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Review article

Probiotics and the Microbiome: Mechanisms, Strain Selection, and the Future of Rational Formulation Design

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ABSTRACT

This article highlights the expanding role of the microbiome in human health, showcasing a significant shift in scientific understanding thanks to advances in sequencing and metagenomics. Once viewed primarily through the lens of pathogens, the microbiome is now recognized as integral to human biology, playing critical roles in digestion, immune function, and vitamin production. The Microbiome Revolution has reframed microbial communities as vital contributors to health. Gut microbiota, which produce short-chain fatty acids, support gut health, immune regulation, and protection against conditions like inflammatory bowel disease, obesity, and diabetes. Dysbiosis, or microbial imbalance, is associated with these diseases, paving the way for therapies like probiotics, prebiotics, and fecal microbiota transplantation. The article explores personalized microbiome-targeted therapies and Artificial Intelligence's role in optimizing probiotics. Additionally, it discusses the gut-brain axis, where microbes influence mood and cognition. Despite regulatory challenges, microbiome-based therapies offer potential for personalized and highly effective healthcare solutions.

Keywords: microbiome; human health; dysbiosis; probiotics; prebiotics; gut-brain axis

Probióticos y el microbioma: mecanismos, selección de cepa y el futuro del diseño de formulación racional

RESUMEN

Este articulo destaca el papel en expansión del microbioma en la salud humana y muestra un cambio significativo en la comprensión científica gracias a los avances de la secuenciación y la metagenómica. Visto antes primordialmente a través del lente de los patógenos, el microbioma es reconocido en la actualidad como integral para la biología humana, jugando papeles críticos en la digestión, función inmune y producción de vitaminas. La revolución del microbioma ha replanteado las comunidades microbianas como contribuyentes vitales para la salud. La microbiota del intestino, que produce ácidos grasos de cadena corta, mantiene la salud del intestino, la regulación inmune y la protección contra condiciones como la

enfermedad de inflamación intestinal, obesidad, y diabetes. La disbiosis o desbalance microbiano está asociado con estas enfermedades, preparando el camino para terapias como los probióticos, los prebióticos y el trasplante de microbiota fecal. El articulo explora terapias personalizadas dirigidas al microbioma, así como el papel de la Inteligencia artificial en la optimización de probióticos. Adicionalmente, se discute el eje intestinos-cerebro, donde los microbios influencian en el carácter y la cognición. A pesar de los desafíos regulatorios, las terapias basadas en el microbioma ofrecen un potencial para la solución de problemas de salud personalizados y con alta efectividad.

Palabras clave: microbioma; salud humana; disbiosis; probióticos; prebióticos; eje intestino-cerebro

INTRODUCTION

Defining the Microbiome: An Evolving Concept

The term microbiome was first coined by Joshua Lederberg in the early 2000s to describe the collective genomes of microorganisms —bacteria, archaea, viruses, fungi, and other microbial eukaryotes— that inhabit a specific environment. [1] In humans, the microbiome primarily refers to microbial communities residing in and on the body, such as in the gut, skin, mouth, and respiratory tract. [1] These microorganisms form complex ecosystems, interacting with their host in ways crucial to health and disease. [2,3,4] It is essential to distinguish between microbiota and microbiome. While microbiota refers to the community of microorganisms in each environment, the microbiome encompasses their entire genetic material and interactions with the host. [1,5]

Historically, research on human-associated microorganisms focused on pathogens and their role in disease. However, advancements in high-throughput sequencing and metagenomics have revealed the crucial role of microbiota in maintaining health. [6,7,8] This modern view recognizes the microbiome as a dynamic and integral component of human biology, with microbes playing key roles in metabolism, immunity, and protection. [9,10,11,12,13,14]

The concept of the microbiome has shifted from viewing microorganisms solely as pathogens to recognizing them as vital contributors to human health. Microbes within the body perform essential metabolic, immunological, and protective functions, creating a dynamic ecosystem that interacts continuously with the host. This ecosystem is influenced by external factors like diet, antibiotics, lifestyle, and environment, which can shift microbial balance and impact health. [15,16,17]

A deeper understanding of the microbiome has highlighted its critical role in disease prevention. [18,19,20,21] For example, commensal gut bacteria not only outcompete harmful pathogens for resources and adhesion sites but also produce beneficial metabolites, such as short-chain fatty acids (SCFAs), that support anti-inflammatory responses and maintain gut barrier integrity. [22,23,24] This expanded view of the microbiome has led to new therapeutic strategies. Probiotics, prebiotics, and fecal microbiota transplantation (FMT) are among the approaches aimed at modulating the microbiome to prevent and treat diseases. These interventions underscore the microbiome's potential in innovative therapeutic applications. [25,26,27,28,29]

DEVELOPMENT

The Microbiome Revolution: transforming our understanding of health and disease

In recent decades, the study of the human microbiome has undergone a transformative shift, often referred to as the Microbiome Revolution. This revolution stems from groundbreaking discoveries revealing that the trillions of microorganisms residing in and on the human body are not mere passengers but active participants in human health and disease. Advances in sequencing technologies and computational biology have illuminated the profound influence that these microbial communities exert on the host, sparking a wave of research into their roles in immunity, metabolism, brain function, and overall well-being. [6]

Historically, microbiology focused primarily on pathogenic microorganisms and their role in causing infectious diseases. The development of antibiotics and vaccines revolutionized medicine in the 20th century by reducing mortality from bacterial infections. However, this focus on pathogens overlooked the fact that most microorganisms inhabiting the human body are either harmless or beneficial to their host. [30]

The Microbiome Revolution marked a fundamental shift in this thinking. Instead of viewing microbes solely as agents of disease, scientists began to recognize the symbiotic relationships between humans and their resident microbiota.

These microorganisms perform essential functions, such as aiding in digestion, modulating immune responses, producing vitamins, and even protecting against pathogens by outcompeting harmful microbes. [31]

This paradigm shift was largely driven by the advent of high-throughput sequencing technologies, such as 16S rRNA gene sequencing and shotgun metagenomics, which allowed researchers to analyze the composition and function of microbial communities without the need for traditional culture techniques. [32] As a result, scientists could explore the vast diversity of the human microbiome and its intricate interactions with the host. Early studies, such as the Human Microbiome Project (HMP) and MetaHIT (METAgenomics of the Human Intestinal Tract), provided the first comprehensive maps of microbial diversity across different human body sites, uncovering the complexity and variability of microbial ecosystems (Human Microbiome Project Consortium) [33]

The Microbiome Revolution has brought a holistic perspective to health, underscoring the deep interconnectedness between microbial ecosystems and host biological processes. This paradigm shift has led to significant insights into how the microbiome helps maintain homeostasis and prevent disease. One of the key roles of the gut microbiota is its ability to digest complex carbohydrates and fibers, producing beneficial metabolites such as short-chain fatty acids (SCFAs). Among these, butyrate is particularly important as an energy source for colonic cells and for its anti-inflammatory properties. [18] These SCFAs not only contribute to gut health but also play a role in regulating immune responses and supporting overall metabolic health. Additionally, the gut microbiome synthesizes essential vitamins, such as vitamin K and certain B vitamins, which are indispensable for human metabolism. For example, vitamin K is crucial for blood clotting, while B vitamins are involved in energy production and DNA synthesis.

However, when microbial communities are disrupted —a condition known as dysbiosis— this balance is lost, contributing to a wide range of health disorders. Dysbiosis has been linked to chronic diseases such as inflammatory bowel disease (IBD), obesity, diabetes, cardiovascular disease, and even mental health conditions like anxiety and depression. [34] These associations highlight the microbiome's far-reaching influence beyond the gut, affecting systemic health through various pathways, including immune modulation, metabolic regulation, and the gut-brain axis. As research continues to uncover these links, it has prompted the development of therapies aimed at targeting the microbiome to restore balance and improve health outcomes. [35]

Among these microbiome-targeted therapies are probiotics, prebiotics, and fecal microbiota transplantation (FMT). Probiotics introduce beneficial bacteria into the gut to enhance microbial diversity and function, while prebiotics serve as food for these bacteria, promoting their growth and activity. FMT is an emerging therapy where a healthy donor's microbiota is transplanted into a patient's gut to re-establish a balanced microbial community. These interventions are increasingly being explored as therapeutic strategies for managing conditions related to dysbiosis, with promising results in treating gastrointestinal diseases, metabolic disorders, and even neurological conditions. [28,36] As the field continues to evolve, the potential for microbiome-targeted therapies to become a cornerstone of preventive and therapeutic healthcare becomes ever more apparent, offering a more integrated approach to managing health and disease.

The growing understanding of the microbiome's role in health and disease has opened a new chapter in medicine-personalized medicine based on individual microbiome profiles. As advancements in metagenomic sequencing and bioinformatics progress, it has become possible to analyze the microbiome in unprecedented detail. This detailed analysis allows scientists and healthcare providers to identify variations in microbial composition that may predispose individuals to certain diseases or influence how they respond to treatments. [37] By examining the unique microbial communities of individuals, it becomes clear that the microbiome is not only a marker of health but also a potential tool for predicting, diagnosing, and treating a wide variety of conditions.

One of the most exciting aspects of microbiome-based personalized medicine is its potential to tailor therapies based on an individual's microbiome. For instance, research has revealed that variations in gut microbial composition can influence how different individuals metabolize certain drugs. A prominent example is the chemotherapeutic agent irinotecan, which is metabolized by gut bacteria. Differences in microbial activity can lead to variations in drug toxicity and efficacy, making it critical to understand a patient's microbiome before administering the drug. Similarly, responses to dietary interventions, such as those aimed at managing conditions like type 2 diabetes, are also influenced by the composition of an individual's microbiome. [38] For example, some individuals may benefit more from certain dietary components, such as fibers or specific carbohydrates, because their microbiota are better equipped to metabolize those compounds into beneficial metabolites, like short-chain fatty acids.

This emerging evidence supports the idea that microbiome-based diagnostics and therapeutics could one day transform healthcare. By using microbiome profiles to guide treatment decisions, healthcare providers could personalize medical interventions, ensuring more precise and effective

therapies. For example, soon, clinicians may use a patient's microbiome data to determine which probiotic, or prebiotic formulations would be most beneficial, or to select dietary plans tailored to optimize metabolic health based on microbial composition.

Beyond diagnostics and tailored therapies, the microbiome also has the potential to revolutionize drug development. [39] By incorporating microbiome analyses into clinical trials, pharmaceutical companies could better predict how different patient populations might respond to a new treatment based on their microbiota. This approach could help identify patient subgroups more likely to benefit from a particular therapy, ultimately leading to more targeted and efficient clinical trials. Furthermore, microbial engineering could be employed to develop therapeutic probiotics or microbiome modulators that are customized for specific patient needs, providing long-term health benefits by reshaping the microbial ecosystem.

However, while the potential is vast, significant challenges remain in bringing microbiome-based personalized medicine to widespread clinical practice. Standardization of microbiome testing, regulatory approval of microbiome-based therapies, and ethical considerations related to microbiome data privacy are some of the hurdles that need to be addressed. Nevertheless, the integration of microbiome profiles into personalized medicine promises to offer a new level of precision in healthcare, with the ability to provide highly individualized, effective treatments that improve patient outcomes while minimizing side effects. This new frontier represents a transformative shift in how we approach the treatment of diseases, harnessing the power of the microbiome to tailor healthcare to the unique biological makeup of everyone.

Another key aspect of the Microbiome Revolution is the recognition that human health cannot be viewed in isolation from the environment. Just as biodiversity is important for the health of ecosystems, microbial diversity is critical for the stability and resilience of the human microbiome. Studies have shown that populations in non-industrialized societies tend to have more diverse gut microbiomes compared to those in industrialized countries, likely due to differences in diet, lifestyle, and exposure to environmental microbes. [40]

The rise of chronic diseases in industrialized nations, such as obesity, type 2 diabetes, and autoimmune disorders, has been linked to a loss of microbial diversity, driven in part by modern diets that are low in fiber and high in processed foods, as well as the overuse of antibiotics. [41] This shift in microbiome composition may have far-reaching consequences, not only for human health but also for the environment, as microbial communities in the soil, water, and air are interconnected with those in the human body.

The gut microbiome plays a pivotal role in modulating the gut-brain axis. These microorganisms produce a diverse array of metabolites, including short-chain fatty acids (SCFAs), neurotransmitters, and signaling molecules, that can exert profound effects on brain function. [42] The gut-brain axis operates through multiple pathways, including the vagus nerve, the immune system, and microbial metabolites such as short-chain fatty acids and neurotransmitters (figure 1). Gut bacteria can produce or modulating a range of neuroactive compounds, including serotonin, dopamine, and gamma-aminobutyric acid (GABA), which are critical for regulating mood and cognition. [43,44] Approximately 90% of the body's serotonin, a neurotransmitter that plays a key role in mood regulation, is produced in the gut, primarily by enteric cells in response to signals from gut bacteria. [45]

The diagram illustrates the bidirectional communication between the brain and the digestive system, highlighting the gut-brain axis. The anterior cingulate cortex (ACC) plays a key role in this communication, influencing emotional regulation, decision-making, and autonomic functions. Through the vagus nerve and other neural, hormonal, and immune pathways, the brain sends signals to the gut, affecting digestive processes, motility, and the secretion of digestive enzymes and hormones. This, in turn, influences the gut microbiota. The gut, in response, communicates back to the brain via microbial metabolites such as short-chain fatty acids (SCFAs), neurotransmitters, and hormones produced by gut bacteria, which can enter the bloodstream, cross the blood-brain barrier, and modulate brain function, mood, and behavior. Immune signaling also plays a crucial role in this feedback loop, as gut microbes influence immune responses that can impact brain activity. The diagram emphasizes how this constant flow of information between the gut and the brain contributes to overall health, with disruptions potentially leading to disorders such as anxiety, depression, and gastrointestinal conditions.

Gut bacteria can also produce neurotransmitters, including serotonin, dopamine, and gamma-aminobutyric acid (GABA). These neurotransmitters play crucial roles in regulating mood, cognition, and behavior. Dysbiosis, or an imbalance in the gut microbiome, can lead to alterations in neurotransmitter production and contribute to various neurological disorders. [43,44]

The immune system is another key player in the gut-brain axis. The gut is home to a significant portion of the body's immune cells, and the microbiome can influence the development and function of these cells. Imbalances in the gut microbiome can lead to chronic inflammation, which has been implicated in a variety of neurological disorders, including Alzheimer's disease and Parkinson's disease. [46] As our understanding of the

Fig. 1. The Gut-Brain Axis

gut-brain axis deepens, it is likely that therapeutic approaches targeting this system will become an integral part of treating not only gastrointestinal diseases but also a wide range of neurological and psychiatric conditions. This complex interplay between the gut, immune, and endocrine systems emphasizes the importance of viewing health from a holistic perspective, where interventions that improve gut health could have far-reaching effects on mental and neurological well-being.

Bacteria make up most of the human microbiome, particularly in the gut, where they play essential roles in maintaining health. It is estimated that the human gut alone contains more than 1,200 bacterial species, and the total number of genes in the gut microbiome is at least 150 times larger than the human genome. [47] Most gut bacteria belong to a few dominant phyla: Bacillota (formerly Firmicutes), Bacteroidota (formerly Bacteroidetes), Actinomycetota (formerly Actinobacteria), and Pseudomonadota (formerly Proteobacteria). [48,49] Each of these phyla performs critical functions within the gut ecosystem. For instance, members of the Bacillota phylum, such as Lactobacillus and Clostridium, are crucial for fermenting complex carbohydrates and producing short-chain fatty acids (SCFAs) like butyrate, which supports gut health by reducing inflammation and maintaining the integrity of the intestinal barrier. [18,50,51,52,53,54] Similarly, Bacteroidota, dominated by the genus Bacteroides, specializes in breaking down polysaccharides and fibers, contributing to energy metabolism and immune regulation. [55,56]

Actinobacteriota, in particular the genus Bifidobacterium, is important for immune modulation, particularly in early life, and contributes to the production of essential vitamins like B12 and folate Meanwhile, Pseudomonadota encompasses both beneficial and opportunistic facultative anaerobic bacteria, such as Escherichia coli, involved in vitamin K production and nitrogen cycling. [57,58,59,60,61] These bacteria are also implicated in dysbiosis-related diseases when overgrown as they impact the anaerobic environment of the gut, necessary for maintaining a healthy microbiome. [62,63,64,65,66] Together, these bacterial communities are not only vital for digestion but also for developing and regulating the

immune system, as well as synthesizing essential metabolites that influence human health.

In addition to these dominant phyla, several less abundant phyla play specialized roles in the gut microbiome. Verrucomicrobiota, particularly Akkermansia muciniphila, is important for maintaining the gut mucus layer and metabolic health. [67,68] Fusobacteriota, while primarily found in the oral cavity, includes species like Fusobacterium nucleatum, which has been associated with both health and disease, including colorectal cancer. [69,70,71] Spirochaetota, Synergistota, Lentisphaerota, and Elusimicrobiota are also present in smaller numbers but contribute to metabolic functions like fiber degradation, protein digestion, and nutrient recycling. Although these phyla are less abundant, they complement the metabolic activities of the dominant phyla and contribute to the overall diversity and stability of the gut microbiome, playing crucial roles in maintaining gut homeostasis and overall health [72,73]

Archaea, though less prevalent than bacteria, are significant contributors to gut health. While Methanobrevibacter smithii is a well-known methane-producing species, other archaea like Methanosphaera stadtmaniae and Methanosarcina mazei also inhabit the gut. These species, along with M. smithii, collectively contribute to polysaccharide digestion and regulate bacterial fermentation. The archaea convert hydrogen and carbon dioxide, fermentation byproducts, into methane through methanogenesis. This process is vital, preventing hydrogen buildup that can hinder bacterial fermentation. By removing H+, these archaea allow bacteria to produce short-chain fatty acids (SCFAs), crucial for colon health and energy supply. [74,75] Archaea thus optimize complex carbohydrate breakdown, enhancing energy extraction from food. The presence of methanogens can vary among individuals and is linked to health conditions. Higher methane levels are often associated with slower gut transit and constipation-predominant IBS, while lower levels may be observed in inflammatory or metabolic disorders. This symbiotic relationship underscores archaea's crucial role in maintaining gut balance and overall well-being. [76,77,78]

The mycobiome, the fungal component of the human microbiome, is a relatively understudied yet increasingly important aspect of human health. Fungi such as Candida, Aspergillus, and Saccharomyces species colonize various body sites, including the skin, respiratory tract, and gut, playing significant roles in both health and disease. The composition of the mycobiome is dynamic, varying between individuals and influenced by factors like diet, lifestyle, immune function, and environmental exposure. Unlike bacterial populations, which tend to be more stable, fungal communities are more susceptible to fluctuations, particularly in response to interactions with the host and bacterial microbiome.

Fungi contribute to health in several ways, such as promoting immune tolerance and preventing autoimmune conditions. In the gut, fungi like Saccharomyces boulardii support intestinal health by enhancing barrier function, regulating inflammation, and competing with pathogenic microorganisms. [79,80,81] Fungi also engage in symbiotic relationships with bacteria, helping maintain microbial diversity and balance in the gut. [82,83]

However, fungi can also become pathogenic under certain conditions. For example, Candida species, particularly Candida albicans, are common commensals in the body but can cause infections like oral thrush and invasive candidiasis when the immune system is weakened or when the microbial balance is disrupted. [84] Similarly, Aspergillus fumigatus is associated with respiratory infections, especially in immunocompromised individuals, such as those undergoing chemotherapy or suffering from chronic lung diseases. [85] Moreover, fungi can form biofilms, where they can collaborate with bacteria to promote more severe infections, making treatment difficult. Advances in sequencing technologies have expanded our understanding of the mycobiome, and emerging research suggests that fungal imbalances, or dysbiosis, may contribute to conditions like inflammatory bowel disease, metabolic disorders, and chronic infections. [86]

The virome, the viral component of the microbiome, encompasses a vast and diverse collection of viruses, including both eukaryotic viruses, which infect human cells, and bacteriophages, which specifically target bacteria. Eukaryotic viruses, such as herpesviruses, papillomaviruses, and enteric viruses, can establish persistent infections in human cells, influencing the immune system in complex ways. [87] While some eukaryotic viruses can trigger chronic inflammation or contribute to diseases like cancer, others may have beneficial effects by priming the immune system or controlling harmful bacterial populations. [88,89] Among the most extensively studied elements of the virome are bacteriophages, or phages, which play a key role in shaping bacterial populations and driving microbial evolution within the host. [90,91] Phages influence bacterial communities by lysing bacterial cells, transferring genetic material through horizontal gene transfer, and acting as selective pressure agents. This not only controls bacterial numbers but also encourages the evolution of bacterial traits, such as antibiotic resistance and virulence. [92]

Protozoa and helminths are important, though less frequently discussed, components of the gut microbiome, contributing to the complex ecosystem that influences human health. [93,94] Protozoa, such as Entamoeba, Giardia, and Blastocystis species, can exist in both pathogenic and commensal forms, with some aiding in digestion or interacting with the immune system, while others cause gastrointestinal infections. These

organisms often interact with bacteria, influencing microbial composition and the immune response. Helminths, or parasitic worms such as Ascaris, Trichuris, and Strongyloides, also inhabit the human gut and can have significant effects on the microbiome. While they are typically seen as harmful parasites, some helminths have been found to modulate the immune system in ways that could reduce inflammation and potentially help in managing autoimmune conditions. [95,96] Studies suggest that helminth infections can alter the balance of gut bacteria, promoting a microbial environment that may reduce the risk of inflammatory disorders, such as inflammatory bowel disease (IBD). [97,98] The interactions between protozoa, helminths, and the gut microbiota are complex, and while they can contribute to disease in some cases, they may also play a role in maintaining immune tolerance and microbial diversity.

The human microbiome is a complex ecosystem comprising bacteria, fungi, viruses, and parasites, each with unique roles in health. The bacteriome is essential for digestion, immunity, and pathogen defense. The mycobiome influences immune modulation and gut health. The virome shapes bacterial populations, while protozoa and helminths interact with the gut microbiota, affecting immune function and microbial balance. Understanding these components is crucial for developing new therapeutic strategies.Advancements in next-generation sequencing (NGS), mass spectrometry (MS), and nuclear magnetic resonance (NMR) have transformed microbiome research by enabling the analysis of complex microbial communities and metabolites, far beyond what traditional culture-based techniques could achieve.

16S rRNA gene sequencing remains a fundamental tool for identifying bacterial communities by targeting conserved regions of the bacterial 16S ribosomal RNA gene. [32] However, it provides only taxonomic data, lacks functional insight, and is limited to genus-level identification. [99,100,101] Bioinformatics tools like LEfSe and PICRUSt address some of these limitations by identifying differentially abundant taxa and inferring microbial functions. [102,103,104]

Shotgun metagenomics offers a more comprehensive approach by sequencing all microbial genomes present in a sample, enabling species-level identification and functional analysis. This method covers bacteria, archaea, viruses, and fungi, providing a detailed view of microbial diversity, metabolic pathways, and antibiotic resistance genes. [105,106,107] Although it requires more computational power and sequencing depth, it offers unparalleled insights into the microbiome.

Metatranscriptomics goes beyond metagenomics by focusing on active gene expression, offering real-time insights into microbial function. [108] By analyzing RNA transcripts, it reveals how microbial communities respond to environmental changes, though it poses challenges due to RNA instability and more complex analysis. [109,110]

Metabolomics examines microbial metabolites, giving direct insight into the metabolic activities of the microbiome. Techniques such as MS and NMR identify metabolites involved in processes like energy production and immune modulation. [111] Despite its complexity, metabolomics is crucial for linking microbial function to health and disease. [112] Single-cell genomics allows for the sequencing of individual microbial cells, revealing the diversity and function of rare or unculturable microorganisms. While technically challenging, it provides granular data on microbial roles and interactions that bulk sequencing methods might miss. [113]

These methodologies collectively advance our understanding of the microbiome's structure, function, and influence on health, enabling a more nuanced exploration of microbial ecosystems. The human microbiome plays a critical role in various biological functions, including digestion, vitamin synthesis, xenobiotic metabolism, and immune modulation, essential for maintaining homeostasis and overall health. A balanced microbiome supports nutrient metabolism, immune function, and inflammation control, underscoring its importance in preventing disease.

The gut microbiome ferments dietary fiber into short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, which are vital for gut health and metabolism. [114] SCFAs help maintain gut barrier integrity, regulate energy production, and influence processes like gluconeogenesis and lipogenesis. [115] Gut bacteria also synthesize vitamins, such as vitamin K and B12, essential for blood clotting and cell metabolism, and contribute to fat digestion through secondary bile acids. [116,117] Additionally, the microbiome plays a key role in metabolizing drugs and environmental chemicals, influencing their bioavailability and toxicity. [118]

The microbiome plays a critical role in educating and modulating the immune system, helping the body distinguish between harmful pathogens and harmless or beneficial microbes. [31,119] This process is essential for maintaining immune homeostasis and preventing overactive immune responses that can lead to chronic inflammation or autoimmune conditions. From early development, gut bacteria interact with immune cells in the gut-associated lymphoid tissue (GALT), influencing the maturation of immune components such as regulatory T cells (Tregs) and dendritic cells, which are crucial for immune tolerance. These interactions help the immune system learn to tolerate beneficial microbes and food antigens while being prepared to defend against potential pathogens.

One of the principal ways the gut microbiota affects the immune system is through the production of metabolites

such as short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate. These SCFAs are produced when specific gut bacteria ferment dietary fibers. Among them, butyrate has been extensively researched for its strong anti-inflammatory properties. It acts as an energy source for colonocytes, the cells lining the colon, and supports gut barrier integrity, reducing gut permeability, commonly known as "leaky gut." A strong gut barrier prevents the translocation of harmful bacteria and their toxins into the bloodstream, which would otherwise trigger systemic inflammation. [14,120]

Moreover, butyrate and other SCFAs regulate immune responses by promoting the differentiation of Tregs, which suppress excessive immune reactions and help maintain immune tolerance. This is particularly important in preventing autoimmune diseases, where the immune system mistakenly attacks the body's own tissues. Butyrate also inhibits the production of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and promotes the release of anti-inflammatory cytokines like IL-10, contributing to a balanced immune environment. This modulation of inflammation is crucial not only for gut health but also for overall systemic health.

When the gut microbiome becomes imbalanced —a condition known as dysbiosis— the immune system can lose its ability to differentiate between harmful and harmless microbes. Dysbiosis can result from factors like poor diet, antibiotic overuse, infections, or stress, leading to a weakened gut barrier and increased gut permeability. This weakened barrier allows harmful bacteria, endotoxins (like lipopolysaccharides, LPS), and undigested food particles to enter the bloodstream, triggering systemic inflammation. Chronic inflammation is a major contributor to various diseases, including metabolic syndrome, type 2 diabetes, and cardiovascular diseases. In autoimmune disorders like rheumatoid arthritis or inflammatory bowel disease (IBD), dysbiosis has been linked to the overactivation of immune pathways, leading to prolonged inflammation and tissue damage.

In addition to physical health, the gut-immune axis also affects mental health. [121,122] Dysbiosis has been associated with an increased risk of mental health disorders such as anxiety, depression, and stress-related conditions, possibly due to the inflammatory response reaching the central nervous system. Chronic systemic inflammation can disrupt the blood-brain barrier and influence the production of neurotransmitters like serotonin and dopamine, which are critical for mood regulation. This connection between the gut, immune system, and brain is often referred to as the "gut-brain-immune axis," highlighting the complex interplay between these systems in maintaining overall health.

Microbial disorders like obesity and type 2 diabetes, where changes in microbial composition can lead to inflammation and disrupt key metabolic processes. In these conditions, certain gut bacteria promote a pro-inflammatory state by producing lipopolysaccharides (LPS) and other harmful metabolites that enter the bloodstream, triggering low-grade systemic inflammation. [123,124] This inflammation affects insulin sensitivity and glucose metabolism, contributing to insulin resistance, weight gain, and the development of type 2 diabetes. Additionally, dysbiosis can alter the production of short-chain fatty acids (SCFAs), which play a vital role in maintaining metabolic health. A reduction in beneficial SCFAs like butyrate may further impair glucose regulation and energy balance, exacerbating metabolic disorders.

In neuropsychiatric disorders, dysbiosis also plays a significant role through the gut-brain axis, a bidirectional communication network between the gut microbiota and the central nervous system. Gut microbes produce neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), as well as SCFAs, all which influence mood, behavior, and cognitive function. [46,125] Disruptions in this microbial communication system have been associated with conditions like depression, anxiety, and autism spectrum disorder (ASD). For example, research suggests that individuals with depression often exhibit altered gut microbiota, which may contribute to the dysregulation of serotonin production and inflammatory pathways, worsening mood and emotional health. Similarly, gut dysbiosis in individuals with autism spectrum disorder has been linked to changes in microbial metabolites that can affect brain development and behavior.

In response to these findings, microbiome-targeted therapies, including probiotics and fecal microbiota transplantation (FMT), are being actively explored as potential interventions to restore microbial balance and improve health outcomes in both metabolic and neuropsychiatric disorders. [28,126]

Overall, the growing understanding of the link between dysbiosis and metabolic and neuropsychiatric disorders highlights the critical role of the gut microbiome in health. These insights pave the way for innovative treatments that target the microbiome, offering the potential to mitigate the underlying causes of these disorders and improve patient outcomes.

The Microbiome and Human Health: A Symbiotic Relationship

The human body is host to a vast and diverse population of microorganisms collectively known as the microbiome. These microbial communities —composed of bacteria, archaea, fungi, viruses, and other microorganisms— play an essential role in maintaining human health. The microbiome is increasingly recognized as an "organ" in its own right, influencing everything from digestion and immunity to metabolism

and even brain function. Disruptions to this complex ecosystem, known as dysbiosis, are linked to a wide range of diseases, from gastrointestinal disorders to metabolic syndromes and mental health conditions. This evolving understanding has fueled a revolution in medicine, positioning the microbiome as a central player in health and disease management.

One of the microbiome's primary roles is to aid in the digestion of complex carbohydrates and fibers that human enzymes cannot break down. Microbes in the gut, particularly in the colon, ferment these dietary fibers into short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. These SCFAs are absorbed by the host and serve as an energy source for colonic epithelial cells, while also playing anti-inflammatory and protective roles in maintaining gut barrier integrity. [18,127,128]

Butyrate plays a key role in supporting colonic health by serving as the primary energy source for colonocytes, promoting cell differentiation, and reducing inflammation. Its production is closely tied to a diverse and healthy gut microbiome. When levels of butyrate-producing bacteria decrease, it is often linked to gastrointestinal disorders, including inflammatory bowel disease (IBD) and colorectal cancer. [129]

Beyond SCFAs, the gut microbiota is involved in the synthesis of essential nutrients that humans cannot produce on their own. For instance, certain gut bacteria synthesize vitamins like vitamin K and several B vitamins (e.g., B12, biotin, folate), which are essential for various metabolic processes, including blood clotting, DNA synthesis, and energy production. [31,116,130]

The microbiome plays a crucial role in the development and modulation of the immune system. From birth, the microbiota helps "educate" the immune system to differentiate between harmless commensals and harmful pathogens, a process that is critical for immune tolerance and preventing autoimmune responses. [131] The gut-associated lymphoid tissue (GALT) is in constant communication with gut microbes, promoting an environment where the immune system can respond appropriately to infections without triggering chronic inflammation

Microbial signals are essential for the regulation of T cells, especially regulatory T cells (Tregs), which help maintain immune tolerance. Commensal bacteria such as *Bacteroides fragilis* produce polysaccharides that promote the differentiation of Tregs, fostering an anti-inflammatory environment. [120] Similarly, SCFAs, produced during the fermentation of dietary fibers, have been shown to influence immune cell differentiation and function, contributing to the regulation of systemic inflammation. [132]

Dysbiosis, or an imbalance in microbial communities, has been implicated in immune dysregulation and is linked to several autoimmune and inflammatory diseases. For instance, altered gut microbiota composition is a feature of inflammatory bowel diseases like Crohn's disease and ulcerative colitis, where an exaggerated immune response leads to chronic inflammation and tissue damage. [34] In autoimmune diseases such as multiple sclerosis and type 1 diabetes, shifts in the gut microbiota are thought to contribute to the loss of immune tolerance. [133]

The gut microbiome is a key regulator of host metabolism, influencing energy balance, fat storage, and glucose homeostasis. Changes in the composition of the gut microbiota are associated with obesity and metabolic diseases such as type 2 diabetes and metabolic syndrome. Studies have shown that the microbiomes of obese individuals differ significantly from those of lean individuals, with a relative increase in bacteria from the Bacillota phylum and a decrease in Bacteroidota. [134]

Gut microbes affect metabolism by regulating the extraction of energy from food and influencing the host's fat storage pathways. For example, certain gut bacteria can increase the breakdown of complex carbohydrates into SCFAs, which are absorbed and used as energy by the host, potentially contributing to weight gain if caloric intake exceeds energy expenditure. [135] Additionally, the gut microbiota influences the production of lipopolysaccharides (LPS), bacterial endotoxins that can enter the bloodstream and trigger low-grade systemic inflammation. Chronic inflammation induced by endotoxemia is a key factor in the development of insulin resistance, obesity, and type 2 diabetes. [136,137]

Probiotics and prebiotics have emerged as potential therapeutic strategies to combat obesity and metabolic disorders by modulating the gut microbiota. Studies have shown that certain probiotic strains, such as *Lactobacillus* and *Bifidobacterium*, can improve metabolic outcomes by reducing inflammation, improving gut barrier function, and modulating the production of SCFAs and other metabolites that influence energy metabolism. [138]

The gut microbiome has a profound impact on mental health through the gut-brain axis, a bidirectional communication system between the gastrointestinal tract and the central nervous system (CNS). This communication occurs via multiple pathways, including the vagus nerve, immune system modulation, and microbial metabolites that act as neurotransmitters or precursors to neurotransmitters. [139]

Gut bacteria are known to produce a variety of neuroactive compounds, including gamma-aminobutyric acid (GABA), serotonin, and dopamine, which are involved in regulating mood, anxiety, and cognition. [45,140,141] Approximately 90% of the body's serotonin, a neurotransmitter that plays a key role in mood regulation, is produced in the gut, primarily by enteric cells in response to signals from gut bacteria. [140] Changes in gut microbiota composition have been linked to neuropsychiatric conditions such as anxiety, depression, and autism spectrum disorder (ASD). [142]

One key mechanism through which the gut microbiota affects brain function is by influencing the hypothalamic-pituitary-adrenal (HPA) axis, the body's central stress response system. Dysbiosis has been shown to enhance the release of pro-inflammatory cytokines, which can cross the blood-brain barrier and promote neuroinflammation, contributing to mood disorders. [143] Conversely, beneficial gut microbes can reduce stress-induced responses and improve resilience to anxiety and depression by regulating both immune and neurochemical pathways. [144]

Dysbiosis, or an imbalance in the microbial communities of the microbiome, has been implicated in a wide range of diseases beyond those affecting the gastrointestinal tract. For example, the loss of microbial diversity and an increase in pathobionts (opportunistic pathogens) have been associated with conditions such as cardiovascular disease, allergies, asthma, and certain cancers. [122,145]

In cardiovascular disease, recent studies have linked the metabolism of dietary nutrients by gut bacteria to the production of harmful metabolites, such as trimethylamine-N-oxide (TMAO), which has been shown to promote atherosclerosis. [146] Similarly, changes in gut microbiota composition have been implicated in the development of colorectal cancer, with specific microbial signatures linked to tumor progression. [147,148]

Research into the microbiome's role in allergic and autoimmune diseases is also expanding. The "hygiene hypothesis" suggests that a lack of microbial exposure in early life, particularly in industrialized societies, may lead to an underdeveloped immune system, increasing susceptibility to allergies and autoimmune conditions like asthma, type 1 diabetes, and multiple sclerosis. [149] Restoration of microbial balance through dietary interventions, probiotics, and fecal microbiota transplantation (FMT) is being explored as a strategy to treat these conditions.

As the links between the microbiome and human health become clearer, microbiome-targeted therapies have gained increasing attention. Probiotics (live beneficial bacteria) and prebiotics (non-digestible food components that promote the growth of beneficial bacteria) are among the most common interventions aimed at modulating the gut microbiome. These therapies are being explored not only for their ability to improve digestive health but also for their potential to treat metabolic disorders, mental health conditions, and immune-related diseases. [150]

Fecal microbiota transplantation (FMT) has emerged as a highly effective treatment for recurrent *Clostridioides difficile* infections, with cure rates exceeding 90%. This success has prompted research into the use of FMT for other conditions associated with dysbiosis, such as IBD, metabolic syndrome, and even autism. [151] The potential to "reset" the gut microbiota using FMT or other microbiome-based therapies opens exciting possibilities for treating a wide range of diseases.

Probiotic organisms are live microorganisms that, when administered in adequate amounts, provide health benefits to the host by supporting gut health and enhancing immune function. These beneficial microbes work by modulating the gut microbiota, producing essential metabolites, and interacting with the host's biological systems to promote overall well-being. [152]

Probiotic organisms are widely recognized for their ability to improve gut health, support immune function, and influence various aspects of overall well-being, such as mental health, metabolism, and even skin health. [25,153] These live microorganisms, when taken in adequate amounts, help restore balance to the gut microbiota, inhibit the growth of harmful pathogens, produce beneficial compounds, and interact with the host's immune system. However, it is essential to understand that not all strains within a probiotic species are functionally equivalent, and their effects on health can vary significantly. Even though two strains may belong to the same species, their impact may differ because of variations in their genetic makeup.

The functional capacity of probiotics is determined by specific genes that influence how well they can survive in the gastrointestinal tract, produce bioactive compounds like short-chain fatty acids, or communicate with the host's immune system. Therefore, relying solely on the species-level identification of probiotics without considering strain-specific gene content can lead to less effective health outcomes. This highlights the need to shift the focus from taxonomic classification to a more detailed understanding of a strain's functional properties and its genetic capabilities. Figure 2 summarizes the levels functionality required for the identification of a probiotic property in microorganisms presumed to have probiotic properties.

For example, one strain of *Lactobacillus rhamnosus* may promote gut barrier integrity by producing certain exopolysaccharides, while another strain of the same species may not. Similarly, some strains may have better tolerance to bile salts and gastric acid, improving their survival and efficacy in the digestive system. These differences underscore the importance of identifying the specific genes responsible for these beneficial traits, allowing for the targeted selection of probiotic strains that can address health needs, such as reducing inflammation, enhancing the gut-brain axis, or strengthening the immune response. By focusing on a strain's function and gene content, rather than just its species, we can develop more effective, personalized probiotic therapies that optimize health outcomes.

This figure illustrates the different levels of information required to evaluate probiotic strains, progressing from desired health outcomes to the underlying genetic basis. The first layer outlines the desired activity or function of the probiotic, such

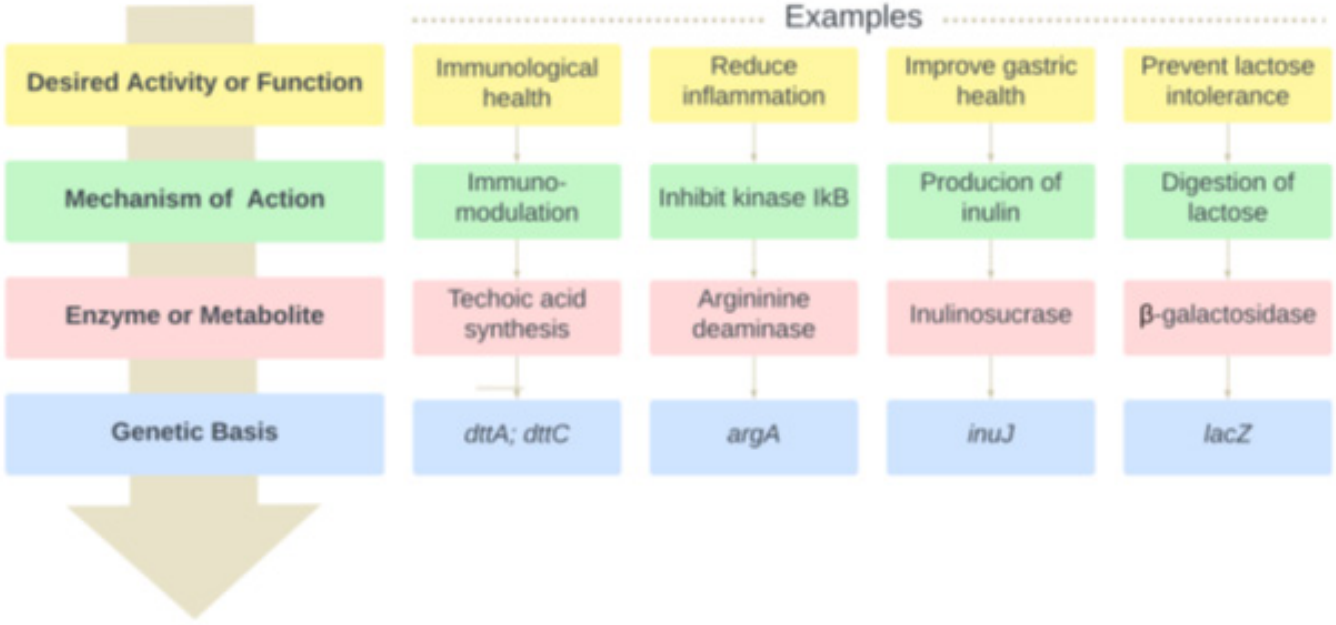

Fig. 2. Levels of information required for the characterization of of putative probiotic strains

as improving gut health or modulating immune responses. The second layer details the mechanisms of action, which may include adhesion to the gut epithelium, immune modulation, or metabolite production. The third layer highlights specific enzymes or metabolites produced by the probiotic strains, such as short-chain fatty acids or antimicrobial peptides, which contribute to their beneficial effects. The final layer reveals the genetic basis for these activities, including the genes responsible for the production of these metabolites or for traits like bile resistance and survival in the gastrointestinal tract.

The microbiome is a dynamic and integral part of human physiology, influencing multiple aspects of health, including digestion, immunity, metabolism, and even mental well-being. Understanding the complex interactions between the microbiome and its host has revolutionized our approach to medicine, offering new opportunities for disease prevention, diagnosis, and treatment. Maintaining a balanced and diverse microbiome is essential for promoting long-term health, and the development of microbiome-based therapies holds great promise for addressing some of the most pressing public health challenges of our time.

Designing Probiotic Strategies: Conventional, Metabolic Modeling, and AI Approaches

Probiotic development has evolved significantly, now incorporating advanced tools like metabolic modeling and artificial intelligence (AI) alongside traditional methods. While conventional approaches have produced effective probiotics, they are often slow, resource-intensive, and unable to predict complex microbial interactions. New technologies allow for more efficient design and optimization of probiotics, offering improved precision and personalized formulations.

Traditionally, probiotic development begins by isolating strains from natural environments like the gut, fermented foods, or soil. Key genera include Lactobacillus, Bifidobacterium, and Saccharomyces. These strains are identified using molecular techniques like 16S rRNA sequencing, followed by in vitro tests to assess their ability to survive gastric acidity, adhere to the gut lining, and inhibit pathogens. In vivo studies and clinical trials then evaluate their efficacy in promoting health benefits such as improving digestion, modulating gut microbiota, or enhancing immune function.

However, this process is labor-intensive and can be limited by a trial-and-error approach. Conventional methods often struggle to predict how probiotic strains interact with each other or the host's microbiome, especially in multi-strain formulations. This is where metabolic modeling and AI provide a significant advantage.

Metabolic modeling uses genome-scale metabolic models (GEMs) to predict how probiotic strains will behave in the gut. GEMs reconstruct the metabolic pathways of a microorganism based on its genome, allowing researchers to simulate nutrient metabolism and metabolite production. [154] This is particularly useful in predicting how strains will interact in complex microbial communities like the gut.

For example, metabolic modeling can simulate cross-feeding, where one strain produces metabolites that serve as nutrients for another, enhancing the overall effectiveness of multi-strain formulations. Models can also predict the production of beneficial metabolites, such as short-chain fatty acids (SCFAs), which are key for gut health. [155] This approach helps optimize probiotic formulations for specific health outcomes, such as reducing inflammation or improving nutrient absorption. Moreover, by incorporating an individual's microbiome data, metabolic models can be used to design personalized probiotics that target specific imbalances or deficiencies.

Artificial intelligence (AI), particularly machine learning, is transforming the field of probiotic design by leveraging vast amounts of genomic, microbiome, and clinical data. [156] This revolution is driven by AI's ability to process and analyze these complex datasets far more efficiently than traditional methods, making it possible to identify probiotic strains with specific, desirable characteristics in a fraction of the time. For instance, AI can rapidly pinpoint bacterial strains that exhibit strong immune-modulating properties, produce essential metabolites like short-chain fatty acids (SCFAs), or possess traits such as resistance to bile salts and acidic environments. These characteristics are critical for ensuring that probiotics can survive and function effectively in the human gastrointestinal tract, particularly under harsh conditions like low pH or high bile concentrations (figure 3).

This figure outlines the stepwise process of developing a probiotic consortium. It begins with the selection of candidate strains, which are chosen based on their desired functions (e.g., Function A, Function B). The selected strains are then combined to form a consortium. The next phase involves conducting in vitro assays to assess the metabolic profiles and the functionality of the strains within the consortium. Once the optimal formulation is identified, the development process proceeds to preparation methods, including culture media optimization, lyophilization, and sporulation techniques. Various methods of administration are considered, such as oral capsules, suppositories, or gels, tailored to the intended use. Data is continuously processed and analyzed using AI algorithms to refine and improve the probiotic formulation. After validation through laboratory testing, the successful formulation is implemented in the product line, with ongoing data reviews ensuring continuous optimization.

AI's role in probiotic design extends beyond identifying individual strains. It can also predict how well a particular probiotic strain will perform in specific populations by considering genetic, dietary, and environmental factors. For example, a probiotic that is effective for one population might not

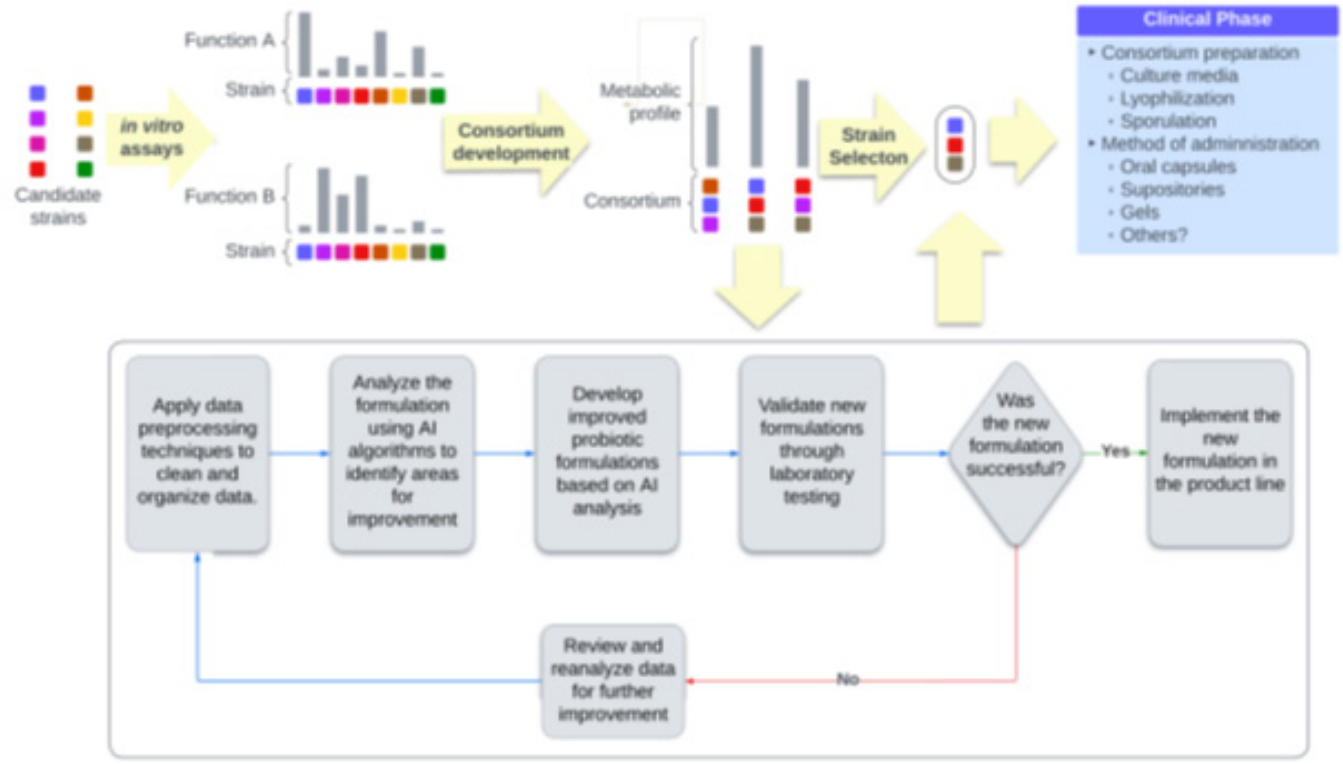

Fig. 3. Process of probiotic development employing artificial intelligence

perform as well in another due to differences in microbiome composition, diet, or even cultural habits. By analyzing these variables, AI can tailor probiotics to meet the needs of specific demographic or clinical groups, enhancing their effectiveness for targeted health outcomes such as reducing inflammation, improving digestion, or supporting mental health.

One of AI's most powerful contributions to probiotic development is its ability to accelerate the design of multi-strain formulations. Probiotics are often more effective when multiple bacterial strains work together synergistically, [157] but identifying the best combinations can be a time-consuming and complex process. AI-driven models can predict the interactions between different strains, identifying potential synergies or antagonistic relationships. This optimization of strain combinations not only improves the overall efficacy of probiotic products but also ensures that the selected strains work harmoniously within the gut environment. AI can also optimize the dosages and ratios of these strains to maximize their health benefits while minimizing any potential negative interactions.

AI's capabilities also extend to clinical trial design, where it can streamline the process by selecting the most promising strains and identifying the ideal patient groups for testing. Traditional clinical trials can be lengthy and expensive, with a significant amount of uncertainty in terms of which strains or combinations will yield the best results. By using AI to analyze preliminary data and make informed predictions, companies can focus their resources on testing only the most likely successful candidates, significantly reducing both the cost and duration of clinical trials. [155] Additionally, AI can help identify biomarkers in patient data that indicate which individuals are most likely to benefit from a particular probiotic intervention, further refining the selection of trial participants.

Moreover, AI-driven feedback systems are poised to continuously improve probiotic formulations post-launch. These systems can integrate real-time health data, such as changes in a person's microbiome composition or specific health outcomes, to adjust and refine probiotic formulations dynamically. For example, if a probiotic is intended to improve gut health but ongoing data suggests it is less effective in individuals with a particular microbial profile, the formulation could be adjusted to include strains better suited to that profile. This real-time adaptability ensures that probiotic products remain effective across diverse populations and changing health conditions.

In summary, AI and machine learning are revolutionizing probiotic design by enabling the rapid identification of beneficial bacterial strains, optimizing multi-strain formulations, and streamlining the clinical trial process. AI's ability to predict interactions between strains and personalize probiotics based on genetic and environmental factors ensures that products are not only effective but also tailored to specific populations. In addition, AI-driven feedback systems provide a mechanism for continuous improvement, allowing probiotic formulations to evolve and adapt based on real-time health data. This powerful integration of AI into probiotic design is paving the way for more personalized, efficient, and effective microbiome-targeted therapies.

Applications and Future Directions

The integration of genome-scale metabolic models (GEMs) into microbiome research and probiotic design offers a transformative approach to understanding and utilizing microorganisms for health applications. The key areas for application and future directions of this technology include:

Probiotic Formulation. GEMs enable precision in designing probiotics tailored to address specific health conditions. For example, strains can be selected for their ability to produce anti-inflammatory compounds for conditions like IBS and IBD, enhance nutrient absorption for digestive health, or influence metabolic pathways to address obesity and metabolic syndrome. These models allow the optimization of strain combinations that work synergistically, enhancing their overall therapeutic effects.

Clinical Trial Design. Traditionally, clinical trials for probiotics rely on trial-and-error methods for selecting strains and dosages. By using GEMs, researchers can simulate the metabolic interactions of probiotics within the human microbiome before trials begin. This allows for optimizing strain selection, predicting the best combinations, and identifying the most effective dosages. As a result, this approach can reduce the time and costs associated with product development by focusing on formulations that have the highest potential for success in specific patient populations.

Personalized Medicine. Personalized probiotic therapies represent a future where treatments are tailored to the unique composition of an individual's microbiome. GEMs allow researchers to model a person's specific microbial ecosystem, incorporating probiotic strains into simulations that predict how they would interact within that environment. This personalized approach could lead to customized interventions for conditions like gastrointestinal disorders (e.g., Crohn's disease), metabolic diseases (e.g., diabetes), or immune disorders, thus improving efficacy and reducing side effects.

Microbiome Engineering. Beyond probiotics, GEMs open doors to microbiome engineering, where genetically modified or naturally occurring microorganisms are designed to fulfill specific therapeutic functions. For example, engineered strains could be used to deliver therapeutic compounds directly to the gut, degrade harmful metabolites, or modulate immune

responses. This approach could have long-term benefits for managing chronic conditions by creating a more balanced and functional microbiome environment.

CONCLUSIONS

Challenges and Future Considerations

Despite the promise of microbiome-based therapies, there are challenges that must be addressed. One of the primary obstacles is the inherent complexity of modeling diverse microbial ecosystems, where interactions between different microbial species can lead to unexpected outcomes. These interactions are dynamic and context-dependent, making it difficult to predict how microbial communities will behave in different environments or individuals. Additionally, achieving regulatory approval for genetically engineered strains and other microbiome-modulating therapies remains a significant challenge. Such therapies require rigorous safety evaluations to ensure they do not inadvertently disrupt microbial balance or introduce harmful effects, especially given the potential for genetically modified organisms (GMOs) to raise public concerns about safety and long-term impact.

Furthermore, ethical issues around microbiome data privacy, consent for microbial interventions, and the potential unintended consequences of altering human-associated microbial communities must be considered. Future research should focus on refining genome-scale metabolic models (GEMs) to better capture the complexity of microbial ecosystems, improving their predictive accuracy, and addressing regulatory and ethical hurdles. This will involve advancing computational models that can simulate not only microbial behavior but also the complex interactions between microbiota and host systems in a variety of conditions.

Looking forward, these advancements point to a future where microbiome-based therapies, supported by sophisticated computational models, could become a cornerstone of both preventive and therapeutic healthcare. The continuous development of GEMs holds great potential for driving the next generation of personalized medicine and microbial interventions, potentially transforming the way diseases are managed and treated at an individualized level.

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