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Modulación de la Microbiota Intestinal: Una Nueva Frontera en el Manejo de las Enfermedades Gastrointestinales y Metabólicas

Gut Microbiota Modulation: A New Frontier in the Management of Gastrointestinal and Metabolic Diseases

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RESUMEN

La microbiota intestinal desempeña un papel esencial en la regulación metabólica, inmunológica y gastrointestinal. La disbiosis—caracterizada por la disminución de la diversidad microbiana, la pérdida de *Bifidobacterium* y *Akkermansia muciniphila*, y un aumento en la relación *Firmicutes/Bacteroidetes*—se asocia estrechamente con resistencia a la insulina, inflamación crónica y síndrome metabólico. Esta revisión analiza la evidencia multidisciplinaria sobre la

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modulación de la microbiota a través de intervenciones dietéticas, probióticas, postbióticas y de trasplante fecal, integrando hallazgos globales con el contexto sanitario de México, Colombia y Ecuador. Los resultados destacan que los ácidos grasos de cadena corta (AGCC), especialmente butirato y propionato, median los efectos beneficiosos del metabolismo microbiano al fortalecer la barrera epitelial, regular hormonas del apetito y reducir la inflamación sistémica mediante las vías GPR41, GPR43 y GPR109A. Los datos clínicos muestran que el trasplante de microbiota fecal de donantes delgados y la suplementación con *Akkermansia muciniphila* mejoran la sensibilidad a la insulina y el metabolismo lipídico, mientras que los postbióticos ofrecen bioactividad estandarizada sin requerir colonización. A nivel regional, las estrategias deben seguir un modelo escalonado: nutrición personalizada centrada en fibra, formulaciones microbianas validadas por ISAPP y restablecimiento ecológico con consorcios estandarizados o trasplante fecal en casos de disbiosis grave. Estas intervenciones se alinean con los Objetivos de Desarrollo Sostenible de las Naciones Unidas (ODS 3, 9 y 12), promoviendo una atención médica sostenible, equitativa y basada en evidencia. En conjunto, la modulación de la microbiota representa una herramienta mecanísticamente fundamentada y culturalmente adaptable para la prevención y tratamiento de enfermedades crónicas, uniendo la medicina de precisión global con las realidades dietéticas y ecológicas locales.

PALABRAS CLAVE

Microbiota intestinal; Ácidos grasos de cadena corta; Probióticos; Postbióticos; Nutrición personalizada; Síndrome metabólico.

ABSTRACT

The gut microbiota plays a critical role in metabolic, immune, and gastrointestinal homeostasis. Dysbiosis—characterized by reduced microbial diversity, loss of *Bifidobacterium* and *Akkermansia muciniphila*, and an increased *Firmicutes/Bacteroidetes* ratio—has been consistently linked to insulin resistance, chronic inflammation, and metabolic syndrome. This review analyzes multidisciplinary evidence on microbiota modulation through dietary, probiotic, postbiotic, and transplantation-based interventions, integrating findings from global research and contextualizing them within the health frameworks of Mexico, Colombia, and Ecuador. The results highlight that short-chain fatty acids (SCFAs), primarily butyrate and propionate, mediate the beneficial effects of microbial metabolism by enhancing epithelial barrier integrity, regulating appetite hormones, and reducing systemic inflammation through GPR41, GPR43, and GPR109A signaling. Clinical data demonstrate that lean-donor fecal microbiota transplantation and *Akkermansia muciniphila* supplementation improve insulin sensitivity and lipid metabolism, while postbiotics offer standardized, colonization-independent bioactivity. Regionally, implementation strategies should follow a tiered model: fiber-centered personalized nutrition, ISAPP-aligned microbial formulations, and ecological reset through standardized consortia or fecal microbiota transplantation in severe dysbiosis. These interventions align with the United Nations Sustainable Development Goals (SDG 3, 9, and 12) by promoting sustainable, equitable, and evidence-based healthcare. Overall, microbiota modulation represents a mechanistically grounded and culturally adaptable tool for the prevention and treatment of chronic diseases, bridging global precision medicine with local dietary and ecological realities.

KEYWORDS

Gut microbiota; Short-chain fatty acids; Probiotics; Postbiotics; Personalized nutrition; Metabolic syndrome.

INTRODUCCIÓN

In recent years, the gut microbiota has emerged as a central determinant of human health, representing one of the most complex and influential ecosystems within the body. Comprising trillions of microorganisms—including bacteria, archaea, viruses, and fungi—the intestinal microbiota orchestrates a wide array of physiological processes that extend far beyond digestion. It modulates the immune response, regulates host metabolism, and maintains the integrity of the intestinal barrier (Thursby & Juge, 2017; Valdes et al., 2018). Alterations in this microbial balance, a condition known as dysbiosis, have been consistently associated with the development of gastrointestinal and metabolic disorders, as well as systemic diseases that include obesity, type 2 diabetes, inflammatory bowel disease (IBD), and even neurological and cardiovascular pathologies (Lynch & Pedersen, 2016; Qin et al., 2012). These findings have redefined

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the understanding of the gut not merely as a digestive organ, but as a key metabolic and immunological interface whose equilibrium is essential for maintaining health.

Early metagenomic studies revealed profound differences in the composition and functionality of gut microbiota between healthy individuals and those with metabolic disorders. Qin et al. (2012) conducted a metagenome-wide association study that identified specific bacterial profiles linked to type 2 diabetes, providing one of the first pieces of evidence that microbial dysbiosis contributes to insulin resistance. Similarly, Ridaura et al. (2013) demonstrated that the microbiota from obese individuals can transmit metabolic phenotypes when transferred to germ-free mice, establishing causality between microbial composition and host metabolism. Complementary clinical investigations, such as those by Vrieze et al. (2012) and Kootte et al. (2017), further confirmed that fecal microbiota transplantation (FMT) from lean donors to patients with metabolic syndrome can significantly improve insulin sensitivity, underscoring the therapeutic potential of manipulating the gut microbial ecosystem.

Parallel to these metabolic findings, the role of the microbiota in gastrointestinal health has also gained increasing attention. Van Nood et al. (2013) demonstrated that duodenal infusion of donor feces was highly effective for recurrent *Clostridium difficile* infection, establishing FMT as a clinical reality. Later, Feuerstadt et al. (2022) developed SER-109, an oral microbiome-based therapy, which showed efficacy in preventing recurrent *Clostridioides difficile* infection, thus paving the way for standardized microbiota-based pharmacotherapies. Moreover, randomized controlled trials, such as those conducted by Paramsothy et al. (2017) and Costello et al. (2019), evidenced that FMT can induce clinical remission in patients with active ulcerative colitis, revealing a promising horizon for microbiota-centered interventions in inflammatory bowel diseases.

Beyond FMT, numerous strategies have been proposed to modulate the gut microbiota, including the use of probiotics, prebiotics, postbiotics, and synbiotics. The International Scientific Association for Probiotics and Prebiotics (ISAPP) has played a crucial role in providing unified definitions and scientific criteria for these agents (Hill et al., 2014; Gibson et al., 2017; Salminen et al., 2021; Swanson et al., 2020). Probiotics—defined as live microorganisms that confer health benefits when administered in adequate amounts—can reinforce intestinal barrier function, regulate immune responses, and produce beneficial metabolites. Prebiotics, on the other hand, are substrates selectively utilized by beneficial microorganisms to promote their growth and activity (Gibson et al., 2017). More recently, postbiotics (non-viable microbial cells and their components) have been recognized for their anti-inflammatory and metabolic regulatory effects, while synbiotics—combinations of probiotics and prebiotics—represent an integrated approach designed to optimize microbial activity and host benefit (Salminen et al., 2021; Swanson et al., 2020).

Experimental and clinical data suggest that these microbial interventions may significantly impact glucose metabolism, lipid regulation, and energy balance. Canfora et al. (2015) emphasized the importance of short-chain fatty acids (SCFAs)—notably acetate, propionate, and butyrate—produced by gut bacteria through fiber fermentation, in modulating body weight and insulin sensitivity. Similarly, Kovatcheva-Datchary et al. (2015) demonstrated that diets enriched in dietary fiber improved glucose metabolism through the proliferation of *Prevotella* species, which promote SCFA production. These findings highlight how diet and microbiota interact in the regulation of host metabolism and suggest dietary modulation as a non-pharmacological avenue for the prevention of metabolic disorders.

On the other hand, lifestyle and environmental factors have been shown to alter the composition of the microbiota, sometimes in detrimental ways. Suez et al. (2014) reported that artificial sweeteners induce glucose intolerance in mice and humans by altering gut microbial composition. This observation was later expanded by Suez et al. (2022), who demonstrated that the metabolic impact of non-nutritive sweeteners depends on individual microbiome profiles, reinforcing the notion that personalized approaches are crucial in microbiome research and clinical translation. Furthermore, Zmora et al. (2018) found that probiotic colonization varies among individuals according to their baseline microbiome and host genetic factors, emphasizing the complexity of host–microbe interactions and the need for precision-based interventions.

An important milestone in this field was the identification of *Akkermansia muciniphila* as a next-generation probiotic. Depommier et al. (2019) conducted a proof-of-concept clinical trial demonstrating that supplementation with *Akkermansia* improved insulin sensitivity and reduced markers of inflammation in overweight and obese individuals. These results suggest that targeted microbial therapies may offer new opportunities for treating metabolic disorders through specific bacterial strains.

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In parallel, personalized nutrition research has integrated microbiome profiling to predict glycemic responses to different foods. Zeevi et al. (2015) introduced a predictive algorithm based on individual microbiome and clinical data, revealing that personalized dietary interventions can more effectively regulate glucose levels than generalized dietary recommendations. This personalized framework underscores the transition from population-based to individualized therapeutic strategies.

From a global health perspective, understanding the gut microbiota has particular relevance for regions such as Latin America, where metabolic and gastrointestinal diseases represent major public health burdens. Collaborative research efforts among Mexico, Colombia, and Ecuador have begun to explore microbiome–host interactions under diverse dietary, genetic, and environmental contexts, aiming to adapt global findings to regional realities. These collaborations reflect a growing scientific movement that integrates microbiome science with population-specific factors to optimize prevention and treatment approaches.

Despite remarkable progress, significant challenges remain. The long-term effects, reproducibility, and safety of microbiota-targeted interventions require further investigation. Variations in microbial composition across individuals and populations complicate the generalization of results, emphasizing the necessity of robust, multicentric, and longitudinal studies. Moreover, the translation of microbiota science into clinical practice demands standardized protocols, well-defined biomarkers, and regulatory frameworks ensuring efficacy and safety.

Therefore, this review aims to provide an integrative analysis of current evidence on gut microbiota modulation as a novel therapeutic frontier for gastrointestinal and metabolic diseases. It synthesizes data from experimental and clinical studies, consensus statements, and translational research to answer a central question: *How can the modulation of gut microbiota contribute to the prevention and management of gastrointestinal and metabolic diseases?* By aligning theoretical, mechanistic, and clinical perspectives, this work seeks to consolidate the role of the microbiome as a pivotal target for future medical interventions that bridge metabolic regulation, immune homeostasis, and gastrointestinal health.

DESARROLLO

The gut microbiota represents a highly dynamic and metabolically active ecosystem whose interactions with the human host are fundamental to maintaining health and preventing disease. Increasing evidence has revealed that microbial communities residing in the gastrointestinal tract perform essential functions such as the fermentation of dietary fibers, the synthesis of vitamins, the regulation of bile acid metabolism, and the modulation of immune responses (Thursby & Juge, 2017; Valdes et al., 2018). When this microbial equilibrium is disrupted—a state referred to as dysbiosis—it can trigger metabolic and inflammatory cascades that contribute to the pathophysiology of numerous chronic diseases (Lynch & Pedersen, 2016). This understanding has opened a new frontier in modern medicine: the modulation of gut microbiota as a therapeutic approach to gastrointestinal and metabolic disorders.

From a biological perspective, gut microbiota modulation aims to restore microbial diversity and function through targeted interventions. These include the administration of probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation (FMT), all of which have shown clinical relevance in metabolic and inflammatory pathologies. For instance, *Akkermansia muciniphila* supplementation has been demonstrated to improve insulin sensitivity and metabolic markers in obese individuals (Depommier et al., 2019), while dietary fibers stimulate the growth of beneficial taxa such as *Prevotella*, increasing short-chain fatty acid (SCFA) production, which enhances glucose metabolism (Kovatcheva-Datchary et al., 2015). Moreover, clinical evidence has indicated that FMT not only restores microbial balance but also reduces the recurrence of *Clostridioides difficile* infection (van Nood et al., 2013; Feuerstadt et al., 2022) and may induce remission in ulcerative colitis (Paramsothy et al., 2017; Costello et al., 2019).

At the metabolic level, SCFAs play a crucial role in linking microbiota composition to host physiology. Canfora et al. (2015) described how SCFAs interact with G-protein-coupled receptors to regulate energy expenditure, appetite, and insulin sensitivity. Furthermore, studies by Suez et al. (2014, 2022) and Zeevi et al. (2015) highlighted the individualized response to dietary components and artificial sweeteners, revealing that the microbiota mediates host metabolic adaptation. These findings support the concept of personalized microbiota-based interventions, emphasizing that therapeutic success depends on each individual's baseline microbial profile (Zmora et al., 2018).

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Globally, gut microbiota research has evolved from descriptive to translational and precision-oriented approaches. In Latin America, emerging research networks across Mexico, Colombia, and Ecuador are contributing to this paradigm by studying the microbiome under region-specific dietary and environmental conditions. These collaborations are essential to contextualize microbiota research in diverse populations and to adapt therapeutic strategies to local nutritional and genetic backgrounds, reinforcing the importance of a cross-national framework for precision medicine.

Ultimately, the modulation of gut microbiota represents a bridge between molecular biology, clinical nutrition, and public health. By understanding the mechanisms through which microbiota impacts metabolism and inflammation, researchers can design interventions that not only treat but also prevent chronic diseases—aligning scientific progress with global health objectives such as the Sustainable Development Goals (SDG 3: Good Health and Well-being).

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To **analyze and integrate** current scientific evidence regarding gut microbiota modulation as a therapeutic and preventive strategy for gastrointestinal and metabolic diseases, emphasizing its physiological, clinical, and translational implications across international research contexts.

Specific Objectives

Cognitive Domain (Bloom's Taxonomy)

1. **Understand** the mechanisms through which the gut microbiota influences metabolic and gastrointestinal health.
2. **Analyze** current microbiota modulation strategies, including probiotics, prebiotics, synbiotics, postbiotics, and FMT.
3. **Evaluate** the efficacy and limitations of microbiota-targeted interventions based on existing scientific evidence.
4. **Synthesize** information from multicenter studies conducted in Mexico, Colombia, and Ecuador to propose future research directions.

Psychomotor Domain

1. **Apply** analytical methodologies to compare microbiota composition and function across distinct populations.
2. **Develop** schematic models illustrating microbiota–host interactions and the mechanisms underlying therapeutic modulation.
3. **Integrate** microbiota analysis tools and experimental protocols for educational and clinical purposes.

Affective Domain

1. **Promote** ethical awareness regarding the impact of microbiota research on human health and its implications for global well-being.
2. **Encourage** interdisciplinary collaboration and scientific curiosity among students and professionals in the biomedical field.
3. **Value** microbiota modulation as a potential paradigm shift in preventive and personalized medicine.

OBJETO DE ESTUDIO

The present research centers on the **gut microbiota as a complex biological system**, composed of trillions of microorganisms—primarily bacteria, but also archaea, fungi, viruses, and protozoa—that inhabit the gastrointestinal tract and establish a dynamic and bidirectional interaction with the human host. This microbial ecosystem exerts crucial influence over numerous physiological processes, including digestion, absorption, energy regulation, immune modulation, and neuroendocrine communication (Thursby & Juge, 2017; Valdes et al., 2018). Far from being a passive inhabitant, the microbiota constitutes a fundamental organ-like entity that plays an active role in maintaining homeostasis and protecting against external and internal perturbations.

The object of study is, therefore, defined as the **interaction between the intestinal microbiota and the host metabolic–inflammatory network**, with emphasis on the modulation of microbial composition and function as a

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preventive and therapeutic strategy for gastrointestinal and metabolic diseases. This includes examining the mechanisms through which microbial communities influence insulin sensitivity, lipid metabolism, and immune tolerance, as well as their role in the development of disorders such as type 2 diabetes, obesity, metabolic syndrome, and inflammatory bowel disease (Qin et al., 2012; Ridaura et al., 2013; Canfora et al., 2015; Lynch & Pedersen, 2016).

In this context, the study focuses on **analyzing how microbiota modulation—through interventions such as probiotics, prebiotics, postbiotics, synbiotics, and fecal microbiota transplantation (FMT)—can restore balance to dysbiotic ecosystems and improve host health**. Evidence suggests that FMT from healthy, lean donors enhances insulin sensitivity in individuals with metabolic syndrome (Vrieze et al., 2012; Kootte et al., 2017), and that *Akkermansia muciniphila* supplementation contributes to improved metabolic and inflammatory profiles in obese subjects (Depommier et al., 2019). Moreover, the use of multi-donor FMT has shown therapeutic promise in ulcerative colitis (Paramsothy et al., 2017; Costello et al., 2019), while oral microbiome-based formulations such as SER-109 have achieved clinical efficacy against *Clostridioides difficile* infections (Feuerstadt et al., 2022).

The object of study also encompasses the **ecological, biochemical, and clinical dimensions of the microbiota**, emphasizing its role as both a mediator and a potential biomarker of health and disease. In metabolic disorders, for example, specific bacterial genera—such as *Prevotella*, *Bacteroides*, and *Akkermansia*—have been correlated with improved glucose metabolism, reduced systemic inflammation, and enhanced mucosal integrity (Kovatcheva-Datchary et al., 2015; Depommier et al., 2019). Conversely, an increased abundance of pathogenic or pro-inflammatory species, often observed in individuals with poor dietary habits or chronic stress, is associated with metabolic endotoxemia and insulin resistance (Suez et al., 2014, 2022).

Furthermore, the study investigates **how dietary patterns, environmental exposures, and pharmacological factors interact with the microbiota to shape human health outcomes**. For instance, artificial sweeteners, widely used in modern diets, have been shown to alter microbial composition and induce glucose intolerance in a microbiome-dependent manner (Suez et al., 2014). This finding highlights the profound impact of environmental and lifestyle factors on microbial ecosystems and underscores the necessity of designing personalized interventions that consider individual variability in microbiome responses (Zmora et al., 2018; Zeevi et al., 2015).

From a translational perspective, this research seeks to contextualize global advances within the frameworks of **Latin American public health**, with particular focus on **Mexico, Colombia, and Ecuador**. These nations face a dual epidemiological burden characterized by the coexistence of infectious and chronic non-communicable diseases, both of which may be influenced by microbiome composition and function. Exploring microbiota modulation in these regions offers a unique opportunity to integrate global scientific insights into locally relevant applications, considering regional dietary habits, socioeconomic conditions, and genetic diversity. Such integration contributes to the development of **sustainable, accessible, and culturally adapted health strategies** that align with international goals for disease prevention and metabolic health optimization.

In this regard, the object of study extends beyond the biological dimension to encompass a **multidisciplinary scope** that integrates microbiology, immunology, clinical medicine, nutrition, and public health. The goal is not only to understand how microbial modulation works at a mechanistic level but also to determine how it can be applied as a **public health tool** for reducing the prevalence and impact of chronic diseases. This aligns with contemporary global health frameworks that prioritize the interconnection between individual well-being, environmental sustainability, and microbial ecology.

Finally, the object of study positions the gut microbiota as a **bridge between fundamental research and clinical practice**, a paradigm capable of redefining prevention and treatment models in medicine. By focusing on the microbiome as a therapeutic axis, this investigation aims to advance a holistic understanding of human health—one that recognizes the gut ecosystem as both a reflection and a determinant of systemic equilibrium. This conceptualization not only strengthens biomedical knowledge but also promotes a **shift toward precision medicine**, where individualized microbiota-based interventions may one day become a cornerstone of gastrointestinal and metabolic disease management worldwide.

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METODOLOGÍA

This study was conducted under a **structured and integrative methodological framework**, designed to ensure rigor, transparency, and replicability in the analysis of existing scientific evidence regarding gut microbiota modulation as a therapeutic and preventive approach in gastrointestinal and metabolic diseases. The selected methodological model combines two complementary paradigms: the **Scientific Method**, for its universality and logical progression, and the **DMAIC methodology** (Define, Measure, Analyze, Improve, Control), commonly applied in biomedical research for process optimization and evidence-based decision-making. This hybrid approach allowed the research to maintain a balance between theoretical depth and analytical precision, ensuring the consistency required for a high-level international review.

The methodological design emphasizes a **qualitative-quantitative integrative approach**, drawing upon both empirical data from clinical and experimental studies and conceptual frameworks derived from microbiology, immunology, and metabolic science. The primary objective of this methodological design was to establish a comprehensive synthesis of current evidence, allowing reproducibility by other investigators who wish to replicate or expand upon this work in future studies.

1. Definition Phase (D – Define)

In this first phase, the central research problem was identified and precisely delimited: *How can gut microbiota modulation contribute to the prevention and management of gastrointestinal and metabolic diseases?* This question was derived from the increasing prevalence of metabolic disorders and gastrointestinal pathologies linked to microbial dysbiosis and from the growing need for sustainable, non-pharmacological interventions that target underlying pathophysiological mechanisms (Lynch & Pedersen, 2016; Valdes et al., 2018).

The **theoretical construct** was developed through the identification of key variables—such as microbial diversity, dysbiosis, immune response, metabolic regulation, and inflammation—and the establishment of their interrelationships. Operational definitions were adapted from internationally recognized scientific bodies, particularly the **International Scientific Association for Probiotics and Prebiotics (ISAPP)** (Hill et al., 2014; Gibson et al., 2017; Salminen et al., 2021; Swanson et al., 2020), to ensure conceptual clarity and global coherence.

In this stage, the inclusion and exclusion criteria for the literature were defined. The inclusion criteria encompassed:

- Peer-reviewed publications from **2012 to 2024** addressing the gut microbiota, modulation interventions (FMT, probiotics, prebiotics, postbiotics, synbiotics), and clinical or metabolic outcomes.
- Studies conducted in **humans or translational animal models** with relevance to gastrointestinal or metabolic diseases.
- Consensus statements and meta-analyses from high-impact journals such as *Nature*, *The New England Journal of Medicine*, *Gastroenterology*, *BMJ*, *Cell*, and *The Lancet*.

Exclusion criteria included non-peer-reviewed material, duplicated records, and papers with incomplete methodological descriptions or lacking statistical validity.

2. Measurement Phase (M – Measure)

This phase focused on data collection and documentation. Advanced searches were conducted using the following databases: **PubMed, ScienceDirect, Scopus, and Google Scholar**, employing Boolean combinations of keywords such as *gut microbiota*, *dysbiosis*, *microbiota modulation*, *fecal microbiota transplantation*, *probiotics*, *prebiotics*, *metabolic syndrome*, and *type 2 diabetes*.

A total of **120 articles** were initially retrieved. After screening titles, abstracts, and keywords for relevance, **48 publications** were selected for full-text evaluation, of which **20 key sources** were finally included in this review (Appendix A – Reference List). Each article was reviewed systematically, and relevant data—such as study design, population, intervention type, and outcomes—were extracted and organized into an analytical matrix.

In this phase, a **data validation grid** was developed to assess methodological quality. Each source was evaluated according to:

- Research design validity (randomization, control, or blinding methods).
- Reproducibility and transparency of results.
- Ethical compliance and conflict of interest declarations.
- Relevance to gastrointestinal and metabolic disease contexts.

This rigorous evaluation ensured that only high-quality, reliable, and ethically sound evidence formed the analytical foundation of the study.

3. Analysis Phase (A – Analyze)

The analysis stage consisted of a **comparative synthesis** that integrated results from multiple studies into a unified conceptual framework. The synthesis process followed three levels:

- **Descriptive Analysis:** Characterization of microbiota composition, dominant phyla (Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria), and their functional roles in metabolism, inflammation, and gut barrier maintenance (Thursby & Juge, 2017; Valdes et al., 2018).
- **Relational Analysis:** Examination of associations between microbial alterations and disease manifestations, as described by Qin et al. (2012), Ridaura et al. (2013), and Kovatcheva-Datchary et al. (2015), linking specific bacterial taxa with insulin sensitivity, obesity, and glucose metabolism.
- **Interpretive Analysis:** Critical discussion of therapeutic interventions (FMT, probiotics, prebiotics, synbiotics, and postbiotics) based on the outcomes reported by Vrieze et al. (2012), Depommier et al. (2019), Paramsothy et al. (2017), and Costello et al. (2019), to identify key mechanisms of microbiota modulation.

The analytical process also incorporated regional perspectives from Latin America, particularly focusing on the applicability of microbiome research within **Mexico, Colombia, and Ecuador**. These nations, due to their dietary diversity and socioeconomic variability, provide valuable contexts for studying microbiota–host interactions and for designing culturally adapted interventions.

To ensure analytical objectivity, all findings were triangulated across multiple sources. Quantitative data (e.g., microbiota abundance, SCFA concentration, glycemic index changes) were cross-referenced with qualitative observations (e.g., behavioral responses, dietary adherence) to strengthen the interpretive validity of conclusions.

4. Improvement Phase (I – Improve)

This phase aimed to refine and optimize the interpretive framework developed in the previous stages. Based on the analyzed evidence, conceptual models were constructed to represent how microbiota modulation impacts host metabolic and gastrointestinal health.

For example, models were developed to:

- Illustrate the relationship between microbial diversity and metabolic flexibility (Canfora et al., 2015).
- Describe the signaling pathways through which SCFAs interact with host receptors (GPR41, GPR43) to modulate energy balance.
- Depict the beneficial impact of specific bacteria such as *Akkermansia muciniphila* and *Prevotella copri* on insulin sensitivity and intestinal barrier integrity (Depommier et al., 2019; Kovatcheva-Datchary et al., 2015).

Additionally, gaps in current knowledge were identified to propose future research directions, particularly regarding:

- The long-term safety of microbiota transplantation.
- The molecular mechanisms underlying postbiotic activity.
- The personalized prediction of microbiota responses based on genomic and metabolic profiling (Zmora et al., 2018; Zeevi et al., 2015).

The improvement phase also highlighted the importance of integrating **interdisciplinary collaboration** among microbiologists, clinicians, nutritionists, and data scientists to enhance translational applications and ensure that microbiota-based therapies become part of preventive medicine and public health initiatives in Latin America.

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5. Control Phase (C – Control)

The final phase focused on ensuring the **reproducibility, transparency, and ethical compliance** of the study. A methodological checklist was implemented to validate every procedural step, including source verification, data consistency, and citation integrity.

To guarantee replicability:

- All search strategies and inclusion criteria were documented in detail.
- Reference management and formatting followed APA (7th edition) standards.
- Database search logs and analytical matrices were stored to enable future verification.

Ethical considerations were maintained throughout the process by adhering to academic integrity standards, avoiding plagiarism, and ensuring the impartial selection of evidence. Since this study is based exclusively on secondary data from published sources, it does not involve human or animal experimentation, thereby exempting it from the need for institutional ethical approval while remaining consistent with the **Declaration of Helsinki (2013 revision)** principles for research transparency and responsibility.

The control phase also includes recommendations for future replication by other researchers. To reproduce this review, future teams should:

1. Reapply the same search parameters and databases, updating the time window as needed.
2. Maintain the same inclusion and exclusion criteria for comparability.
3. Use the DMAIC structure as a procedural guideline for data extraction, synthesis, and validation.
4. Integrate emerging data from clinical trials or microbiome-based pharmacotherapies to enhance longitudinal evaluation.

FASES DEL DESARROLLO

The development of this international research followed a structured sequence of stages aligned with the **Scientific Method** and the **DMAIC cycle** (Define, Measure, Analyze, Improve, Control). Each phase was designed to ensure methodological consistency, reproducibility, and analytical depth while maintaining alignment with the central objective of understanding gut microbiota modulation as a therapeutic and preventive approach to gastrointestinal and metabolic diseases. Below, each stage is detailed comprehensively to illustrate the logical progression and internal coherence of the investigation.

Phase I: Definition and Delimitation of the Problem (Define)

The first phase consisted of the conceptual formulation and delimitation of the research problem. Given the growing global prevalence of gastrointestinal and metabolic disorders, particularly obesity, type 2 diabetes, and inflammatory bowel diseases, the need to identify alternative and complementary therapeutic strategies became evident. Previous evidence had shown that the gut microbiota plays a critical role in metabolic regulation, energy balance, and immune modulation (Lynch & Pedersen, 2016; Valdes et al., 2018).

In this stage, the **main research question** was defined: *How can gut microbiota modulation contribute to the prevention and management of gastrointestinal and metabolic diseases?*

To answer this, a conceptual map was developed linking the main constructs:

- **Microbiota composition** (diversity, richness, dominant species).
- **Modulatory interventions** (probiotics, prebiotics, postbiotics, synbiotics, and fecal microbiota transplantation).
- **Clinical and metabolic outcomes** (insulin sensitivity, inflammatory markers, intestinal barrier integrity, and lipid metabolism).

The phase concluded with the establishment of a theoretical foundation based on the **ISAPP consensus documents** (Hill et al., 2014; Gibson et al., 2017; Salminen et al., 2021; Swanson et al., 2020) to standardize terminology and

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ensure conceptual precision. The variables were operationally defined, and the analytical criteria were selected to guide the study through subsequent stages.

Phase II: Literature Compilation and Database Structuring (Measure)

Once the research problem was defined, the second phase focused on systematically compiling the most relevant and current scientific evidence. Advanced searches were conducted across major academic databases—**PubMed, Scopus, ScienceDirect, and Google Scholar**—using Boolean logic and combinations of keywords such as *gut microbiota*, *microbiome modulation*, *metabolic syndrome*, *probiotics*, *prebiotics*, *synbiotics*, *postbiotics*, and *fecal microbiota transplantation*.

The initial search yielded 120 studies. Through a multi-stage filtering process, publications were reviewed based on their titles, abstracts, and keywords, which led to a refined corpus of 48 potentially relevant studies. These were then evaluated according to inclusion and exclusion criteria defined in the methodology, resulting in a final sample of **20 high-impact peer-reviewed articles**, which constitute the evidentiary basis of the present review.

For each selected source, an **analytical matrix** was created containing:

- Study reference (authors, year, DOI).
- Population and design (clinical, experimental, or translational).
- Type of intervention (dietary modification, probiotic, prebiotic, FMT, etc.).
- Measured outcomes (metabolic, inflammatory, or gastrointestinal parameters).
- Main results and limitations.

This matrix served as a foundation for comparative synthesis, facilitating the subsequent analytical and interpretative phases. The accuracy of data extraction was independently cross-verified to minimize interpretative bias, ensuring transparency and methodological rigor.

Phase III: Comparative and Interpretative Analysis (Analyze)

The third phase centered on the **comparative synthesis and critical evaluation** of the compiled evidence. The analysis aimed to integrate findings from diverse methodologies—ranging from metagenomic sequencing to clinical trials—into a coherent framework explaining how microbiota modulation influences metabolic and gastrointestinal health.

Three analytical dimensions were established:

1. **Descriptive Dimension:**

This level focused on summarizing the biological and ecological characteristics of the gut microbiota. Studies such as those by Thursby & Juge (2017) and Valdes et al. (2018) were used to describe microbial diversity, ecological interactions, and metabolic contributions (e.g., SCFA synthesis, bile acid metabolism).

2. **Relational Dimension:**

Here, associations between microbiota alterations and specific disease phenotypes were explored. Qin et al. (2012) and Ridaura et al. (2013) demonstrated links between dysbiosis and metabolic diseases such as obesity and diabetes. These findings were contrasted with therapeutic interventions like those reported by Vrieze et al. (2012) and Kootte et al. (2017), which revealed that transferring microbiota from lean donors improved insulin sensitivity.

3. **Interpretative Dimension:**

This final analytical level involved a deep evaluation of microbiota-targeted strategies and their clinical implications. Evidence from Depommier et al. (2019) on *Akkermansia muciniphila*, along with data from Paramsothy et al. (2017) and Costello et al. (2019) on fecal microbiota transplantation, was integrated to discuss safety, efficacy, and personalization of treatments. Additionally, emerging data on the individual variability of responses to probiotics and artificial sweeteners (Suez et al., 2014, 2022; Zmora et al., 2018; Zeevi et al., 2015) were incorporated to highlight the challenges of translational application.

This phase also included a **regional comparative analysis** of research contexts in **Mexico, Colombia, and Ecuador**, integrating sociocultural and dietary factors that may influence microbiome composition and intervention outcomes.

This integrative lens positioned the study within a global–local continuum, aligning with the goal of generating findings applicable to diverse populations.

Phase IV: Synthesis, Conceptual Integration, and Model Optimization (Improve)

The fourth phase focused on transforming the analytical findings into an integrated conceptual framework. Through the **Improve** stage of the DMAIC model, patterns and causal pathways were synthesized to construct a theoretical model illustrating how microbiota modulation contributes to metabolic and gastrointestinal homeostasis.

Several models and diagrams were developed to conceptualize these relationships:

- **Microbial-Metabolic Axis Model:** Illustrating how SCFAs produced by beneficial bacteria (e.g., *Prevotella*, *Bifidobacterium*) regulate insulin signaling, lipid metabolism, and energy expenditure (Canfora et al., 2015).
- **Barrier Integrity and Immunomodulation Model:** Showing how probiotics and postbiotics enhance mucosal barrier integrity and modulate inflammatory cytokines.
- **Translational Framework for Latin America:** Adapting international findings to regional contexts, integrating dietary diversity, socioeconomic variables, and environmental influences typical of Mexico, Colombia, and Ecuador.

Additionally, gaps in current knowledge were identified. For example, the long-term safety of fecal microbiota transplantation remains uncertain, and postbiotic mechanisms still require further exploration (Salminen et al., 2021). The need for **personalized and precision-based interventions** was emphasized, encouraging collaboration among clinicians, microbiologists, and data scientists to develop individualized therapeutic protocols.

The Improve phase culminated in a proposal for a **standardized framework** that can be applied in future research to evaluate the efficacy of microbiota modulation therapies and their potential role in achieving the Sustainable Development Goals (SDG 3: Good Health and Well-being).

Phase V: Validation, Replicability, and Ethical Control (Control)

The final phase ensured that all processes adhered to the principles of scientific rigor, transparency, and reproducibility. This stage focused on consolidating documentation, validating analytical coherence, and establishing guidelines for replication by future research teams.

The following control mechanisms were applied:

1. **Verification of Data Integrity:** Cross-checking all data points and references to confirm their consistency and correspondence with original sources.
2. **Replication Protocol Design:** A structured guide was created to allow other researchers to reproduce the search strategy, inclusion criteria, and analytical framework, ensuring the continuity of the research line.
3. **Ethical Assurance:** Although no human or animal subjects were directly involved, the research maintained compliance with the **Declaration of Helsinki (2013 revision)** and adhered to academic integrity standards to prevent plagiarism and ensure appropriate citation of all intellectual contributions.
4. **Quality Assurance:** Application of a methodological checklist assessing relevance, accuracy, and bias risk across all selected sources, guaranteeing that conclusions were based solely on validated scientific evidence.

Additionally, to strengthen inter-institutional collaboration, the control phase promoted the establishment of **academic and research partnerships among Mexico, Colombia, and Ecuador**, encouraging multidisciplinary teams to expand the study through longitudinal and intervention-based designs.

RESULTADOS Y DISCUSIÓN

In this section, the findings most relevant to the objectives of this research are presented, offering an integrative overview of the evidence supporting the role of gut microbiota modulation in the prevention and management of gastrointestinal and metabolic diseases. The analysis consolidates data derived from experimental, clinical, and

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translational studies published between 2012 and 2024, encompassing multidisciplinary perspectives from microbiology, endocrinology, and nutrition science.

The presentation of results follows a systematic organization in **five figures**, each designed to summarize a key dimension of the research: (1) microbiota composition and diversity in health and disease, (2) clinical outcomes of microbiota modulation therapies, (3) metabolic effects of short-chain fatty acids (SCFAs), (4) emerging therapeutic applications of next-generation probiotics and postbiotics, and (5) international and regional trends in microbiota research, including contributions from Mexico, Colombia, and Ecuador.

Each figure integrates the quantitative and qualitative findings extracted from the selected literature and provides visual and conceptual clarity to the trends observed across the studies analyzed. While this section does not engage in interpretive discussion—which will be reserved for the following part—it establishes a coherent empirical foundation for understanding how microbiota-targeted strategies contribute to systemic and gastrointestinal homeostasis.

The results demonstrate converging evidence that alterations in the gut microbial ecosystem are closely associated with metabolic and inflammatory dysfunction, while targeted modulation—via fecal microbiota transplantation (FMT), probiotics, prebiotics, postbiotics, and dietary interventions—has shown measurable benefits in restoring physiological balance. These findings collectively reinforce the hypothesis that microbiota modulation constitutes a viable and promising therapeutic frontier in contemporary medicine.

Figure 1.
Comparative Composition and Diversity of the Gut Microbiota in Healthy Individuals and Patients with Metabolic or Gastrointestinal Disorders

Phylum / Dominant Genera	Approximate Relative Abundance (%) in Healthy Individuals	Approximate Relative Abundance (%) in Metabolic / GI Disease	Main Functional Role
Firmicutes (*Clostridium*, *Faecalibacterium*, *Ruminococcus*)	50 – 60 %	↑ 65 – 75 %	Fermentation of carbohydrates; production of SCFAs (butyrate, acetate); regulation of intestinal pH
Bacteroidetes (*Bacteroides*, *Prevotella*)	20 – 30 %	↓ 10 – 15 %	Degradation of polysaccharides and dietary fibers; synthesis of propionate; modulation of immune tolerance
Actinobacteria (*Bifidobacterium*)	5 – 10 %	↓ 2 – 4 %	Strengthening of mucosal barrier; vitamin K and B production; anti-inflammatory activity
Proteobacteria (*Escherichia*, *Desulfovibrio*)	1 – 3 %	↑ 5 – 10 %	Potential pathogens; induction of oxidative stress and low-grade inflammation
Verrucomicrobia (*Akkermansia muciniphila*)	1 – 2 %	↓ < 0.5 %	Maintenance of mucin layer; improvement of insulin sensitivity and lipid metabolism
Microbial Diversity (Shannon Index)	**High (≥ 4.5)**	**Low (≤ 3.0)**	Diversity linked to metabolic flexibility and immune equilibrium

Figure 1 provides a comparative overview of the gut microbiota's composition and diversity between healthy individuals and those affected by metabolic or gastrointestinal disorders. The data synthesized from multiple studies (Thursby & Juge, 2017; Lynch & Pedersen, 2016; Valdes et al., 2018; Qin et al., 2012; Ridaura et al., 2013; Depommier et al., 2019) reveal clear taxonomic and functional shifts that explain how microbial imbalance—commonly referred to as **dysbiosis**—contributes to disease pathogenesis and metabolic dysfunction.

In healthy conditions, the intestinal microbiota is dominated primarily by the **Firmicutes** and **Bacteroidetes** phyla, which together account for approximately 70–90% of total bacterial abundance (Thursby & Juge, 2017). These microorganisms play a central role in maintaining gut homeostasis by metabolizing complex carbohydrates, producing short-chain fatty acids (SCFAs), synthesizing essential vitamins, and modulating the immune system. *Firmicutes*, particularly genera such as *Faecalibacterium* and *Ruminococcus*, are key producers of **butyrate**, a vital SCFA that nourishes colonocytes, regulates epithelial barrier function, and exhibits anti-inflammatory properties (Valdes et al., 2018). *Bacteroidetes*, on the other hand, are specialists in the degradation of dietary polysaccharides and promote immune tolerance through the production of metabolites like **propionate** and **acetate**, which interact with host G-protein-coupled receptors to influence energy metabolism and appetite regulation (Canfora et al., 2015).

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However, the microbial equilibrium observed in healthy individuals is substantially altered in those suffering from obesity, diabetes, and inflammatory bowel disease. Multiple studies have reported a **significant increase in the Firmicutes/Bacteroidetes ratio** in these populations, which correlates with higher caloric extraction efficiency and fat storage (Qin et al., 2012; Ridaura et al., 2013). This phenomenon suggests that an increased abundance of *Firmicutes* relative to *Bacteroidetes* favors energy harvesting from the diet, contributing to obesity and metabolic syndrome. Ridaura et al. (2013) provided compelling experimental evidence of causality by demonstrating that transplantation of microbiota from obese human donors into germ-free mice resulted in increased adiposity and altered metabolic profiles compared to mice receiving microbiota from lean donors.

At the same time, individuals with metabolic diseases often show **reduced representation of Actinobacteria**, particularly the beneficial genus *Bifidobacterium* (Valdes et al., 2018). This group of bacteria contributes to the maintenance of intestinal barrier integrity, prevention of pathogen adhesion, and synthesis of vitamins B and K. A decline in *Bifidobacterium* levels is associated with increased intestinal permeability—often described as a "leaky gut"—which allows lipopolysaccharides (LPS) from Gram-negative bacteria to enter the bloodstream, triggering low-grade systemic inflammation and promoting insulin resistance (Lynch & Pedersen, 2016).

Furthermore, Figure 1 highlights the **overrepresentation of Proteobacteria**—a phylum containing potentially pathogenic species such as *Escherichia* and *Desulfovibrio*—in individuals with metabolic or inflammatory diseases. The expansion of Proteobacteria has been recognized as a marker of microbial instability and dysbiosis (Lynch & Pedersen, 2016). These organisms produce endotoxins and reactive oxygen species that contribute to oxidative stress, disrupt epithelial integrity, and activate pro-inflammatory cytokine cascades. Chronic exposure to these inflammatory mediators underlies the pathophysiology of diseases such as type 2 diabetes and non-alcoholic fatty liver disease.

Conversely, the **decline of Verrucomicrobia**, represented by *Akkermansia muciniphila*, stands out as one of the most relevant dysbiotic features in metabolic disorders. *Akkermansia* plays a crucial role in maintaining the mucin layer of the intestinal epithelium, enhancing mucosal immunity, and modulating glucose and lipid metabolism. Depommier et al. (2019) demonstrated that supplementation with *A. muciniphila* in overweight and obese individuals improved insulin sensitivity, reduced plasma cholesterol, and decreased markers of systemic inflammation. Therefore, its depletion represents not only a biomarker of dysbiosis but also a potential therapeutic target for restoring metabolic balance.

Another fundamental aspect depicted in Figure 1 is the **reduction in microbial diversity**, which has emerged as a key indicator of health status. Ecological measures such as the Shannon and Simpson diversity indices consistently show that lower microbial diversity correlates with greater metabolic dysfunction (Ridaura et al., 2013). A rich and balanced microbiota confers resilience to environmental and dietary perturbations, whereas reduced diversity compromises the ecosystem's stability and adaptability. This microbial impoverishment limits the production of beneficial metabolites like SCFAs and bile acid derivatives, further aggravating metabolic and inflammatory dysregulation (Valdes et al., 2018).

Dietary and environmental influences are also pivotal in shaping microbial diversity. Diets high in saturated fats and low in fiber promote an increase in *Firmicutes* and *Proteobacteria* at the expense of *Bacteroidetes*, leading to a pro-inflammatory microbial profile. In contrast, diets rich in whole grains, legumes, and fermented foods enhance *Bacteroides* and *Prevotella* abundance, fostering SCFA production and metabolic flexibility (Kovatcheva-Datchary et al., 2015). Additionally, Suez et al. (2014) reported that artificial sweeteners can induce glucose intolerance through microbiota alterations, and later studies confirmed that individual responses to these compounds depend on baseline microbial configurations (Suez et al., 2022), reinforcing the concept of microbiota-driven personalization in metabolic health.

Taken together, the data represented in Figure 1 demonstrate that **a balanced and diverse gut microbiota is essential for metabolic and gastrointestinal health**, while dysbiosis—characterized by reduced diversity, increased Firmicutes/Bacteroidetes ratio, enrichment of Proteobacteria, and depletion of *Akkermansia muciniphila*—is closely associated with chronic low-grade inflammation and metabolic impairment. These microbial shifts are not merely correlative but mechanistically linked to energy regulation, immune modulation, and endocrine signaling.

The evidence thus supports the central premise of this study: that **microbiota composition acts as both a determinant and a modifiable factor in human metabolic health**. This understanding provides the theoretical basis for exploring

targeted microbiota modulation—through diet, probiotics, prebiotics, postbiotics, or fecal microbiota transplantation—as a therapeutic strategy capable of reversing dysbiosis and restoring metabolic equilibrium. The patterns observed across diverse studies underscore the global relevance of microbiome research and its potential to redefine preventive medicine by addressing the microbial foundations of disease.

Figure 2.
Clinical and Metabolic Outcomes of Gut Microbiota Modulation Therapies

Type of Intervention	Mechanism of Action	Clinical / Metabolic Outcome	Population / Study Type
Probiotics (*Lactobacillus*, *Bifidobacterium*, *Akkermansia*)	Colonization of intestinal mucosa; production of SCFAs; reduction of oxidative stress; modulation of immune responses	↓ Pro-inflammatory cytokines (TNF-α, IL-6); ↑ insulin sensitivity; ↓ intestinal permeability	Human clinical trials (T2DM, obesity)
Prebiotics (inulin, fructooligosaccharides, resistant starch)	Selective stimulation of beneficial microbes (*Bifidobacterium*, *Prevotella*); enhancement of SCFA production	↑ *Prevotella* abundance; ↑ GLP-1 secretion; ↓ fasting glucose	Dietary intervention studies
Synbiotics (probiotic + prebiotic combination)	Synergistic interaction improving microbial stability and metabolic regulation	↑ butyrate and propionate levels; improved gut integrity	RCTs in metabolic syndrome
Postbiotics (non-viable microbial cells, peptides, metabolites)	Induction of anti-inflammatory responses; modulation of epithelial signaling; reinforcement of mucosal barrier	↓ NF-κB activation; ↑ mucosal regeneration	Human and in vitro studies
Fecal Microbiota Transplantation (FMT)	Restoration of microbial diversity through transfer of healthy donor microbiota	↑ insulin sensitivity; ↓ intestinal inflammation; remission of ulcerative colitis and recurrent *C. difficile* infection	Clinical trials (metabolic syndrome, IBD)
Next-Generation Probiotic Therapy (*Akkermansia muciniphila*)	Strengthening of mucin layer; modulation of lipid and glucose metabolism; enhancement of gut barrier integrity	↓ total cholesterol; ↓ fasting insulin; improved insulin sensitivity	Exploratory human clinical trial

Figure 2 integrates outcomes across the principal strategies used to modulate the gut microbiota—probiotics, prebiotics, synbiotics, postbiotics, next-generation probiotics, and fecal microbiota transplantation (FMT)—and maps these strategies to metabolic and gastrointestinal endpoints reported in human and translational studies. Taken together, the evidence supports a graded, mechanism-anchored effect on host metabolism, barrier function, and inflammation, while also underscoring inter-individual variability that argues for personalization of therapy.

1) Probiotics (ISAPP definition and clinical signal).
Under the ISAPP consensus, probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit (Hill et al., 2014). Across trials in obesity and insulin resistance, strains within *Lactobacillus* and *Bifidobacterium* consistently reduce low-grade inflammation and markers of barrier dysfunction, coincident with increases in short-chain fatty acids (SCFAs) and improved insulin sensitivity proxies (e.g., HOMA-IR) (Hill et al., 2014; Valdes et al., 2018; Canfora et al., 2015). Mechanistically, probiotic effects converge on: (i) butyrate-linked enhancement of tight-junction integrity and epithelial oxygenation; (ii) down-modulation of NF-κB signaling; and (iii) bile-acid deconjugation with downstream FXR/TGR5 signaling that can influence glucose and lipid homeostasis (Canfora et al., 2015; Valdes et al., 2018). Clinical magnitude varies with baseline microbiome context—an observation later echoed by personalization studies (Zmora et al., 2018).

2) Prebiotics (selective substrates and metabolic readouts).
Per ISAPP, prebiotics are substrates selectively utilized by host microorganisms conferring a health benefit (Gibson et al., 2017). Fermentable fibers such as inulin and resistant starch enrich *Bifidobacterium* and *Prevotella*, increase SCFA pools (propionate, acetate, butyrate), and support enteroendocrine GLP-1/PYY secretion with downstream improvements in glucose handling (Gibson et al., 2017; Canfora et al., 2015). A pivotal human study linked fiber-induced *Prevotella* expansion to better post-prandial glycemia, tying a discrete taxonomic shift to a measurable metabolic benefit (Kovatcheva-Datchary et al., 2015). These data argue that feeding the right substrates to the right guilds can shift host metabolism without introducing exogenous microbes.

3) Synbiotics (designed synergy).
Synbiotics strategically combine a probiotic with a complementary prebiotic to enhance microbial persistence and functional output; the ISAPP framework formalizes this as either "complementary" or "synergistic" designs (Swanson et al., 2020). Reported benefits—improvements in lipid fractions, glucose tolerance, and barrier function—are

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biologically coherent with additive increases in SCFAs and reduced epithelial inflammation (Swanson et al., 2020; Canfora et al., 2015). While aggregated effects in metabolic syndrome cohorts trend larger than using either component alone, inter-study heterogeneity remains, reinforcing the need for strain- and substrate-level specification (Swanson et al., 2020).

4) Postbiotics (functions without colonization).
Postbiotics—preparations of inanimate microorganisms and/or their components—offer immunomodulatory and barrier-protective effects without the requirement for live colonization (Salminen et al., 2021). Their mechanisms include pattern-recognition receptor signaling (e.g., MAMPs engaging TLRs/NODs), induction of tolerogenic pathways, and reinforcement of tight junctions, with downstream reductions in NF-κB activity (Salminen et al., 2021). Clinically, postbiotics are attractive where colonization is unreliable or contraindicated, and they align with a precision-moiety view of microbiome therapeutics.

5) Next-generation probiotics (Akkermansia muciniphila).
A. muciniphila exemplifies a mucin-specialist associated with leanness and metabolic fitness. In a proof-of-concept human trial, pasteurized *Akkermansia* improved insulin sensitivity, reduced total cholesterol, and lowered inflammatory markers in overweight/obese participants, consistent with enhanced mucus-layer integrity and reduced metabolic endotoxemia (Depommier et al., 2019). Ecologically, *Akkermansia* sits at the diet–host interface, translating fiber-linked substrate flux into barrier support and anti-inflammatory tone—an effect mirrored by its depletion in dysbiosis profiles (Valdes et al., 2018).

6) Fecal microbiota transplantation (FMT) and standardized consortia.
FMT resets community structure and function at scale. Its strongest, most reproducible clinical signal remains in recurrent *Clostridioides difficile* infection—initially via colonoscopic/duodenal infusion (van Nood et al., 2013)—and now with oral microbiome therapies such as SER-109 showing reduced recurrence in randomized trials (Feuerstadt et al., 2022). In inflammatory bowel disease, multidonor FMT increased remission rates versus placebo in ulcerative colitis, implicating diversity restoration and bile-acid/SCFA re-balancing as candidate mechanisms (Paramsothy et al., 2017; Costello et al., 2019). Importantly for metabolic disease, lean-donor FMT improved insulin sensitivity in metabolic syndrome, with responders distinguished by baseline microbiome features—an early clinical demonstration that **who you are before intervention** conditions **what you gain after** (Vrieze et al., 2012; Kootte et al., 2017).

Cross-cutting mechanisms and personalization.
Across modalities, SCFAs emerge as a shared mechanistic currency connecting microbial activity to host endpoints—engaging GPR41/GPR43, modulating hepatic gluconeogenesis, adipose lipolysis, and gut hormones (Canfora et al., 2015). Equally, diet and xenobiotics can counter-steer these benefits: non-nutritive sweeteners altered glycemic control through microbiome shifts, with effects contingent on the individual's baseline community (Suez et al., 2014; Suez et al., 2022). Personalized nutrition work further demonstrated that glycemic responses are predictable from microbiome features, arguing for algorithm-guided, microbially informed diet prescriptions (Zeevi et al., 2015). Probiotic colonization itself is person-specific and gated by host and microbial ecology, explaining variable clinical readouts and motivating pre-intervention profiling (Zmora et al., 2018).

Figure 3.
Metabolic Axis of Short-Chain Fatty Acids (SCFAs): Receptors, Target Tissues, and Physiologic Readouts

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SCFA	Primary host receptors / transporters	Key target tissues / cells	Dominant mechanisms
Butyrate	HCAR2 (GPR109A); FFAR2/FFAR3 (GPR43/41); MCT1/SMCT1	Colonocytes; epithelial tight junctions; colonic Tregs; liver (via portal); skeletal muscle	Principal fuel for colonocytes; ↑ mucin & tight-junction proteins; **HDAC inhibition** → anti-inflammatory gene programs; ↑ β-oxidation; ↓ endotoxemia
Propionate	FFAR2 (GPR43) > FFAR3; MCT1	Enteroendocrine L-cells; liver; adipose tissue	↑ GLP-1 / PYY secretion; ↓ hepatic lipogenesis; vagal signaling to appetite centers
Acetate	FFAR2 (GPR43); FFAR3; systemic diffusion	Hypothalamus (indirect); adipose; skeletal muscle	Substrate for acetyl-CoA pools; gut-brain axis signaling; modulation of lipolysis via FFAR2
Mixed SCFA pool (dietary fiber → microbiota)	Combined FFAR2/3 & transporters	Gut barrier; immune cells; bile-acid metabolism	**Guild-level effects** (e.g., *Prevotella*, *Bifidobacterium*) → ↑ SCFAs; secondary bile-acid signaling (FXR/TGR5)

Figure 3 maps a coherent, mechanism-first explanation of how fiber-driven microbial fermentation translates into measurable benefits on host metabolism and intestinal integrity. **Butyrate** emerges as the colon's preferred energy source and a potent **epigenetic modulator**: through **HCAR2 (GPR109A)** engagement and **HDAC inhibition**, butyrate strengthens tight-junction architecture, promotes tolerogenic immune programs (e.g., Treg induction), and dampens NF-κB–dependent inflammation—mechanistically linking microbial activity to reduced endotoxemia and improved insulin signaling (Canfora et al., 2015; Valdes et al., 2018). These barrier-centric effects help explain why higher butyrate availability associates with lower systemic CRP/IL-6 and better metabolic flexibility in human cohorts (Valdes et al., 2018).

Propionate, acting predominantly through **FFAR2 (GPR43)** on enteroendocrine L-cells, elevates **GLP-1** and **PYY**, enhancing insulinotropic signaling and satiety while simultaneously constraining hepatic de novo lipogenesis—yielding lower post-prandial glycemia and more favorable lipid handling (Canfora et al., 2015; Gibson et al., 2017). **Acetate**, the most abundant SCFA systemically, participates in gut–brain crosstalk and peripheral energy partitioning via FFAR2/3, with context-dependent effects on adipose lipolysis and skeletal-muscle substrate use (Canfora et al., 2015).

Diet is the principal lever that shifts this axis. A landmark human study demonstrated that **increased dietary fiber** expanded **Prevotella** guilds and improved glycemic control, tightly coupling a taxonomic change to a functional SCFA-mediated benefit (Kovatcheva-Datchary et al., 2015). In parallel, consensus criteria for **prebiotics** emphasize substrates selectively used by beneficial microbes to amplify these SCFA-linked pathways (Gibson et al., 2017). These findings rationalize why fiber-rich diets and targeted prebiotics reproducibly improve glycemic excursions and intestinal barrier status across diverse settings (Canfora et al., 2015; Gibson et al., 2017).

Importantly, the SCFA axis also helps unify outcomes from interventional studies summarized previously. **Lean-donor FMT** improved insulin sensitivity in metabolic syndrome—an effect plausibly mediated by rapid restoration of SCFA-producing consortia and barrier function (Vrieze et al., 2012; Kootte et al., 2017). In IBD, **multidonor FMT** increased remission versus placebo, consistent with diversity recovery and SCFA/bile-acid re-balancing (Paramsothy et al., 2017; Costello et al., 2019). **Next-generation strategies** such as *Akkermansia muciniphila* likely complement the SCFA axis by thickening the mucin layer and lowering inflammatory translocation, thereby reducing the host's SCFA demand for barrier repair and freeing it for systemic metabolic effects (Depommier et al., 2019; Valdes et al., 2018).

The same framework clarifies **why responses are person-specific**. Baseline microbiome composition governs substrate utilization, SCFA yields, and receptor expression landscapes—explaining variable colonization and efficacy of probiotics (Zmora et al., 2018). Moreover, **non-nutritive sweeteners** can perturb these pathways, inducing glucose intolerance via microbiota changes, with effects **personalized** to the existing community structure (Suez et al., 2014; Suez et al., 2022). Microbiome-informed algorithms predicting **glycemic responses** show that diet can be tuned to an individual's SCFA-competent guilds, operationalizing precision nutrition (Zeevi et al., 2015).

Synthesis: The SCFA axis forms a mechanistic backbone linking diet–microbe interactions to clinical endpoints: **more fiber → more SCFAs → stronger barrier, lower inflammation, better glycemic control**. This axis integrates and helps predict outcomes of prebiotics, probiotics/synbiotics, FMT, and next-generation microbial therapies. It also

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justifies regional adaptation (Mexico, Colombia, Ecuador), where diet patterns and baseline microbiomes differ, and supports pre-intervention profiling to personalize targets and substrates (Canfora et al., 2015; Gibson et al., 2017; Zmora et al., 2018; Zeevi et al., 2015).

Figure 4.
Emerging Microbiome-Targeted Therapies: Next-Generation Strains, Defined Postbiotics, and Standardized Consortia

Modality	Composition / Agent	Primary Mechanisms	Clinical Setting / Indication
Next-generation probiotic	*Akkermansia muciniphila* (pasteurized)	Strengthens mucin layer; tight-junction support; lowers metabolic endotoxemia; immunomodulation	Overweight/obesity; insulin resistance
Defined postbiotic	Inactivated cells/cell fragments/metabolites (per ISAPP definition)	PRR engagement (TLR/NOD); anti-inflammatory signaling; barrier reinforcement; no colonization needed	Adjunct in metabolic & inflammatory conditions where colonization is unreliable
Standardized spore-based consortium	SER-109 (oral purified Firmicutes spores)	Ecological reset after antibiotics; bile-acid & SCFA rebalance; colonization resistance to *C. difficile*	Recurrent *Clostridioides difficile* infection
Fecal microbiota transplantation (FMT)	Multidonor/lean-donor stool preparations	Diversity restoration; SCFA and bile-acid remodeling; pathogen suppression	Ulcerative colitis; recurrent CDI; metabolic syndrome (insulin resistance)
Algorithm-guided precision nutrition	Diets tailored by microbiome-host features	SCFA-centric substrate routing; glycemic response prediction; personalization	Glycemic control in diverse adults

Figure 4 brings together four therapeutic "archetypes" for microbiome modulation—**ecological reset (FMT/standardized consortia), precision agents (next-generation strains), mechanism-defined bioactives (postbiotics),** and **algorithm-guided nutrition**—and positions them along a continuum from broad community restructuring to highly targeted, data-driven personalization. The common therapeutic currency is restoration of barrier integrity, reduction of inflammatory tone, and improvement of metabolic signaling, with the specific route depending on baseline dysbiosis, disease context, feasibility of colonization, and need for standardization.

1) Next-generation strains: Akkermansia muciniphila as a barrier-centric metabolic tool
The pasteurized preparation of *A. muciniphila* improved insulin sensitivity, lowered total cholesterol, and reduced inflammatory markers in overweight/obese adults (proof-of-concept RCT), aligning with its biology as a mucin specialist that thickens the mucus layer and stabilizes tight junctions (Depommier et al., 2019). Mechanistically, *Akkermansia* likely reduces metabolic endotoxemia and improves epithelial–immune cross-talk, indirectly easing hepatic and adipose inflammatory signaling that worsens insulin resistance. As a **precision agent**, it suits phenotypes with barrier compromise and low *Akkermansia* abundance, offering an alternative where broad ecological upheaval (FMT) is unnecessary or impractical (Depommier et al., 2019; Valdes et al., 2018).

Clinical positioning. Useful for insulin resistance with suspected barrier fragility; complements diet/prebiotics that supply fermentable substrates to SCFA-producing guilds (Kovatcheva-Datchary et al., 2015; Gibson et al., 2017). Its **pasteurized** format also sidesteps colonization unpredictability while preserving immunometabolic benefits (Depommier et al., 2019).

2) Defined postbiotics: standardized bioactivity without colonization

ISAPP defines postbiotics as preparations of inanimate microorganisms and/or their components that confer health benefits (Salminen et al., 2021). By engaging pattern-recognition receptors (e.g., TLRs/NODs) and reinforcing epithelial programs, postbiotics dampen NF-κB signaling, enhance barrier proteins, and can be **manufactured to tight specifications**, a regulatory advantage versus live products (Salminen et al., 2021). Because efficacy is **independent of engraftment**, postbiotics fit contexts where colonization is unreliable (antibiotic exposure, severe dysbiosis) or contraindicated.

Clinical positioning. Adjunct for inflammatory phenotypes when reproducibility and safety margins are paramount; can be layered with diet, prebiotics, or next-generation strains to stack mechanisms (Salminen et al., 2021; Gibson et al., 2017).

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3) Standardized consortia/spore products (e.g., SER-109): scalable ecological repair

SER-109 (purified Firmicutes spores) reduced recurrent *Clostridioides difficile* infection in RCTs, illustrating a **defined-composition** path to community repair after antibiotics, with durable engraftment signals and improved colonization resistance (Feuerstadt et al., 2022). Spore-based consortia balance the power of ecological reset with greater batch-to-batch standardization than donor stool.

Clinical positioning. First-line in recurrent CDI and a template for future consortia that target bile-acid and SCFA remodeling beyond CDI (Feuerstadt et al., 2022). Potential in metabolic or inflammatory settings remains an area for expansion once indications and consortia are precisely matched to mechanism.

4) Fecal microbiota transplantation (FMT): maximal reset for severe dysbiosis

FMT remains the **highest-effect ecological intervention** where pathogenesis is tightly linked to community collapse. Landmark work established efficacy for recurrent CDI (van Nood et al., 2013). In ulcerative colitis, multidonor FMT improved remission over placebo—likely via diversity repletion and metabolite re-balancing (Paramsothy et al., 2017; Costello et al., 2019). In metabolic syndrome, FMT from lean donors improved insulin sensitivity, and responders were predicted by baseline microbiome features—an early clinical demonstration of **baseline-dependent benefit** (Vrieze et al., 2012; Kootte et al., 2017).

Clinical positioning. Consider where rapid, broad reconstruction is needed (recurrent CDI; selected UC cases). For metabolic indications, **phenotyping the baseline microbiome** helps forecast response (Kootte et al., 2017).

5) Algorithm-guided precision nutrition: operationalizing personalization

Microbiome-informed models predict individual glycemic responses and produce **diet plans that outperform generalized advice**, effectively routing substrates to a person's SCFA-competent guilds (Zeevi et al., 2015). This approach "personalizes the prebiotic," aligning daily intake with the host–microbe metabolic interface.

Clinical positioning. Foundational and scalable in metabolic health programs; can be paired with any biologic modality to sustain gains (Zeevi et al., 2015; Gibson et al., 2017).

Cross-cutting themes and patient selection

- **Mechanistic convergence on SCFAs and barrier integrity.** The modalities differ in entry points—community reset (FMT/consortia), barrier reinforcement (*Akkermansia*), receptor-level immunomodulation (postbiotics), or substrate routing (diet)—but converge on **SCFA signaling, tight-junction support, and lower inflammatory tone** (Canfora et al., 2015; Valdes et al., 2018; Gibson et al., 2017).
- **Baseline matters.** Colonization capacity and metabolic benefit depend on the **pre-intervention microbiome**; probiotic engraftment and clinical effects vary with host and community features (Zmora et al., 2018). Even dietary xenobiotics like non-nutritive sweeteners exert **microbiome-dependent, individualized** glycemic effects (Suez et al., 2014; Suez et al., 2022).
- **Standardization vs. breadth.** Postbiotics and consortia favor **manufacturing control and regulatory clarity**; FMT provides **maximal breadth** but with donor-screening demands. Next-gen strains strike a middle ground with defined mechanisms and growing human data (Salminen et al., 2021; Feuerstadt et al., 2022; Depommier et al., 2019).
- **Stacking strategies.** A rational sequence often begins with **personalized nutrition** and **prebiotic substrates**, adds **precision agents** (e.g., *Akkermansia*), escalates to **consortia** for recalcitrant dysbiosis, and reserves **FMT** for indications with strong evidence or failure of narrower tools (Zeevi et al., 2015; Depommier et al., 2019; Feuerstadt et al., 2022; Paramsothy et al., 2017).

Figure 5.

Regional Landscape of Microbiome-Directed Strategies: Mexico, Colombia, and Ecuador

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Domain	Mexico	Colombia	Ecuador
Dietary pattern signals (microbiome-relevant substrates)	Maize/bean–based staples; chiles, squash, nopal, whole grains; rising ultra-processed foods (urban); fermented dairy common. Fiber diversity enables SCFA production when emphasized.	Andean–Caribbean diversity: maize, plantain, cassava, legumes, fruits; regional fermented foods; urban shift to refined carbs/UPFs. Broad substrate range for SCFA guilds with targeted counseling.	Sierra–Costa–Amazonía heterogeneity: corn, tubers, legumes; tropical fruits; localized fermented products; variable access to fiber-rich staples. High potential for community-tailored prebiotic strategies.
Health-burden focus (microbiome-relevant)	Obesity, T2DM, NAFLD/NASH; IBD clusters in tertiary centers; recurrent CDI in high-risk settings.	Metabolic syndrome, T2DM, IBD in referral centers; antibiotic exposure patterns relevant to CDI.	Metabolic risk rising in urban hubs; pockets of enteric/infectious burden affecting early-life microbiota.
Research & infrastructure signals	Growing clinical research networks; access to sequencing/clinical labs in major cities; nutrition programs in academia.	Established academic hubs with translational capacity; diverse cohorts possible across regions.	Emerging capacity; collaboration with regional centers; strong potential for community-based interventions.
Priority interventions (by feasibility and mechanism)	Personalized nutrition (algorithm-guided); prebiotics from local staples; selected probiotic/postbiotic adjuncts; pilot *Akkermansia* programs in insulin resistance.	Personalized diet frameworks; synbiotics targeting barrier function; standardized consortia in CDI; FMT in defined indications.	Community-tailored prebiotic food strategies; low-cost postbiotics for barrier/inflammation; step-up to synbiotics as access allows.
Implementation challenges	UPF penetration; variable access to high-fiber foods; adherence.	Regional heterogeneity; cost and supply chains for standardized products.	Resource constraints; geographic access; need for local training and supply.

Figure 5 frames how microbiome-directed strategies can be translated across Mexico, Colombia, and Ecuador by aligning mechanisms (SCFA pathways, barrier repair, inflammation control) with each country's dietary substrates, health burdens, research capacity, and logistics. The unifying insight is **"precision-within-culture"**: leverage local, fiber-rich staples to drive SCFA production (Canfora et al., 2015; Gibson et al., 2017), then layer ISAPP-aligned probiotics/postbiotics (Hill et al., 2014; Salminen et al., 2021; Swanson et al., 2020) and, when necessary, escalate to standardized consortia or FMT for severe dysbiosis (van Nood et al., 2013; Paramsothy et al., 2017; Costello et al., 2019; Feuerstadt et al., 2022). Baseline microbiome profiling and clinical phenotype guide **who responds to what**, consistent with responder biology in lean-donor FMT (Vrieze et al., 2012; Kootte et al., 2017) and person-specific diet/probiotic effects (Zeevi et al., 2015; Zmora et al., 2018; Suez et al., 2014, 2022).

Country-tailored program design

Mexico — "Fiber-forward metabolic clinics"

Rationale. High burdens of obesity/T2DM/NAFLD, strong availability of legume/maize staples, and tertiary centers capable of clinical trials.
Program pillars.

1. **Personalized nutrition as foundation.** Use microbiome-informed algorithms in metabolic clinics to tailor fiber patterns (maize/beans/nopal/whole grains) toward **Prevotella/Bifidobacterium** guilds and SCFA yield (Zeevi et al., 2015; Gibson et al., 2017; Kovatcheva-Datchary et al., 2015).
2. **Adjuncts.** Introduce ISAPP-aligned **pre/pro/synbiotics** to reinforce barrier function and reduce inflammatory tone (Hill et al., 2014; Swanson et al., 2020; Canfora et al., 2015).
3. **Precision add-ons.** Pilot **pasteurized Akkermansia muciniphila** in insulin-resistant phenotypes with barrier compromise (Depommier et al., 2019).
4. **Escalation pathway.** Reserve **consortia/FMT** for recurrent CDI and selected UC cases; explore responders in metabolic syndrome per baseline profiling (van Nood et al., 2013; Paramsothy et al., 2017; Vrieze et al., 2012; Kootte et al., 2017).

Key metrics. HOMA-IR, fasting insulin, CRP/IL-6, stool SCFAs, permeability markers (zonulin/occludin), and diet adherence.

Colombia — "Regionalized synbiotics + consortia hubs"

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Rationale. Heterogeneous diets (Andean–Caribbean), established academic hubs, and referral centers handling IBD/CDI.

Program pillars.

1. **Region-specific counseling.** Tailor substrates (maize, plantain, cassava, legumes) to local patterns; track person-specific glycemic responses (Zeevi et al., 2015).
2. **Synbiotic emphasis.** Combine well-characterized strains with matching fibers to stabilize colonization and increase **butyrate/propionate** (Swanson et al., 2020; Canfora et al., 2015).
3. **Standardized consortia for CDI.** Deploy **SER-109**-like protocols in recurrent CDI; build implementation science around access and supply chains (Feuerstadt et al., 2022).
4. **FMT centers of excellence.** Multidonor FMT in defined UC indications with strict donor/quality SOPs (Paramsothy et al., 2017; Costello et al., 2019).

Key metrics. Clinical remission rates (IBD/CDI), engraftment signals (16S/metagenomics where available), lipid and glycemic profiles, adverse-event surveillance.

Ecuador — "Community-led prebiotics + postbiotic access"

Rationale. Diverse geography (Sierra–Costa–Amazonía), rising urban metabolic risk, resource variability.

Program pillars.

1. **Primary-care fiber programs.** Leverage local tubers/legumes/tropical fruits to drive **SCFA** output via community health workers; simple meal-pattern algorithms adapted from personalization frameworks (Gibson et al., 2017; Zeevi et al., 2015).
2. **Low-cost postbiotics.** Use **defined, inactivated preparations** where colonization is unreliable, to reduce NF-κB–mediated inflammation and reinforce barrier integrity (Salminen et al., 2021).
3. **Step-up synbiotics.** Introduce synbiotics as supply permits for barrier/immune support (Swanson et al., 2020).
4. **Referral pathways.** Establish regional links for CDI/IBD cases needing consortia or FMT (van Nood et al., 2013; Costello et al., 2019).

Key metrics. Weight, waist/hip ratio, fasting glucose, basic inflammatory markers (CRP), stool consistency/symptom scores; program reach and adherence.

Cross-cutting design criteria (who gets what, when)

1. **Start with diet; personalize early.** Deploy simple screening (diet recall, glycemic excursions) and, where possible, microbiome profiling to route fibers/substrates to SCFA-competent guilds (Zeevi et al., 2015; Gibson et al., 2017; Kovatcheva-Datchary et al., 2015).
2. **Choose live vs. inanimate by colonization likelihood.** If antibiotics/recent illness or severe dysbiosis make engraftment unlikely, prioritize **postbiotics** for consistent anti-inflammatory effects (Salminen et al., 2021).
3. **Match intensity to dysbiosis.**
    - Mild–moderate: diet → pre/pro/synbiotics; consider *Akkermansia* for barrier-centric phenotypes (Depommier et al., 2019).
    - Severe/recurrent CDI or selected UC: **standardized consortia/FMT** under defined indications (Feuerstadt et al., 2022; Paramsothy et al., 2017; Costello et al., 2019; van Nood et al., 2013).
4. **Account for person-specific effects.** Baseline microbiome predicts response to probiotics and even sweeteners; build in reassessment cycles (Zmora et al., 2018; Suez et al., 2014, 2022).
5. **Track barrier & inflammation, not only glucose.** Include permeability and inflammatory panels to capture mechanism-concordant benefit (Canfora et al., 2015; Valdes et al., 2018).

Implementation checklist (clinic & public health)

A. Core SOPs

- ISAPP-aligned definitions for probiotic/prebiotic/postbiotic/synbiotic (Hill et al., 2014; Gibson et al., 2017; Salminen et al., 2021; Swanson et al., 2020).
- Eligibility algorithms by indication (metabolic vs. IBD vs. CDI).
- Dietary templates with local foods mapped to fiber types (inulin-type fructans, resistant starch).

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B. Baseline & follow-up

- Anthropometrics; fasting labs (glucose, insulin, lipids); CRP/IL-6.
- Optional: stool SCFAs; stool sequencing where available (for responder prediction; Kootte et al., 2017; Zmora et al., 2018).
- 8–12 week reassessment; adapt modality (scale up/down; switch to postbiotic or add *Akkermansia*).

C. Safety & quality

- Product traceability and storage SOPs; adverse-event logs.
- For FMT/consortia: donor screening, chain of custody, and outcome registries (van Nood et al., 2013; Paramsothy et al., 2017; Feuerstadt et al., 2022).

D. Education & adherence

- Brief counseling scripts linking foods → microbes → SCFAs → clinical outcomes.
- Digital adherence nudges (meal photos, simple symptom diaries).

E. Research & equity

- Shared data dictionary across sites; harmonized endpoints.
- Subsidized access for postbiotics/basic synbiotics in resource-limited settings; referral networks for advanced therapies.

Practical synthesis

- **Mexico:** hospital-based **precision nutrition** with adjunct *Akkermansia*/synbiotics; escalation to consortia/FMT for defined indications.
- **Colombia: regionalized synbiotic** programs and consortia/FMT hubs integrated with IBD/CDI services.
- **Ecuador: community-led prebiotic** strategies and **postbiotic access**, with referral to regional centers for complex cases.

Across all three, the pathway is **diet first, mechanism-stack second, escalate last**, continuously informed by baseline microbiome and clinical response (Canfora et al., 2015; Gibson et al., 2017; Swanson et al., 2020; Depommier et al., 2019; Vrieze et al., 2012; Kootte et al., 2017; Zeevi et al., 2015; Zmora et al., 2018; Salminen et al., 2021; Suez et al., 2014, 2022; van Nood et al., 2013; Paramsothy et al., 2017; Costello et al., 2019; Feuerstadt et al., 2022).

Discussion

The findings consolidated across Figures 1–5 underscore that modulation of the gut microbiota represents a **multi-dimensional, clinically viable strategy** for managing both gastrointestinal and metabolic diseases. The discussion integrates ecological, mechanistic, clinical, and translational evidence—linking microbial diversity, SCFA signaling, and barrier function to systemic metabolic outcomes—and contextualizes these insights within regional implementation frameworks across Mexico, Colombia, and Ecuador.

1. The gut microbiota as a metabolic organ: from ecology to pathophysiology

The human intestinal microbiota functions as a **dynamic endocrine–metabolic organ**, regulating nutrient absorption, immune balance, and energy homeostasis through its metabolites and structural components (Lynch & Pedersen, 2016; Valdes et al., 2018). In healthy states, **microbial diversity** ensures functional redundancy and resilience against perturbations, whereas dysbiosis—marked by a reduction in *Bacteroidetes* and *Actinobacteria* and expansion of *Firmicutes* and *Proteobacteria*—precipitates systemic low-grade inflammation and insulin resistance (Qin et al., 2012; Ridaura et al., 2013).

This dysbiotic shift compromises intestinal barrier integrity and increases permeability, enabling the translocation of bacterial lipopolysaccharides (LPS) into circulation, which activates Toll-like receptor 4 (TLR4)–mediated inflammation (Lynch & Pedersen, 2016). Elevated inflammatory markers such as TNF-α and IL-6, in turn, inhibit insulin receptor signaling, establishing a **vicious cycle between microbial imbalance and metabolic dysfunction**

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(Canfora et al., 2015; Valdes et al., 2018). The consistency of these patterns across diverse populations affirms that the microbiome is not merely a passive bystander but a **central mediator of host metabolic health**.

2. Mechanistic nexus: SCFAs as signaling molecules

SCFAs—acetate, propionate, and butyrate—emerge as **metabolic mediators linking microbial activity to host physiology** (Canfora et al., 2015; Gibson et al., 2017). Butyrate, produced primarily by *Faecalibacterium prausnitzii* and other *Firmicutes*, serves as the colon's main energy source and exerts anti-inflammatory effects through histone deacetylase (HDAC) inhibition (Valdes et al., 2018). Propionate acts on enteroendocrine L-cells to stimulate GLP-1 and PYY secretion, regulating appetite and insulin sensitivity, while acetate modulates lipid metabolism and communicates with central satiety centers (Canfora et al., 2015).

These SCFAs engage receptors **FFAR2 (GPR43)** and **FFAR3 (GPR41)**, as well as **HCAR2 (GPR109A)**, orchestrating anti-inflammatory and metabolic responses across intestinal, hepatic, and adipose tissues (Canfora et al., 2015). Studies have demonstrated that **higher fiber intake**, leading to increased SCFA levels, correlates with improved insulin sensitivity and reduced inflammation (Kovatcheva-Datchary et al., 2015). Therefore, interventions that enhance SCFA production—via diet, probiotics, or prebiotics—constitute a biologically coherent path for restoring metabolic homeostasis.

This mechanistic framework also rationalizes why individuals with depleted SCFA-producing taxa experience more severe insulin resistance and why microbial reconstitution therapies, such as FMT or synbiotics, can reverse these outcomes (Vrieze et al., 2012; Kootte et al., 2017).

3. Therapeutic modulation: from traditional probiotics to precision approaches

Early microbial interventions relied on broad **probiotic** supplementation, with strains of *Lactobacillus* and *Bifidobacterium* demonstrating moderate improvements in glycemic and inflammatory parameters (Hill et al., 2014). Prebiotics, defined by ISAPP as substrates selectively utilized by beneficial microbes (Gibson et al., 2017), enhanced these effects by promoting the growth of SCFA-producing taxa such as *Prevotella* and *Bifidobacterium*. **Synbiotics** subsequently combined these elements, generating synergistic outcomes through concurrent microbial colonization and substrate availability (Swanson et al., 2020).

However, the field has evolved toward **mechanistically defined, precision therapies**, exemplified by *Akkermansia muciniphila* and postbiotics. *A. muciniphila* strengthens the mucosal barrier, improves lipid metabolism, and reduces inflammation; supplementation in obese, insulin-resistant individuals led to **20–28% improvement in insulin sensitivity** and decreases in plasma cholesterol and CRP (Depommier et al., 2019). Postbiotics—non-viable microbial cells or metabolites—offer standardized bioactivity without colonization dependency, engaging innate immune receptors to reinforce epithelial defense (Salminen et al., 2021).

The **standardization** of such preparations marks a turning point in microbiome therapeutics, allowing for reproducibility and regulatory oversight absent from early probiotic formulations. These modalities retain the ecological benefits of live microbes while addressing variability in colonization and host compatibility, a problem highlighted by colonization-resistance studies (Zmora et al., 2018).

4. Ecological reset: fecal microbiota transplantation and standardized consortia

At the highest level of intervention, **fecal microbiota transplantation (FMT)** and **standardized consortia therapies** reconstitute the gut ecosystem at scale. FMT has achieved remarkable efficacy in recurrent *Clostridioides difficile* infection, with cure rates exceeding 80% in randomized trials (van Nood et al., 2013; Feuerstadt et al., 2022). Expanding its use to metabolic and inflammatory diseases has shown promising results: lean-donor FMT improved insulin sensitivity in metabolic syndrome (Vrieze et al., 2012; Kootte et al., 2017), while multidonor FMT achieved 25–30% remission in ulcerative colitis (Paramsothy et al., 2017; Costello et al., 2019).

These interventions demonstrate that **microbial diversity restoration** is not merely symptomatic but mechanistically corrective, re-establishing SCFA and bile acid signaling networks that regulate glucose and lipid metabolism. Yet,

success remains highly dependent on the recipient's baseline microbiome—a finding that motivates pre-intervention microbiome profiling and the refinement of donor matching protocols (Kootte et al., 2017; Zmora et al., 2018).

The emergence of **standardized spore-based consortia** (e.g., SER-109) further exemplifies the evolution from empiric FMT to **defined microbial consortia**, enabling safe, reproducible ecological resets (Feuerstadt et al., 2022).

5. Individual variability and the case for personalization

Across all modalities, **inter-individual variability** remains a defining feature. The microbiome's composition determines not only baseline metabolic function but also responsiveness to diet, probiotics, or pharmacologic interventions (Zmora et al., 2018). Personalized nutrition studies have shown that glycemic responses can be predicted using microbiome and clinical features, enabling the design of individualized diets that outperform generalized dietary advice (Zeevi et al., 2015). Similarly, the metabolic effects of artificial sweeteners depend on each person's microbial profile—some experience glucose intolerance, others remain unaffected (Suez et al., 2014; Suez et al., 2022).

These findings collectively emphasize the transition from **population-based recommendations** toward **precision microbiome medicine**, where interventions are tailored to microbial ecology, host genetics, and environmental exposures. The ability to **predict responders**—as demonstrated in FMT and diet-personalization trials—marks a critical step toward clinically effective microbiome-guided therapy (Kootte et al., 2017; Zeevi et al., 2015).

6. Translational implementation: Latin American perspective

From a regional standpoint, the integration of microbiome therapeutics in **Latin America** must navigate dietary diversity, health disparities, and resource variability. Figure 5 delineates how Mexico, Colombia, and Ecuador can each operationalize microbiome science in culturally and economically feasible ways.

In **Mexico**, where metabolic disorders are prevalent, hospitals can integrate microbiome-informed dietary algorithms into metabolic clinics, leveraging indigenous fiber sources like maize, beans, and nopal to enhance SCFA pathways (Gibson et al., 2017; Kovatcheva-Datchary et al., 2015; Zeevi et al., 2015). **Colombia**, with strong research infrastructure and a high prevalence of IBD and CDI, can develop regional FMT and consortia hubs while expanding synbiotic use for metabolic syndrome and inflammatory conditions (Swanson et al., 2020; Feuerstadt et al., 2022). In **Ecuador**, where rural and urban health disparities coexist, community-level prebiotic and postbiotic programs led by health workers can address metabolic risk affordably while reserving advanced therapies for referral centers (Salminen et al., 2021).

This tiered, culturally integrated approach embodies **"precision-within-culture"**—the adaptation of global scientific evidence to local dietary substrates, epidemiological patterns, and healthcare capacities.

7. Limitations and future directions

Despite the accumulating evidence, challenges persist. Microbiome research faces **methodological heterogeneity**, from sequencing depth and sample handling to diet recall accuracy. The **cause–effect boundary** between dysbiosis and disease remains partially unresolved—many associations are bidirectional. Interventional reproducibility also varies due to differences in microbial strains, doses, and formulations (Hill et al., 2014; Gibson et al., 2017). Moreover, **ethical and regulatory frameworks** for FMT and live biotherapeutic products are still evolving globally, posing constraints for scalable implementation.

Future research must focus on:

1. **Standardizing analytical pipelines** for cross-study comparability.
2. **Developing defined microbial consortia** with verified functions beyond CDI, especially for metabolic and neuroimmune diseases.
3. **Expanding longitudinal, multi-omics cohorts** in Latin America to capture diet–microbe–host interactions.
4. **Integrating microbiome medicine into public health** through education, nutrition programs, and affordable microbial formulations.

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Equally important is addressing **equity in access**—ensuring that microbiome-based therapies benefit populations beyond tertiary centers. Local production of prebiotic/postbiotic formulations using regional materials could reduce cost and dependency on imported products, making microbiome modulation **socioeconomically sustainable** in Latin America.

8. Integrative perspective

Overall, the discussion demonstrates that the **gut microbiota is both a marker and a modifiable determinant of health**, bridging molecular biology, nutrition, and clinical medicine. The converging evidence shows that restoring microbial diversity and SCFA pathways alleviates systemic inflammation and improves metabolic outcomes across populations.

By moving from empirical supplementation toward **mechanistically and culturally informed modulation**, microbiome science offers a roadmap for precision prevention and therapy—one that merges **global mechanisms with local realities**. This integrative model aligns with international objectives for **sustainable health and chronic disease reduction**, particularly within the frameworks of the **UN Sustainable Development Goals (SDGs)** related to good health, innovation, and responsible consumption.

As Mexico, Colombia, and Ecuador expand their research and implementation capacity, they can collectively transform microbiome modulation into a regional pillar of preventive medicine—anchoring innovation in diversity, science, and equity.

CONCLUSIÓN

The cumulative evidence presented throughout this study confirms that **gut microbiota modulation represents a transformative frontier in the management and prevention of metabolic and gastrointestinal diseases**. Far from being a passive microbial community, the gut ecosystem operates as an active metabolic organ that interfaces with immune, endocrine, and neurological networks. Its composition and functionality shape not only digestive health but also systemic processes such as insulin sensitivity, lipid metabolism, and inflammatory regulation (Lynch & Pedersen, 2016; Valdes et al., 2018).

The findings discussed across Figures 1–5 demonstrate a coherent biological narrative: **health is mirrored in microbial diversity, and disease in ecological simplification**. Dysbiosis, characterized by an increased *Firmicutes/Bacteroidetes* ratio and loss of beneficial taxa such as *Bifidobacterium* and *Akkermansia muciniphila*, drives metabolic inflammation and insulin resistance (Qin et al., 2012; Ridaura et al., 2013; Depommier et al., 2019). Restoration of microbial balance through dietary fibers, probiotics, postbiotics, or fecal microbiota transplantation reactivates **SCFA-centered signaling pathways** that enhance barrier integrity, reduce systemic inflammation, and reestablish metabolic homeostasis (Canfora et al., 2015; Gibson et al., 2017).

1. The mechanistic foundation of clinical improvement

Central to this therapeutic framework is the **SCFA axis**, which links microbial fermentation of dietary fibers to host receptors such as **FFAR2 (GPR43)**, **FFAR3 (GPR41)**, and **HCAR2 (GPR109A)** (Canfora et al., 2015). Butyrate and propionate emerge as metabolic and anti-inflammatory effectors that regulate energy utilization, epithelial integrity, and immune tolerance (Valdes et al., 2018). Interventions that amplify SCFA production—ranging from prebiotic supplementation to *Prevotella*-targeted diets—consistently correlate with improved glucose metabolism and reduced inflammatory markers (Kovatcheva-Datchary et al., 2015; Gibson et al., 2017).

These metabolic improvements are not theoretical: clinical evidence from **lean-donor fecal microbiota transplantation (FMT)** trials shows measurable increases in insulin sensitivity among recipients, with responders identified by their baseline microbial configuration (Vrieze et al., 2012; Kootte et al., 2017). Likewise, **next-generation probiotics** such as *Akkermansia muciniphila* have proven capable of restoring mucosal barrier function and decreasing systemic inflammation, demonstrating translational success from ecological theory to human application (Depommier et al., 2019).

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2. Therapeutic stratification and precision-based interventions

The therapeutic continuum—outlined through the progression from probiotics and prebiotics to postbiotics, next-generation strains, and ecological resets—embodies a **hierarchical model of microbiota intervention** (Hill et al., 2014; Salminen et al., 2021; Swanson et al., 2020).

- **Probiotics** provide moderate but consistent benefits in modulating immune tone and barrier permeability.
- **Prebiotics** selectively nurture endogenous beneficial taxa and promote SCFA biosynthesis.
- **Synbiotics** synergize both functions, yielding superior outcomes in lipid and glucose regulation.
- **Postbiotics** deliver mechanistic precision and safety, offering standardized bioactive effects without requiring colonization (Salminen et al., 2021).
- **Next-generation probiotics**, particularly *Akkermansia muciniphila*, represent targeted agents for metabolic repair (Depommier et al., 2019).
- **FMT and defined microbial consortia** remain the highest-impact tools for severe dysbiosis, offering diversity restoration and metabolic reset (van Nood et al., 2013; Paramsothy et al., 2017; Feuerstadt et al., 2022).

This stratification promotes **personalized, stepwise intervention**—beginning with dietary modulation and escalating according to disease severity, baseline microbiome, and individual response (Zeevi et al., 2015; Zmora et al., 2018).

3. Toward personalized and predictive microbiome medicine

A key insight emerging from this synthesis is that **the microbiome mediates inter-individual variability in therapy response**. Clinical outcomes from diet, probiotics, and pharmacological agents differ widely depending on the initial microbial configuration (Zmora et al., 2018). Personalized nutrition studies have proven that glycemic control can be predicted from microbiome data, paving the way for **algorithm-guided dietary interventions** that align with an individual's SCFA-generating capacity (Zeevi et al., 2015). Similarly, adverse metabolic effects of artificial sweeteners are contingent on baseline microbiota composition (Suez et al., 2014; Suez et al., 2022).

This emerging field of **precision microbiome medicine** advocates integrating metagenomics, metabolomics, and clinical metadata to anticipate therapeutic outcomes. The goal is not only to correct dysbiosis but to **forecast health trajectories** and tailor interventions accordingly—shifting medicine from reactive to proactive.

4. Public health translation: from laboratory to local reality

The regional analysis encompassing **Mexico, Colombia, and Ecuador** illustrates how microbiome science can be localized without compromising scientific rigor. Each country presents unique dietary substrates and epidemiological pressures, yet shares the dual challenge of chronic metabolic disease and inequitable healthcare access.

- **In Mexico**, the priority is integrating microbiome profiling into metabolic clinics and designing culturally resonant diets that stimulate SCFA production through traditional staples such as maize and legumes (Gibson et al., 2017; Kovatcheva-Datchary et al., 2015).
- **In Colombia**, robust research infrastructure supports synbiotic programs and standardized consortia hubs for CDI and IBD, serving as regional centers for evidence-based microbial therapy (Swanson et al., 2020; Feuerstadt et al., 2022).
- **In Ecuador**, the emphasis lies on low-cost, community-led prebiotic and postbiotic initiatives that target early metabolic risk through dietary education and accessible microbial interventions (Salminen et al., 2021).

Together, these approaches define a **tiered implementation model**: start with diet and behavioral modification, reinforce with defined microbial products, and escalate to advanced interventions for severe dysbiosis. Such integration

promotes not only metabolic recovery but also **health equity and sustainability**, aligning with the **UN Sustainable Development Goals (SDG 3, 9, and 12)** for good health, innovation, and responsible production.

5. Research and clinical priorities moving forward

Despite the robust evidence base, several frontiers remain open.

1. **Standardization** — Global harmonization of analytical pipelines and strain identification will be essential for reproducibility and regulatory progress (Hill et al., 2014; Gibson et al., 2017).
2. **Mechanistic specificity** — Understanding host–microbe–metabolite interactions at the receptor and gene-expression level remains incomplete, especially in diverse populations.
3. **Longitudinal data** — Chronic disease outcomes require sustained monitoring of microbiome shifts across years, not months.
4. **Accessibility and affordability** — Developing regionally sourced prebiotics and postbiotics can democratize microbiome therapy in Latin America.
5. **Interdisciplinary collaboration** — Progress demands synergy between clinicians, microbiologists, nutritionists, and data scientists to translate omics data into actionable clinical insights.

As global initiatives advance, Latin American research networks—leveraging their biodiversity, dietary diversity, and emerging sequencing capacities—can contribute unique insights into **how local ecologies shape human microbiomes**.

6. Final synthesis

Collectively, the evidence confirms that **the modulation of the gut microbiota offers a mechanistically grounded, evidence-based, and scalable approach to improve human metabolic and gastrointestinal health**. Through the restoration of microbial diversity and SCFA-mediated communication, it is possible to reshape the inflammatory and metabolic landscape underlying many chronic diseases.

Future medicine will not treat the microbiome as an accessory but as a **therapeutic axis**—a modifiable system intertwined with nutrition, immunity, and pharmacology. The integration of **precision microbiome science with culturally adapted interventions** positions Mexico, Colombia, and Ecuador to become leaders in the translation of microbiome medicine to real-world health systems.

By combining **global scientific rigor with local innovation**, these nations can transform the microbiome from a frontier of research into a pillar of preventive and personalized healthcare—bridging biology, culture, and public policy toward a more sustainable model of health for the 21st century.

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