Systematic Review Protocol Draft

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

## 1. Background & Rationale

The human microbiome is a diverse and dynamic ecosystem of microorganisms residing within the human body, primarily in the gut, skin, oral cavity, and urogenital tract. Recent advances in metagenomics and multi-omics have revealed that the microbiome exerts profound influences on host physiology through:  
  
- Gene regulation (epigenetic modifications, non-coding RNA modulation, histone acetylation, and methylation pathways).  
- Immune and metabolic signaling (short-chain fatty acids, bile acids, microbial metabolites).  
- Disease prevention and pathogenesis, including obesity, diabetes, inflammatory bowel disease, cancer, and neurodegenerative disorders.  
  
However, existing studies vary widely in populations, methods, and outcomes, limiting the ability to draw unified conclusions. A systematic review is needed to consolidate evidence, identify gaps, and inform future translational research.

## 2. Objectives

Primary Objective  
To systematically review and synthesize evidence on the role of the human microbiome in gene regulation and disease prevention.  
  
Secondary Objectives  
- To map associations between specific microbial taxa, microbial metabolites, and host gene expression.  
- To identify pathways linking microbiome changes to chronic disease outcomes.  
- To evaluate methodological strengths and limitations of current studies.

## 3. Research Question (PICO Framework)

Population (P): Humans of all ages, any sex, healthy or with defined disease conditions.  
Intervention/Exposure (I): Human microbiome composition and function (gut, skin, oral, or other niches) assessed through sequencing, metagenomics, metabolomics, or culture-based methods.  
Comparator (C): Different microbiome states (e.g., healthy vs. diseased, high vs. low diversity, pre- vs. post-intervention).  
Outcomes (O):  
- Primary: Gene regulation outcomes (epigenetic modifications, transcriptomic changes, signaling pathways).  
- Secondary: Disease prevention/association outcomes (metabolic, autoimmune, cancer, neurological, infectious diseases).

## 4. Methods

4.1 Eligibility Criteria  
Inclusion  
- Peer-reviewed human studies (observational, interventional, cohort, case-control, RCTs).  
- Studies reporting microbiome assessment and outcomes related to gene regulation and/or disease.  
- Studies published in English.  
- Publication period: 2000–2025.  
  
Exclusion  
- Animal-only studies (unless directly linked to human validation).  
- Narrative reviews, commentaries, editorials.  
- Studies without molecular/genomic assessment of microbiome or gene regulation.  
  
4.2 Information Sources & Search Strategy  
Databases: PubMed, Scopus, Web of Science, Embase, Cochrane Library.  
Grey literature: ProQuest, OpenGrey, ClinicalTrials.gov.  
  
Preliminary PubMed Search String:  
("microbiome"[MeSH] OR "gut microbiota" OR "human microbiota" OR "microbiota") AND ("gene regulation" OR "epigenetics" OR "transcriptome" OR "DNA methylation" OR "histone modification") AND ("disease prevention" OR "chronic disease" OR "metabolic syndrome" OR "cancer" OR "autoimmune disease" OR "neurological disorder")  
  
4.3 Study Records  
- Data Management: All references imported into EndNote or Rayyan.  
- Screening: Two reviewers will screen titles/abstracts and full texts. Disagreements resolved by consensus or third reviewer.  
- PRISMA Flowchart: Used to document study selection.  
  
4.4 Data Extraction  
A standardized form will capture: study characteristics, population details, microbiome method, gene regulation outcomes, disease associations, key findings, limitations.  
  
4.5 Risk of Bias Assessment  
- RCTs: Cochrane RoB 2.0  
- Observational studies: Newcastle–Ottawa Scale (NOS)  
- Cross-sectional studies: AXIS tool  
  
4.6 Data Synthesis  
- Narrative synthesis by disease category.  
- Meta-analysis if feasible, using random-effects model.  
- Subgroup analyses: microbiome site, population type, assessment method.

## 5. Registration & Reporting

Protocol will be registered in PROSPERO.  
Final review will follow PRISMA 2020 reporting guidelines.

## 6. Dissemination Plan

- Manuscript submission to Gut Microbes, Frontiers in Microbiomes, or PLoS Medicine.  
- Presentation at academic conferences.

## 7. Timeline

Phase | Duration | Activities  
Protocol finalization & PROSPERO registration | 2 weeks | Refine protocol, register  
Literature search & screening | 1–2 months | Database searches, PRISMA screening  
Data extraction & risk of bias | 1 month | Develop sheet, assess quality  
Data synthesis & manuscript drafting | 2 months | Narrative/quantitative synthesis  
Manuscript submission | 1 month | Target journal submission