharin, acesulfame-K) with natural sweeteners (e.g. Stevia, erythritol, rebaudioside A), and reported outcomes related to gut microbiota composition or diversity. Human studies required a minimum sample size of  $\geq 10$  participants to ensure adequate statistical power. Animal and in vitro studies were included if they demonstrated methodological rigor.

Studies were excluded if they involved participants with underlying health conditions, were systematic reviews, included fewer than ten participants, or were published before 2015.

Table 2. Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
<b>Age</b>	≥18 years	<18 years
<b>Gender</b>	Male & Female	N/A
<b>Setting/Country</b>	Any country	N/A
<b>Health Status/ Problem/Condition</b>	Good health status	Underlying health conditions
<b>Intervention/Exposure</b>	Synthetic sweeteners (saccharin, sucralose, acesulfame-K) vs natural sweeteners (rebaudioside A, xylitol)	Use of probiotics or antibiotics
<b>Outcome</b>	Health of the gut and microbiome diversity	N/A
<b>Study Design Preferences</b>	Meta-analysis, RCTs	Systematic reviews
<b>Size of Study Groups</b>	Human studies ≥10 participants; animal and in vitro studies with valid design	Human studies <10 participants
<b>Language</b>	English	Any language other than English
<b>Publication Year Range</b>	2015-2025	2014 and earlier
<b>Other</b>	Animal and in vitro	N/A

### 2.3 Data Extraction and Quality Assessment

A standardized data extraction table was used to collect study characteristics, participant demographics, intervention details, and microbiota-related outcomes (Academy of Nutrition and Dietetics, 2021). Methodological quality and risk bias were assessed using the Academy of Nutrition and Dietetics Evidence Analysis Library (EAL) Quality Criteria Checklist (Page et al., 2021). Each study was rated as a positive (+) neutral (Ø), or negative (-) based on these criteria.

### 2.4 Research Design

Because this review synthesizes evidence across human, animal, and in vitro models,

heterogeneity in methodology was expected. Human trials typically used crossover or parallel designs with controlled sweetener exposure. Animal studies used standardized chow with sweetener supplementation. In vitro studies used fecal inocula to simulate colonic fermentation.

This multi-model approach allows triangulation of findings and identification of consistent patterns across biological systems.

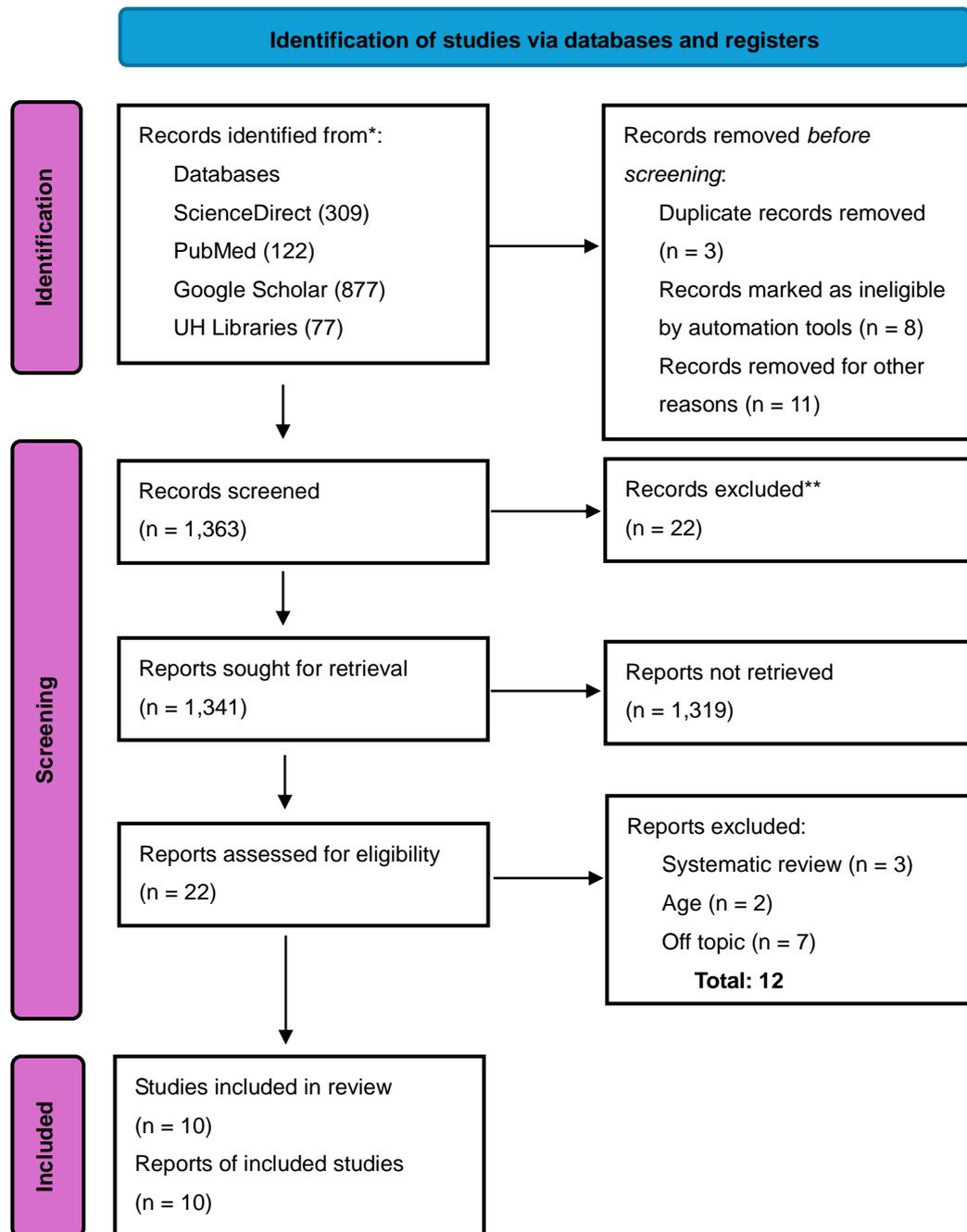


Figure 1. PRISMA 2020 flow diagram illustrating the study selection process for this systematic review

### 3. Results

#### 3.1 Overview of Included Studies

A total of 1,385 records were identified through database searches (ScienceDirect = 309, PubMed = 122, Google Scholar = 877, University of Houston Libraries = 77). After removing duplicates ( $n = 3$ ), automation exclusions ( $n = 8$ ), and other ineligible records ( $n = 11$ ), 1,363 titles and abstracts were screened. Of these, 22 were excluded, and 1,341 reports were sought for retrieval. A total of 1,319 reports were not retrieved, and 22 full-text articles were assessed for eligibility. Twelve were excluded due to being systematic reviews ( $n = 3$ ), age-inappropriate populations ( $n = 2$ ), or off topic ( $n = 7$ ). Ultimately, ten studies met inclusion criteria: four human clinical trials, four animal studies, and two in vitro models. The study selection process is illustrated in **Figure 1**.

The ten studies varied in design, duration, and methodology, offering a broad perspective on sweetener-microbiota interactions. Sample sizes ranged from three (in vitro) to 1,273 participants (human trial). Sweeteners examined included sucralose, saccharin, neotame, acesulfame-K, steviol glycosides, erythritol, and rebaudioside A. Sequencing methods included 16S rRNA gene sequencing, shotgun metagenomics, qPCR, and metabolic assays. All studies received a positive (+) quality rating based on the Academy of Nutrition and Dietetics Evidence Analysis Library (EAL) criteria. Detailed study characteristics are presented in **Table 3**.

#### 3.2 Effects of Synthetic Sweeteners on Gut Microbiota

Synthetic sweeteners, particularly sucralose and neotame, demonstrated consistent and statistically significant disruptions to gut microbial diversity across human, animal, and in vitro models. Sucralose reduced *Lactobacillus acidophilus* by 34% ( $0.66\times$ ,  $p < 0.05$ ) and tripled *Blanta coccoides* abundance ( $p < 0.01$ ) in humans, indicating a shift toward pro-inflammatory taxa (Mendez-Garcia et al., 2022). In mice, Zheng and colleagues (2022) observed that sucralose exposure decreased *Lachnospiraceae* and increased *Staphylococcus* and *Ruegeria* ( $p = 0.05$ , respectively), taxa associated with epithelial inflammation and metabolic dysregulation. Neotame decreased alpha diversity ( $p < 0.05$ ), increased *Bacteroidetes* ( $p < 0.01$ ), and elevated cholesterol ( $p < 0.001$ ) and malic acid ( $p < 0.01$ ), suggesting systemic metabolic effects (Chi et al., 2018).

Saccharin produced mixed results. Serrano et al. (2021) found no significant changes in alpha diversity or glucose tolerance in humans or mice ( $p > 0.05$ ), whereas Bian et al. (2017) reported sex-specific microbial shifts in mice, with decreased *Lactobacillus* in females and increased *Bacteroides* in males ( $p < 0.01$ ). Acesulfame-K increased microbial diversity but disrupted microbial network structure ( $p = 0.04$ ) and was associated with increased body weight ( $p < 0.01$ ) in male mice (Bian et al., 2017).

Overall, synthetic sweeteners consistently reduced microbial diversity and enriched pro-inflammatory taxa across human animal, and in vitro models.

### 3.3 Effects of Natural Sweeteners on Gut Microbiota

Natural sweeteners, including steviol glycosides, erythritol, rebaudioside A, and xylitol, exhibited neutral or beneficial effects on gut microbiota composition and diversity. Erythritol increased butyric acid (~2.1× fold change) and pentanoic acid (~1.8× fold change) in primate models, both SCFAs associated with anti-inflammatory signaling and gut barrier integrity, although statistical significance was not reported (Mahalak et al., 2020). Kidangathazhe et al. (2025) found that rebaudioside A and xylitol preserved microbial diversity and supported beneficial taxa such as *Faecalibacterium* and *Roseburia* in vitro ( $p > 0.05$ ). No inhibitory effects on bacterial growth were observed with steviol glycosides or erythritol, and SCFA production was consistently enhanced.

Across models, natural sweeteners maintained microbial stability and promoted fermentation profiles associated with metabolic resilience.

### 3.4 Microbial Diversity Metrics

Quantitative diversity metrics were reported in seven of the ten studies (Bian et al., 2017; Chi et al., 2018; Kidangathazhe et al., 2025; Mahalak et al., 2020; Romo-Romo et al., 2024; Serrano et al., 2021; Zheng et al., 2022). Alpha diversity significantly decreased with sucralose ( $p < 0.0002$ ), neotame ( $p < 0.05$ ), and saccharin ( $p = 0.01$ ), while natural sweeteners preserved or enhanced diversity. SCFA changes were quantified via GC-MS in Mahalak et al. (2020) and Chi et al. (2018), with erythritol and steviol glycosides increasing butyrate and pentanoate levels. Romo-Romo and colleagues (2024) reported metabolic outcomes in humans: sucralose consumption increased insulin AUC ( $p = 0.02$ ), glucose AUC ( $p = 0.03$ ), and decreased insulin sensitivity ( $p < 0.01$ ).

These findings provide quantitative support for the differential effects of synthetic versus natural sweeteners on microbial diversity and metabolic function.

### 3.5 Risk of Bias

All included studies received a positive (+) rating using the EAL quality Criteria Checklist. Human trials demonstrated strong internal validity with randomized designs, validated sequencing methods, and clinically relevant endpoints. Animal and in vitro studies employed controlled exposures, reproducible assays, and appropriate statistical analyses. Minor limitations included small sample sizes, lack of long-term follow-up, and potential funding bias in select studies. Overall, the consistent methodological rigor across studies supports confidence in the synthesized findings.

Table 3. Summary of included studies evaluating the effects of synthetic and natural sweeteners on gut microbiota composition and diversity

Citation	Design/ Model	Sample Size & Description	Sweeteners Studied	Key Microbiota Outcomes	Quality Rating
Bian et al. (2017)	Animal (mice)	CD-1 mice, sex-stratified	Ace-K	Sex-specific shifts: decreased <i>Lactobacillus</i> ( $p < 0.05$ ) (females), increased <i>Bacteroides</i> ( $p < 0.01$ ) (males); increased weight gain ( $p < 0.01$ )	Positive (+)
Chi et al. (2018)	Animal (mice)	CD-1 mice	Neotame	Decreased Firmicutes ( $p < 0.01$ ); increased Bacteroidetes ( $p < 0.01$ ); increased cholesterol ( $p < 0.001$ ); malic acid decreased ( $p < 0.01$ )	Positive (+)
Kidangathazhe et al. (2025)	In vitro bioreactor	3 healthy adult fecal donors	Saccharin, sucralose, Ace-K, Rebaudioside A, Xylitol	Synthetic sweeteners (Sucralose $p = 0.003$ ); (Saccharin $p = 0.01$ ) decreased microbial diversity; natural sweeteners (Rebaudioside A, Xylitol NS) supported beneficial taxa; Acesulfame K increased diversity but disrupted network structure ( $p = 0.04$ )	Positive (+)
Mahalak et al. (2020)	In vitro + primate	Human fecal fermentation + <i>Cebus apella</i>	SGs, Erythritol	Taxonomic shifts; SCFA changes; Increased butyrate ( $\sim 2.1\times$ ) and pentanoate ( $\sim 1.8\times$ ); no growth inhibition; microbial shifts in <i>Cebus apella</i> not quantified with p-values	Positive (+)

Mendez-Garcia et al. (2022)	Human trial	40 healthy adults	Sucralose	Decreased <i>Lactobacillus acidophilus</i> ( $p < 0.05$ ); increased <i>Blautia coccoides</i> ( $p < 0.01$ ); increased glucose AUC ( $p = 0.03$ )/insulin AUC ( $p = 0.02$ )	Positive (+)
Romo-Romo et al. (2024)	Triple-blind RCT	24 healthy adults	Sucralose	Decreased alpha diversity ( $p < 0.0002$ ); decreased insulin sensitivity; increased <i>Bacteroides fragilis</i> and LPS ( $p < 0.01$ )	Positive (+)
Serrano et al. (2021)	RCT + mouse model	46 adults + C57BL/6 mice	Saccharin	No significant changes in diversity or glucose tolerance	Positive (+)
Thomson et al. (2019)	Double blind RCT	34 healthy males	Sucralose	No global metabolic changes; responders had decreased in <i>Bacteroidetes</i> , increased <i>Firmicutes</i>	Positive (+)
Wang et al. (2018)	Mouse + in vitro	Adolescent mice + bacterial strains	Sucralose, Saccharin, Rebaudioside A, Ace-K	Synthetic sweeteners disrupted microbial balance and suppressed bacterial growth; sucralose increased <i>Firmicutes</i> ( $p = 0.02$ ), decreased <i>Bacteroidetes</i> ( $p = 0.03$ )	Positive (+)
Zheng et al. (2022)	Dose-response animal	40 C57BL/6 mice	Sucralose	Decreased <i>Lachnospiraceae</i> ; increased <i>Staphylococcus</i> and <i>Ruegeria</i> ; inflammatory histology	Positive (+)

#### 4. Discussion

Synthetic and natural sweeteners exert distinct effects on gut microbiota composition, microbial diversity, and metabolic outcomes. Across human, animal, and in vitro models,

synthetic sweeteners consistently demonstrated reductions in alpha diversity, enrichment of pro-inflammatory taxa, and impaired glucose tolerance, whereas natural sweeteners generally preserved microbial richness and supported beneficial microbial functions.

#### *4.1 Interpretation of Findings*

Reduced microbial diversity is a hallmark of dysbiosis and has been linked to increased risk of metabolic disorders, inflammation, and impaired gut barrier function. Several studies in this review demonstrated that synthetic sweeteners contribute to these patterns. For example, sucralose decreased *Lactobacillus acidophilus* by 34% and tripled *Blautia coccoides* abundance, taxa associated with glucose intolerance and inflammatory signaling (Mendez-Garcia et al., 2022). Neotame disrupted the Firmicutes/Bacteroidetes ratio and elevated cholesterol and malic acid levels, suggesting systemic metabolic stress (Chi et al., 2018). These microbial shifts were mirrored by increased insulin and glucose AUCs and reduced insulin sensitivity in human trials (Romo-Romo et al., 2024), even in healthy adults aged 18-35 years, a demographic with relatively low baseline metabolic risk.

In contrast, natural sweeteners demonstrated a more favorable microbial profile. Erythritol increased butyric acid and pentanoic acid levels, SCFAs known to support epithelial integrity and anti-inflammatory pathways (Mahalak et al., 2020). Rebaudioside A and xylitol preserved microbial diversity and supported beneficial taxa such as *Faecalibacterium* and *Roseburia*, both associated with metabolic resilience and mucosal health (Kidangathazhe et al., 2025). These findings suggest natural sweeteners may offer protective effects on gut microbiota and host metabolism.

Collectively, the evidence highlights a concerning pattern of metabolic disruption linked to synthetic sweetener exposure and a comparatively supportive microbial response to natural sweeteners.

#### *4.2 Comparison with Previous Research*

The results of this review align with broader literature suggesting synthetic sweeteners may compromise microbial stability and promote dysbiosis (Suez et al., 2022; Garia et al., 2022). However, not all synthetic sweeteners behaved uniformly. Saccharin, for example, produced mixed results: Serrano et al. (2021) found no significant microbial changes in human or mice, while Bian et al. (2017) reported sex-specific microbial shifts. These inconsistencies underscore the importance of dose, host microbiome baseline, and study design. Plizga et al. (2024) further emphasize that microbial responses to sweeteners are highly individualized, reinforcing the need for personalized nutrition strategies.

Natural sweeteners may have been less extensively studied, but available evidence suggests they exert minimal negative effects on microbial diversity. Mahalak et al. (2020) demonstrated that steviol glycosides and erythritol preserved microbial richness in both human and primate models. These findings support the hypothesis that natural sweeteners may be more compatible with gut microbial ecology.

### *4.3 Strengths and Limitations*

This review highlights the differential impact of synthetic versus natural sweeteners on gut ecology and host physiology. A major strength of this synthesis is the integration of microbial and metabolic endpoints across human, animal, and in vitro designs, allowing for triangulation of findings. The comparative approach strengthens the relevance of results for dietary guidance and public health.

However, interpretation of findings must consider heterogeneity across studies. Differences in sweetener type, dosage, duration of exposure, and delivery method likely contributed to variability in microbiota outcomes. Acute versus chronic dosing may influence microbial adaptation, and delivery via beverage versus capsule may alter fermentation dynamics. The inconsistencies complicate direct comparisons and highlight the need for standardized protocol in future research.

### *4.4 Practical Implications for Practitioners*

This review highlights actionable considerations for nutrition and healthcare professionals. Synthetic sweeteners such as sucralose and neotame were consistently linked to microbial shifts associated with dysbiosis, inflammation, and metabolic instability. Given the widespread use of the compounds in processed foods and beverages, practitioners should be vigilant in assessing potential impact on client health, particularly among populations with existing metabolic or gastrointestinal vulnerabilities.

For patients with metabolic syndrome, insulin resistance, prediabetes, or gastrointestinal conditions such as irritable bowel syndrome (IBS), limiting intake of synthetic sweeteners may be advisable. Evidence from human and animal studies suggests that compounds like sucralose and neotame can reduce beneficial taxa, impair glucose tolerance, and alter SCFA profiles. Practitioners may instead guide patients toward natural alternatives such as Stevia, erythritol, or rebaudioside A, which demonstrated more favorable effects on microbial diversity and SCFA production. Recommendations should be individualized, and patients should be encouraged to monitor symptoms such as bloating, bowel irregularity, or glucose fluctuations when modifying sweetener intake.

Natural sweeteners appear to offer a more microbiota-supportive profile. Stevia-derived compounds, erythritol, and rebaudioside A preserved microbial richness and supported beneficial taxa such as *Faecalibacterium* and *Roseburia*, which are associated with mucosal health and metabolic resilience. Personalized guidance remains essential, as emerging evidence indicates that host-specific microbial composition influences tolerance and metabolic response to sweeteners. In some cases, clinical monitoring of SCFA levels, glucose tolerance, and gastrointestinal symptoms may be warranted for individuals consuming high levels of nonnutritive sweeteners.

Professional organizations provide additional context for clinical decision-making. The Academy of Nutrition and Dietetics affirms nonnutritive sweeteners can be safely incorporated into dietary planning when used in moderation and aligned with the Dietary Guidelines for Americans (Fitch & Keim, 2012). The U.S. Food and Drug Administration

establishes Acceptable Daily Intake (ADI) levels for approved sweeteners, offering benchmarks for patient counseling (U.S. Food and Drug Administration, 2023). Federal agencies, including the U.S. Department of Agriculture and the U.S. Department of Health and Human Services, emphasize the need for ongoing research into long-term health impacts, particularly microbiota outcomes (U.S. Department of Agriculture & U.S. Department of Health and Human Services, 2020; Le Roy & Clement, 2022).

Taken together, these positions highlight that while synthetic sweeteners are considered safe at regulated doses, practitioners should apply individualized recommendations that balance organizational guidance with patient-specific needs, health goals, and microbiota-related considerations.

#### *4.5 Future Research Directions*

Future studies should conduct long-term randomized controlled trials in diverse adult populations. Research should standardize dosage, duration, and delivery methods for sweetener interventions and include sex-specific and age-specific analyses to clarify demographic effects. Additional work is needed to examine mechanistic pathways, including SCFA synthesis, mucosal integrity, and inflammatory signaling. Finally, studies should evaluate combined dietary patterns, as sweeteners rarely occur in isolation in real-world diets. Such research will strengthen the evidence base and support more nuanced dietary recommendations.

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#### **Authors' contributions**

Olivia Cavazos led the systematic review design, literature research, data extraction, data synthesis, and primary manuscript drafting. Dr. Kevin Haubrick provided supervisory oversight, methodological guidance, and critical revisions to the manuscript. Both authors read and approved the final manuscript. No special authorship agreements were made, and both authors contributed substantially to the work.

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#### **Competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Informed consent

Obtained

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The Publication Ethics Committee of the Macrothink Institute.

The journal's policies adhere to the Core Practices established by the Committee on Publication Ethics (COPE).

## Provenance and peer review

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Data sharing statement

No additional data are available.

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