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Probiotics and Their Role in Modulating the Human Microbiome: Mechanisms, Health Effects, and Emerging Perspectives; A Review Article

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Abstract

The human microbiome consists of a complex community of microorganisms that plays an essential role in maintaining host balance, immune function, metabolic processes, intestinal integrity, and protection against pathogens. Disruption of this microbial community (dysbiosis) has been associated with various gastrointestinal and systemic diseases. Probiotics are live microorganisms that, when taken in adequate amounts, offer health benefits to the host. It is becoming increasingly evident that probiotics are able to interact with the resident microbiome and have an impact on the microbial composition, metabolism, intestinal barrier, and immune response and host-microbe interactions. But probiotic activity is strain specific and can be different depending on the host's normal microbiome, diet, age, health and environment. However, recent studies have highlighted that probiotics do not necessarily permanently colonize the gastrointestinal tract, but rather that many probiotic strains have transient and personal effects. Pathogens are competitively excluded, antimicrobial compounds are produced, short-chain fatty acid metabolism is modulated, epithelial tight junctions are regulated, bile acid metabolism is altered, immune signaling is modulated, and resident microbial communities are interacted with. Probiotics have been investigated for a variety of conditions, including metabolic disorders, inflammatory bowel diseases, irritable bowel syndrome, gastrointestinal problems, and diarrhea linked to antibiotics. However, lack of clinical consistency underscores the need for strain specific characterization, individualization and consistency in microbiome analysis and carefully designed clinical trials. The present review compiles the current knowledge about probiotics, the human microbiome, the mechanisms of probiotic-microbiome interactions, the potential health benefits of probiotics, its limitations, safety concerns, and new trends in the development of precision probiotics, synbiotics, postbiotics, and personalized microbiome-based approaches.

Keywords

Probiotics;
Human Microbiome;
Gut Microbiota;
Dysbiosis;
Intestinal Health;
Immune Modulation;
Short-Chain Fatty Acids;
Gut Barrier;
Precision Probiotics;
Microbiome Modulation.



1. Introduction

The human body is home to a wide variety of microorganisms, including bacteria, viruses, fungus, and archaea. The human microbiome is made up of all these microbes and their DNA. One of the human body's most varied and metabolically active microbial communities is found in the gastrointestinal (GI) tract. [1,2]

The role of the intestinal microbiome is to aid in the digestion of food, metabolism of nutrients, synthesis of bioactive metabolites, and regulation of epithelial barrier integrity, immune regulation and defense against invading microbes. Therefore, any disturbance in the physiological balance of the microbial world can affect gut and physiological functions. [1,3,4]

A probiotic is an organism that, when consumed in adequate amounts, can have a positive effect on the host. This concept is based on the FAO/WHO definition, which has been adopted by the International Scientific Association for Probiotics and Prebiotics (ISAPP). [5]

Probiotic microorganisms that are commonly studied in humans include members of the genus *Lactobacillus* (now divided into a number of genera due to taxonomic changes), *Bifidobacterium*, *Lactococcus*, *Streptococcus*, *Saccharomyces* and specific other species of bacteria. [5,6]

The growing interest in probiotics coincides with an increased understanding of the microbiome's function in human health. However, the advantages of probiotics have not been demonstrated to be universally applicable. Variations in the effects of the same strain of a species can occur, and the

reaction might be heavily influenced by the host microbiome and diet. [1,5]

When tested in adults, probiotics were shown to have a meaningful effect on gut microbiota composition, although the size and direction of the effect varied among studies in this comprehensive analysis of RCTs. [7]

The purpose of this study is to investigate how probiotics affect the human microbiome, their primary mode of action, possible advantages to human health, limits, and future prospects.

2. The Human Microbiome

2.1 Definition and Composition

The human microbiome is composed of microorganisms and their genome found in the human body. Four major types of microorganisms are bacteria, virus, fungi and bacteriophages and archaea. [1,2]

Gastrointestinal microbiome is a lot significant since it possesses a very high microbial density and metabolic diversity. [1]

The most common bacteria phyla associated with the human intestine are:

- *Firmicutes*
- *Bacteroidota*
- *Actinobacteriota*
- *Proteobacteria*
- *Verrucomicrobiota*

But, there is a significant variation in the makeup of the microbes between people. [1,2] Some factors that impact the microbiome are:

- age;
- genetics;
- diet;
- geographical environment;

- medications;
- antibiotic exposure;
- physical activity;
- lifestyle;
- immune status; and
- disease. [1,2,8]

3. Gut Microbiome and Human Health

The gut microbiome has various key roles to play. [1]

3.1 Metabolic Functions

The intestinal flora digests substances from the diet which are not completely broken down by human enzymes. Short-chain fatty acids (SCFA) that can be formed by the fermentation of dietary fibres include:

- acetate;
- propionate; and
- Butyrate.

SCFAs can be utilized for energy substrates and signaling molecules, and play a role in intestinal barrier function, immune regulation and metabolism. [1,3,4]

3.2 Protection against Pathogens

Pathogens can be inhibited by resident microorganisms by:

- competition for nutrients;
- agglutination of blood cells; and
- production of antimicrobial compounds; and
- inhibition of peristalsis; and
- production of organic acids; and
- Protection of the host immune defenses from being stimulated.

This is termed as 'colonization resistance'. [1]

3.3 Immune Regulation

The microbiome constantly communicates with cells of the intestinal immune system. [1]

Microbial components/metabolites can affect:

- dendritic cells;
- macrophages;
- T lymphocytes;
- regulatory T cells;
- B cells; and
- Cytokine production.

The disruption of these interactions could be one of the causes of chronic inflammation. [1]

4. Dysbiosis

Dysbiosis is a general term for any disruption in the composition or function of microbes which results in a disruption of host-microbe homeostasis. [1]

Dysbiosis has been investigated in association with:

- inflammatory bowel disease;
- irritable bowel syndrome;
- obesity;
- type 2 diabetes;
- colorectal cancer;
- metabolic disorders;
- antibiotic-associated diarrhea; and
- Some immune-mediated disorders.

Importantly, not all microbial signatures are markers of dysbiosis. The microbiome composition is highly individual and differences in the composition of healthy and diseased populations could be due to several interacting factors. [1]

5. Probiotics

5.1 Definition

According to the current scientific definition, probiotics are:

Live micro-organisms, that when applied in suitable quantities, provide a health benefit to the host. [5]

The above definition focuses on three key elements:

- the microorganisms must be alive;
- they have to be given in sufficient quantities; and
- They should be accompanied by proof of a health benefit.

As a result, not all fermented foods and/or microorganisms should be regarded as probiotics. [5].

6. Major Probiotic Microorganisms

Some of the most used probiotics are:

6.1 Lactobacillaceae and Related Lactic Acid Bacteria

Lactic acid bacteria (LAB) are traditionally one of the most studied probiotics. [5,6,9]

Examples include:

- *Lactiplantibacillus plantarum*
- *Lactocaseibacillus rhamnosus*
- *Limosilactobacillus reuteri*
- *Lactobacillus acidophilus*

6.2 Bifidobacterium

Bifidobacterium spp. play essential roles in the gut microflora of humans and have been thoroughly studied as probiotics. [5]

Examples include:

- *Bifidobacterium longum*
- *Bifidobacterium breve*
- *Bifidobacterium bifidum*

- *Bifidobacterium animalis*

6.3 Saccharomyces

Saccharomyces boulardii has been studied in gastrointestinal diseases, mainly in antibiotic-associated and infectious diarrhea. [6,10]

Table 1. Major probiotic microorganisms and their potential functions

Probiotic group	Examples	Potential effects
<i>Lactobacillaceae</i>	<i>L. plantarum</i> , <i>L. rhamnosus</i>	Barrier support, pathogen inhibition
<i>Bifidobacterium</i>	<i>B. longum</i> , <i>B. breve</i>	Microbiome interaction, metabolic effects
<i>Saccharomyces</i>	<i>S. boulardii</i>	Gastrointestinal protection
Other lactic acid bacteria	<i>Lactococcus</i> , <i>Streptococcus</i>	Metabolic and ecological effects

7. Mechanisms of Probiotic Action

Probiotics can have multiple possible mechanisms of action on the resident and host microbiome. [1,11]

7.1 Competitive Exclusion

Probiotic organisms can be in competition with pathogens:

- nutrients;
- adhesion sites;
- epithelial binding sites; and
- Ecological niches.

This can decrease their capacity to get established by pathogenic microorganisms. [1]

7.2 Production of Antimicrobial Compounds

Some probiotic bacteria produce:

- lactic acid;
- acetic acid;
- bacteriocins;
- hydrogen peroxide; and
- Other antimicrobial metabolites.

These compounds are able to inhibit competitive microorganisms. [1]

7.3 Modulation of the Intestinal Barrier

Through the following pathways, probiotics have been demonstrated to potentially affect the integrity of the intestinal epithelia:

- Tight-junction proteins
- generation of mucin;
- epithelial communication; and
- The survival of epithelial cells.

Preservation of epithelial integrity may minimize exposure of host tissues to inappropriate exposure of microbes. [11]

7.4 Immune Modulation

The relationship between probiotics and innate and adaptive immunity may be affected. [11,1]

Potential influences on:

- Toll-like receptor signaling;
- NF- κ B pathways;
- cytokine production;
- regulation of T-cell responses; and
- Mucosal immune responses.

But, the effects are highly strain specific. [11]

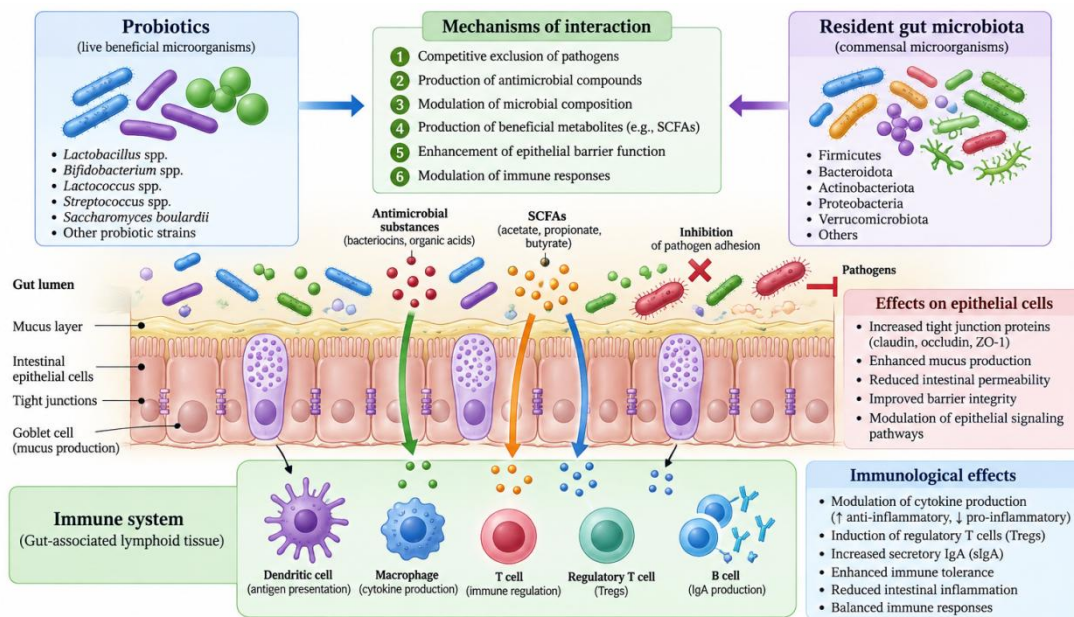


Figure 1 :Interaction between probiotics, resident gut microbiota, intestinal epithelial cells, and the immune system.

8. Probiotics and Microbiome Composition

An important question is whether probiotic organisms settle into the human intestine chronically. At this moment, there is only limited evidence available to indicate that colonization is more or less ephemeral, individual and local. Responses may be influenced by baseline microbiome, probiotic strain, anatomical location in the gastrointestinal tract and host-specific factors. [12] Thus, it is not appropriate to judge probiotic activity just by determining if the strain is colonizing as a permanent

resident. Probiotic can have beneficial effects by transient interaction with resident microorganisms and host tissues.

A comprehensive evaluation of randomized trials found that probiotic administration changed the makeup of the gut microbiota in adults; however, the results varied from study to study. [7] The idea that probiotic effects are "context-dependent" rather than predictable is supported by this finding. [7, 12]

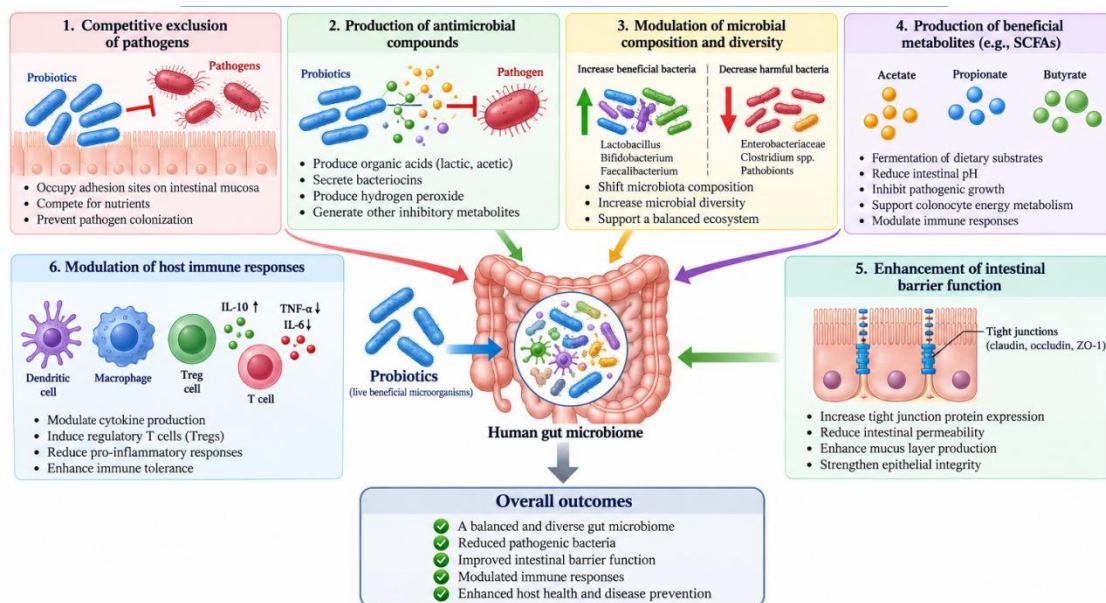


Figure 2 : Mechanisms of probiotic-mediated modulation of the human microbiome.

9. Probiotics and Short-Chain Fatty Acids

SCFAs are one of the most significant metabolites of gut microbial activity. [3,4]

The three big SCFAs are:

SCFA	Major associations
Acetate	Microbial metabolism and systemic signaling
Propionate	Metabolic and immune signaling
Butyrate	Colonocyte energy, epithelial integrity and immune regulation

This effect of probiotic supplementation can happen directly or indirectly by modifying the interaction between probiotics and the indigenous flora. [3,4,13]

But adding more of the SCFAs doesn't necessarily mean they will be added to everyone's body and/or from any strain. [3,4]

10. Probiotics and the Gut Barrier

The intestinal barrier is a combination of several factors such as:

- mucus;
- epithelial cells;
- tight junctions;
- antimicrobial peptides; and
- Mucosal immune mechanisms.

Increased exposure to microbial products and inflammatory reactions may result from the breakdown of the intestinal barrier. [11, 14, 15]. Research has examined how particular probiotic strains impact the tight-junction proteins listed below:

- Occlusion
- claudins; and
- Zonula occludens proteins.

These effects could play a role in better epithelial integrity. [11,14,15].

11. Probiotics and Immune Modulation

The immune system and probiotics have a complex interaction. [1,11].

Pattern-recognition receptors on immunological and epithelial cells may interact with probiotics.

Potential effects include:

- modulation of inflammatory cytokines;
- increased production of antimicrobial peptides; and
- antigen presentation; and
- modulation of T-cell activity; and
- Induction of immune mechanisms that protect against disease.

It is crucial to remember that the benefits of probiotics should be considered strain-specific rather than class-wise. [1,11].

12. Probiotics and Gastrointestinal Disorders

The probiotics have been studied for multiple gastrointestinal diseases. [1]

12.1 Antibiotic-Associated Diarrhea

Antibiotics may alter the "flora" in the gut, which can lead to diarrhea. [10]. Some probiotics are being studied as ways to alleviate gastrointestinal side effects caused by antibiotics. [10,16]. But this is only true for a particular strain of probiotic and a particular clinical population. [10].

12.2 Irritable Bowel Syndrome

The following symptoms have been investigated in relation to probiotics:

- pain in the abdomen;
- bloating
- flatulence; and
- Changed bowel habits.

Various investigations have yielded inconsistent outcomes. [17,18].

12.3 Inflammatory Bowel Disease

The potential use of probiotics as adjunctive methods has been explored in:

- ulcerative colitis;
- Crohn's disease; and
- Pouchitis.

Probiotics should not be used as a typical replacement for conventional medical care because not all probiotics are created equal. [19,20]

13. Probiotics and Metabolic Health

Energy metabolism, bile acid metabolism, inflammatory signaling, and host metabolic regulation are all influenced by the gut flora [21,22,23].

Probiotics have so been investigated in:

- Obesity
- Insulin resistance
- Type 2 diabetes
- In addition to metabolic syndrome,

Fatty liver (nonalcoholic fatty liver disease)

Possible mechanisms are modulation of:

- intestinal permeability;
- inflammatory pathways;
- SCFA production;
- bile-acid signaling;
- microbial metabolites; and
- Energy metabolism.

However, clinical responses tend to be mild and variable. [21-23].

14. Gut-Brain Axis

The gut and brain communicate in both directions through the gut-brain axis. [24,25,26]

The communication channels that could be used are:

- Microbial metabolites
- Immune signaling
- Vagal pathways
- endocrine communication; and
- Pathways connected to neurotransmitters.

Some probiotic products have been thus studied for their effects on mood, stress, cognition, and neurological health. [24-34]

But there is not enough clinical evidence to conclude probiotics as a general treatment for neurological and psychiatric disorders. [24-27].

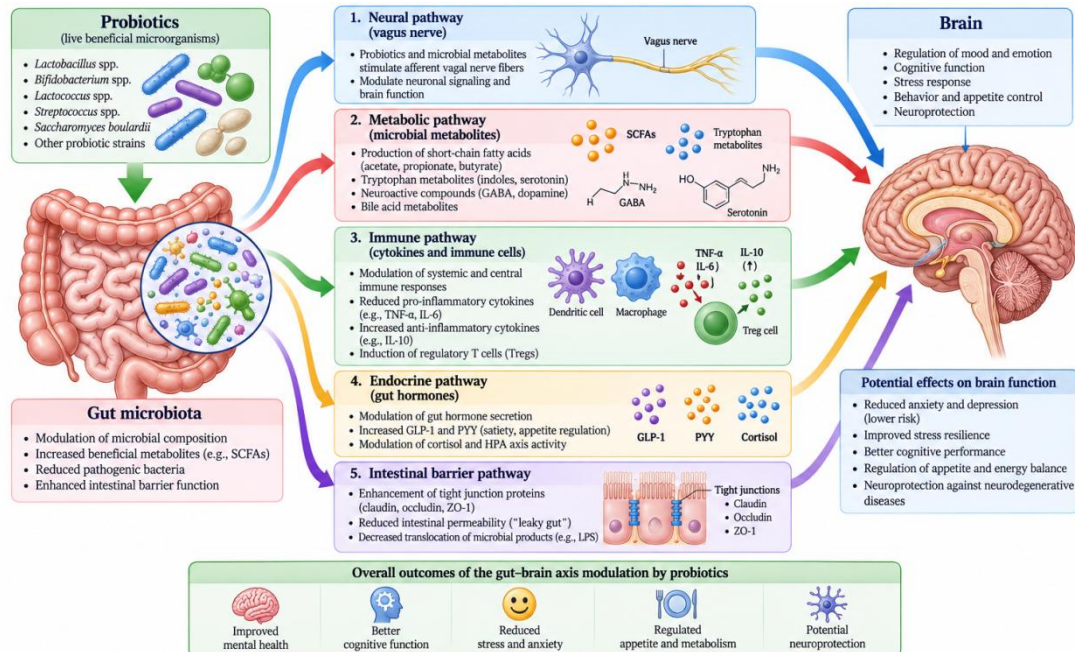


Figure 3 : Potential mechanisms linking probiotics with the gut-brain axis.

15. Role of Diet in Probiotic Effectiveness

Diet is an important factor in determining the composition of the gut microbiome and could affect the efficacy of probiotics. [35]. The perspective article in Nature Microbiology highlighted the importance of taking into account the habitual diet in the design and interpretation of probiotic clinical trials, as dietary patterns may be associated with

changes in the microbiome and the effects of probiotics. [35,36].

This is because different people with the same probiotic strain could react differently because they have different starting microbiomes and diets. [35]. This concept is aligned with the new trend of personalized probiotics. [35]

Table 2. Factors affecting probiotic efficacy

Factor	Potential influence
Probiotic strain	Determines biological activity
Dose	Influences exposure
Baseline microbiome	Determines ecological compatibility
Diet	Provides substrates and modifies microbial ecology
Age	Influences microbiome structure
Antibiotic exposure	Alters microbial ecosystem
Disease status	May alter response
Treatment duration	Influences persistence and effects

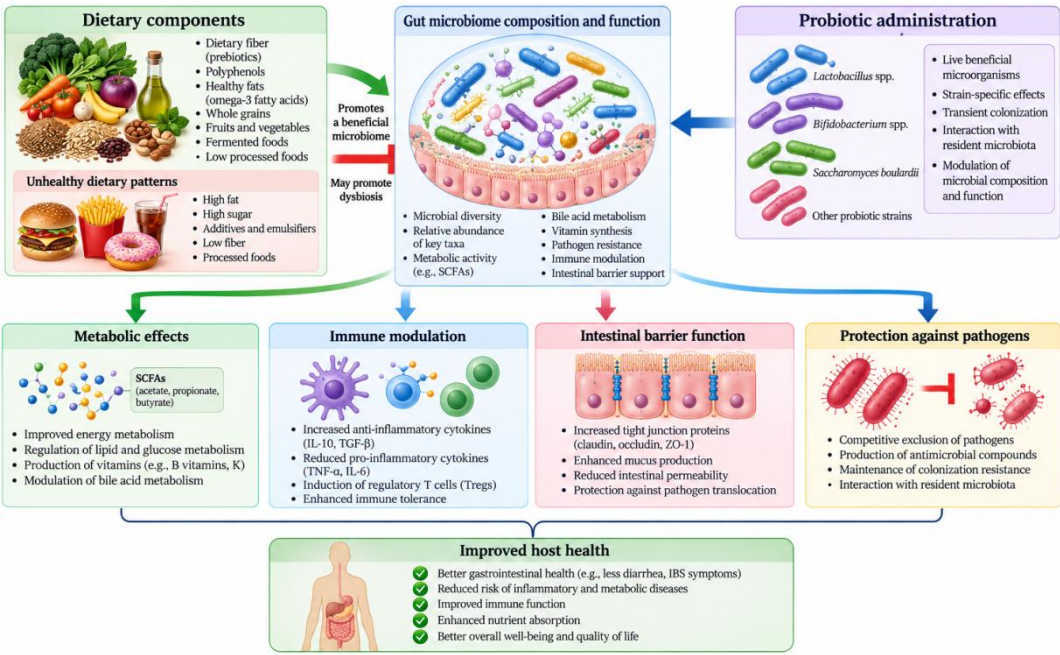


Figure 4 :Relationship between diet, microbiome composition, probiotic administration, and host health.

16. Probiotics, Prebiotics, Synbiotics, and Postbiotics

There are a number of concepts within the modern microbiome field.

- **Probiotics:** Microorganisms that can be alive and beneficial to the health when used in sufficient quantity.
- **Prebiotics:** The substrate used by host microorganism and gives a beneficial effect to health.
- **Synbiotics:** Live microorganisms and substrates selectively utilized by host microorganisms, which provide a health benefit.
- **Postbiotics:** Inactives of microorganisms and/or their parts that are prepared to be beneficial to humans.

This categorization is suggested by ISAPP and it is important that a health benefit be demonstrated as part of the definitions. [5,37,38]

17. Precision Probiotics

The traditional research of probiotics makes the assumption that an individual strain will have the same effect in everyone. [12,39]

But there is a great variation in the individual microbiomes. [12,39]

Probiotics might therefore go into the future as:

Patient microbiome → Microbiome profiling → Selection of probiotic strain → Targeted intervention → Monitoring of response

This approach could improve the consistency of clinical outcomes. [12,39]

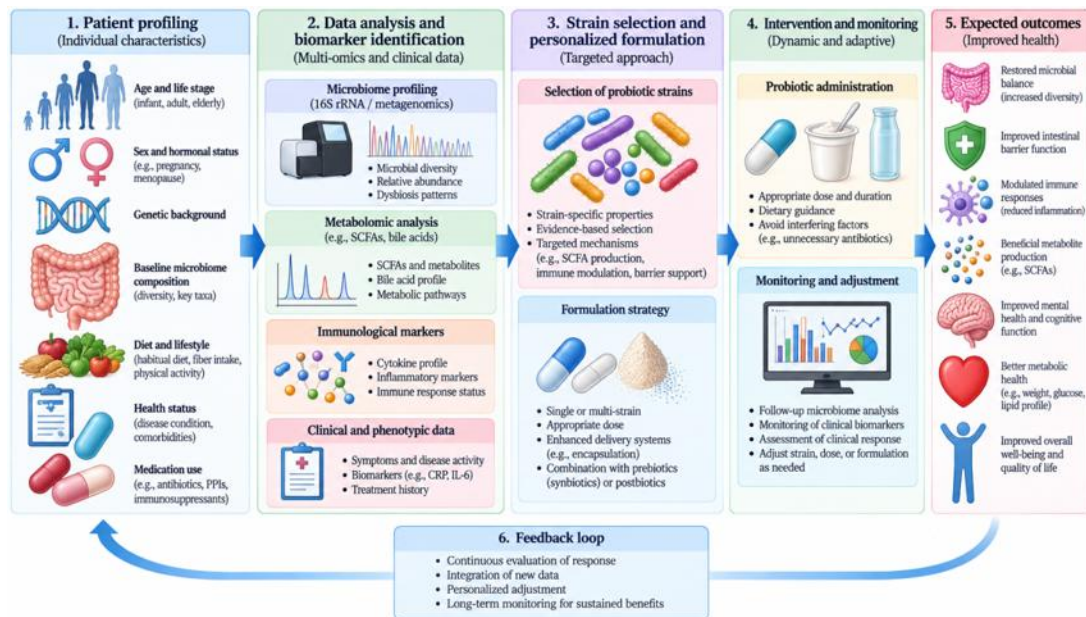


Figure 5 :Conceptual model of precision probiotic therapy.

18. Safety of Probiotics

While probiotics in general are safe for many healthy people, there is no universal safety for everyone. [6,40]

In rare instances probiotics have caused infections, especially in people with severe underlying illness or low resistance to infection. [40]

Potential concerns include:

- bacteremia;
- fungemia;
- spread of antimicrobial-resistance genes;
- interactions with other food or drinks or alcohol.
- Use in the wrong population at high-risk. [6,40]

Hence the following issues should be taken into account when making a safety evaluation:

- strain identity;
- dose;
- route of administration;
- host characteristics; and
- Clinical indication. [6,40]

19. Limitations of Current Evidence

Although a great deal of research has been conducted, there are many restrictions.

19.1 Strain-Specific Effects

The benefits of a single strain of a probiotic do not necessarily translate to the other strains. [7,12]. The heterogeneity of clinical trials. Heterogeneity of clinical trials.

Studies differ in:

- probiotic strains;
- doses;
- treatment duration;
- patient characteristics;

- diets;
- Methods for measuring the microbiome; and
- Clinical endpoints. [7,35].

19.3 Incomplete Understanding of Colonization

Not all individuals are able to maintain the same functionality of probiotics in the gut as others. [12].

19.4 Microbiome Measurement

Study conclusions may vary due to variations in sequencing technologies, bioinformatics pipelines and microbial databases. [35].

19.5 Diet as a Confounding Factor

Probiotics may alter response to diet, which can have a significant impact on the microbiome. [35].

20. Future Perspectives

Further research into probiotics is needed to progress from a general to more specific precision intervention.

Research directions are important:

- strain-specific clinical trials;
- personalized probiotic selection;
- Combining metagenomics and metabolomics;
- longitudinal microbiome monitoring;
- microbiome-based biomarkers;
- probiotic-diet interactions;
- engineered probiotic microorganisms;
- synbiotic formulations;
- postbiotic alternatives;
- Microbiome analysis using artificial intelligence; and
- Standardization of reporting of clinical trials for probiotics.

One of the big challenges is to identify which changes in the microbiome are causal to health benefits, and which are just correlated.

21. Conclusion

Probiotics are a key biological strategy to engage in the human microbiome. They can have a variety of effects beyond direct replacement of beneficial microorganisms, such as modulation of microbial communities, generation of bioactive metabolites, competitive pathogen exclusion, improved epithelial barrier performance, and control of host immunological systems.

Available data suggest strain-specific properties, host characteristics, initial microbiome composition, diet, and clinical setting significantly influence the probiotic properties of strains. Probiotics can not only colonize for a limited time but can also be colonizing without microbiome changes. Precision approaches in which probiotic strains are chosen based on individual microbiome and clinical targets should be focused in the future. Ultimately, integration of microbiology, genomics, metabolomics, and immunology and computation biology could result in more predictable and personalized microbiome-based interventions. [7,12,35,39].

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