Draft Systematic Review Protocol

# Title

The Human Microbiome and Health: A Systematic Review of Its Role in Gene Regulation and Disease Prevention

# Background

The human microbiome has emerged as a central player in health and disease, influencing immune regulation, metabolic pathways, and even host gene expression. Recent advances in sequencing technologies and systems biology have highlighted microbiome alterations in conditions such as obesity, type 2 diabetes, inflammatory bowel disease, cancer, and neuropsychiatric disorders.  
  
Importantly, microbiota-derived metabolites (e.g., short-chain fatty acids, bile acids, tryptophan derivatives) act as signaling molecules that can regulate host gene expression through epigenetic and transcriptional mechanisms. This suggests a potential for microbiome-targeted interventions (e.g., diet, probiotics, prebiotics, synbiotics, fecal microbiota transplantation, and antibiotics) to prevent or modulate disease pathways.  
  
Despite the growing literature, a comprehensive synthesis of how microbiome modulation affects host gene regulation and disease prevention across humans, animals, and mechanistic models is lacking.

# Objectives

## Primary Objective

To systematically review the evidence on how microbiome composition and modulation influence host gene regulation and disease prevention.

## Secondary Objectives

1. To examine the role of specific microbiota-derived metabolites in regulating host molecular pathways.  
2. To compare effects across different interventions (dietary, probiotic, prebiotic, synbiotic, FMT, antibiotics).  
3. To integrate human, animal, and in vitro evidence into a mechanistic framework of microbiome–host interaction.

# Methods

## Eligibility Criteria

- Study designs: Randomized controlled trials (RCTs), cohort studies, case-control studies, quasi-experimental studies, animal studies, in vitro studies.  
- Population: Humans (all ages, sexes, health conditions), relevant animal models, and in vitro systems.  
- Interventions: Any approach that modulates the microbiome (diet, probiotics, prebiotics, synbiotics, antibiotics, fecal microbiota transplantation, lifestyle interventions).  
- Comparators: Placebo, no intervention, or alternative interventions.  
- Outcomes:  
 - Primary: Evidence of gene regulation (epigenetic changes, transcriptomic shifts, signaling pathway activation).  
 - Secondary: Microbiome composition/diversity changes, disease prevention outcomes, biomarkers of health.  
- Timeframe: No restrictions on publication year.  
- Language: English.

## Information Sources

Electronic databases: PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane CENTRAL.  
Grey literature: ProQuest, ClinicalTrials.gov, bioRxiv/medRxiv.  
Hand-searching of reference lists from included studies and reviews.

## Search Strategy

A comprehensive, Boolean-based search will be performed. Full database-specific strategies provided in Appendix 1.

## Study Selection

Titles/abstracts screened by two independent reviewers.  
Full texts assessed for eligibility.  
Discrepancies resolved by discussion or third reviewer.  
PRISMA 2020 flow diagram will be used to report selection.

## Data Extraction

Pre-piloted form (Appendix 2). Two reviewers extract independently. Domains include study characteristics, population, intervention, comparator, outcomes, microbiome methods, key findings, limitations.

## Risk of Bias Assessment

Tools selected according to study design (Appendix 3). Two reviewers independently assess. Results presented narratively and visually.

## Data Synthesis

Narrative synthesis: All included studies will be summarized in structured tables.  
Quantitative synthesis (meta-analysis): Conducted if ≥3 studies with comparable interventions/outcomes.  
- Random-effects model will be default.  
- Subgroup and sensitivity analyses will be conducted (Appendix 4).  
Publication bias: Funnel plots and Egger’s test (≥10 studies).

## Confidence in Cumulative Evidence

GRADE will be applied to rate overall certainty.

# Dissemination

Findings will be submitted to a peer-reviewed journal and presented at conferences.

# Appendices

Appendix 1. Search Strategies  
Appendix 2. Data Extraction Template  
Appendix 3. Risk of Bias Assessment Plan  
Appendix 4. Planned Data Synthesis & Analysis