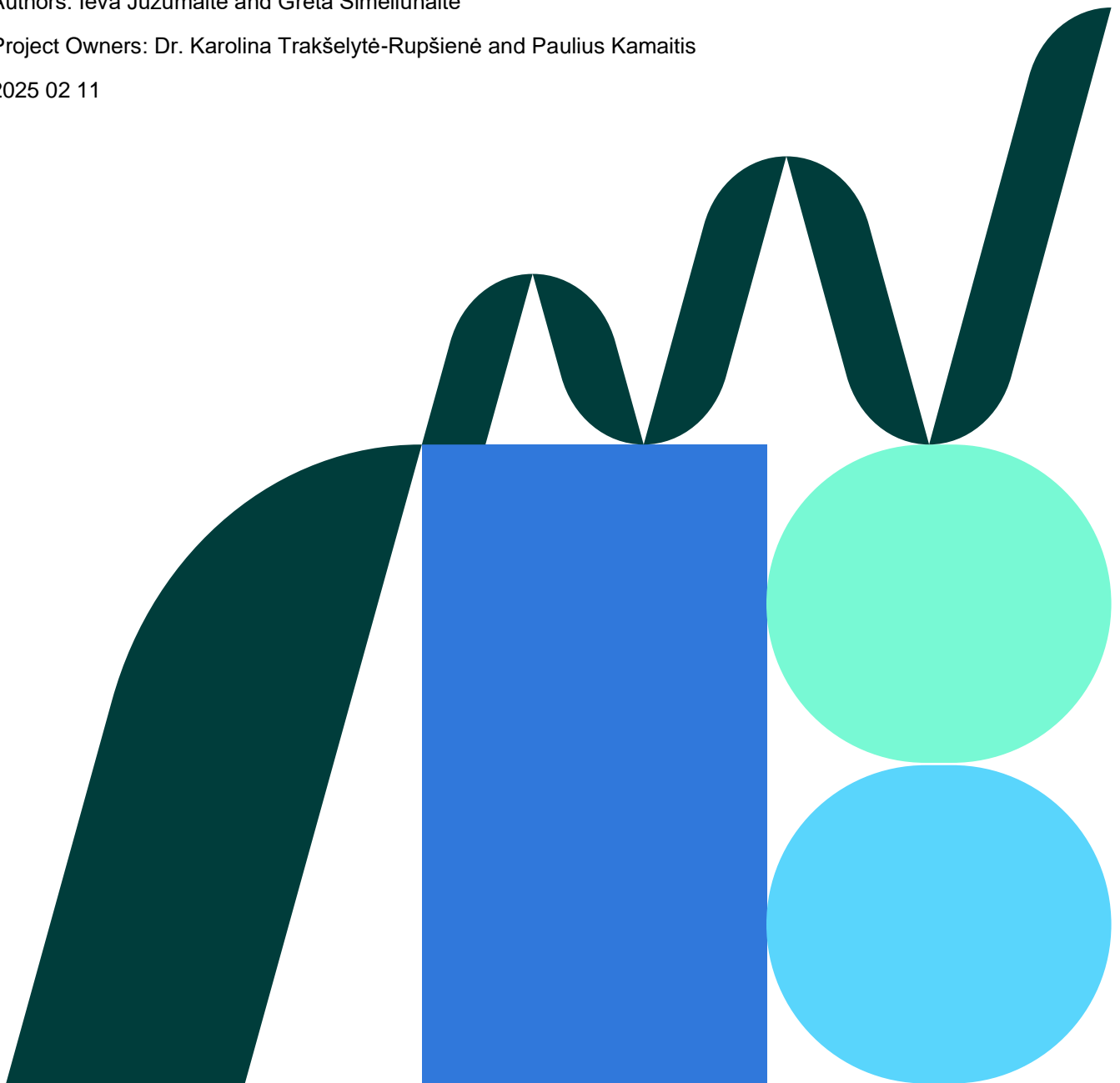


Microbiome Analysis in Lithuania: Overview of the Global and Local Ecosystem, Strengths, Weaknesses, and Recommendations

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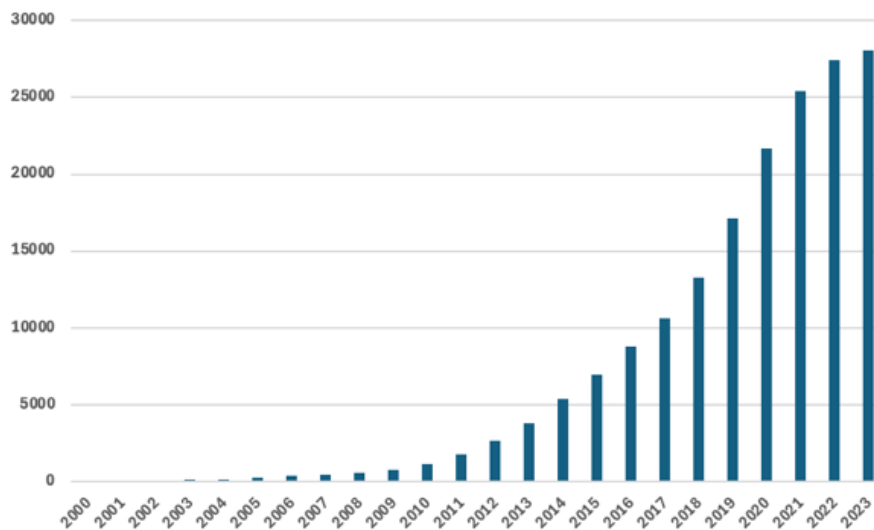
Global Overview and Emerging Trends in the Microbiome Sector

Overview of Microbiome Research and Innovations

Microbiome research has rapidly advanced over the past decade, fueled by breakthroughs in molecular biology and sequencing technologies.¹ Publication rates in this field have surged by 634.39% from 2013 to 2023, reflecting its increasing prominence across academia (**Figure 1**).

Figure 1

Publications with Search Query: Microbiome



Note: prepared by authors from PubMed data.²

Based on the number of published studies by country, the United States has remained the leader in microbiome research since 1985, with over 26,000 publications. Since 2018, China has emerged as a significant contributor, showing a consistent year-over-year increase in its number of publications. In Europe, Germany and the United Kingdom have been the most prominent contributors to microbiome research (**Figure 3**).³

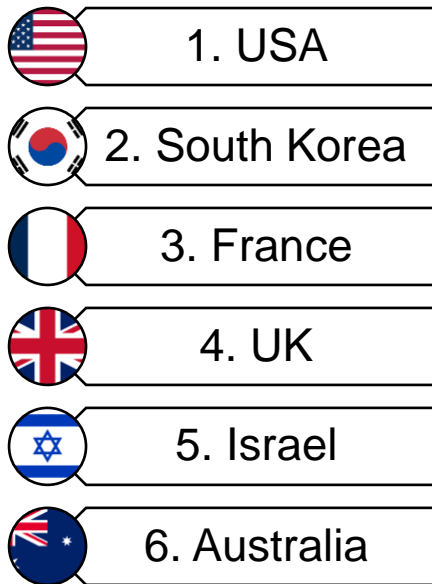
In terms of innovation, based on the number of companies involved in research and development (R&D), as well as the volume of drug and therapy candidates and ongoing clinical trials, the United States is recognized as the global leader in microbiome research, based on 2021 data. In Asia, South Korea leads the field, while France and the United Kingdom are among the top contributors in Europe (**Figure 2**).⁴

¹ <https://doi.org/10.1016/j.soh.2024.100065>

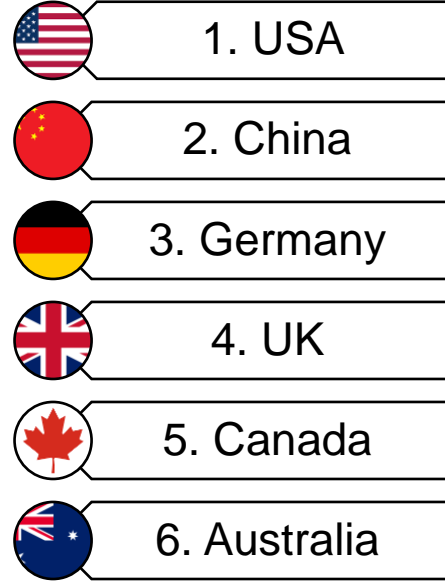
² <https://pubmed.ncbi.nlm.nih.gov/?term=microbiome>

³ <https://doi.org/10.1093/procel/pwad031>

⁴ https://www.gazettelabo.fr/media/files/211007_CP_APM_EtudeSectorielle2021_VF.pdf

Figure 2*Microbiome Innovation Leaders*

Note: prepared by authors, data obtained from Alliance Promotion Microbiote, 2021.⁵

Figure 3*Microbiome Research Leaders*

Note: prepared by authors, data obtained from Gao et al., 2023.⁶

Sector Size

According to PwC, the market for microbiome-based prescription products is still in its early stages, with varying estimates of its global value. Strategic Market Research estimated the prescription-based microbiome market at \$115 million in 2021, with projections to reach \$1.3 billion by 2030. While these figures are small compared to other therapeutics markets, such as oncology, they do not account for the potential of microbiome-based therapies to replace conventional treatments. Given their broad potential applications, microbiome-based prescription products are expected to evolve into a multi-billion-dollar industry by 2030.

In contrast, non-prescription microbiome products, including consumer-focused items like probiotic supplements, are more established and considerably larger in scale. This segment is projected to grow at a compound annual growth rate (CAGR) of 6.4%, reaching \$85.4 billion by 2027.⁷

⁵ https://www.gazettelabo.fr/media/files/211007_CP_APM_EtudeSectorielle2021_VF.pdf

⁶ <https://doi.org/10.1093/procel/pwad031>

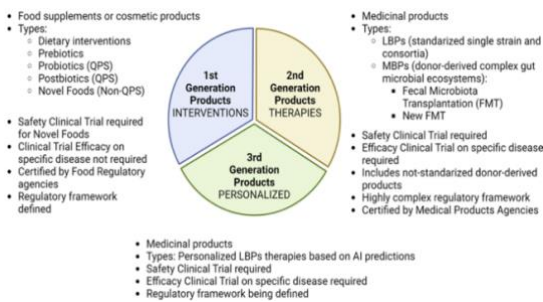
⁷ <https://www.strategyand.pwc.com/de/en/industries/pharma-life-sciences/impact-microbiome-therapeutics.html>

Sector Products

The microbiome sector encompasses a diverse range of products. There is no generalized system of classification, but several authors have designed their own frameworks for categorizing microbiome-related therapies and supplements. Manrique et al. outline three generations of products, where the first generation includes interventions, the second generation encompasses therapies, and the third generation focuses on personalized medicine (Figure 4). Gulliver et al. classify microbiome-based products into nutrients, bacterial, or “microbiome mimetics” (Figure 5).

Figure 4

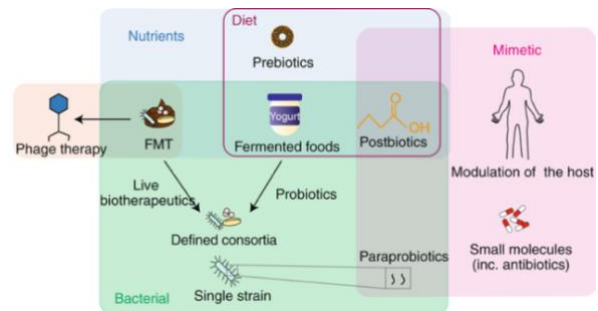
Three Generations of Products (Manrique et al.)



Note : source from Manrique et al., 2024.⁸

Figure 5

Microbiome-Based Product Classification (Gulliver et al.)



Note : source from Gulliver et al., 2022.⁹

The authors of this analysis categorized microbiome-based products into therapeutics, dietary supplements, and food-based approaches. Therapeutics focus on medical interventions, such as fecal microbiota transplantation (FMT) and live biotherapeutic products. Dietary supplements are designed to enhance gut health and are generally not approved to treat disease. Food-based interventions include dietary strategies and functional foods that influence microbiome composition and diversity.

This framework offers a comprehensive view of the sector:

Figure 6

Microbiome Sector Products

Microbiome Sector		
Therapeutics	Dietary Supplements	Food
<ul style="list-style-type: none"> Fecal microbiota transplantation Live biotherapeutic products Genetically modified bacteria Phage therapy Microbiome derived metabolite therapy 	<ul style="list-style-type: none"> Probiotics Prebiotics Synbiotics Postbiotics Psychobiotics 	<ul style="list-style-type: none"> Diet intervention Functional foods

Note: prepared by authors

⁸ <https://doi.org/10.20517/mrr.2023.80>

⁹ <https://www.researchgate.net/publication/360835425> Review article the future of microbiome-based therapeutics

Therapeutics

Microbiome-based therapies are increasingly being researched, as they combat antibiotic resistance and have higher specificity than modern medicines. Therapies targeting the microbiome include fecal microbiota transplantation (FMT), live biotherapeutic products (LBPs), genetically modified bacteria, phage therapy, and microbiome derived metabolite therapy.¹⁰

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is an emerging therapy that involves transferring fecal matter from a healthy donor to a recipient, who confers health benefits through the increase in microbial diversity and altered metabolite production. The healthy donor stool replenishes the recipient's disrupted gut microbiome and reintroduces missing strains, improving the ability to prevent overgrowth of malicious bacteria.¹¹ So far, it has been used successfully to treat recurrent *Clostridioides difficile* infection (CDI), an infectious disease of the colon, and is being researched for treatment of other diseases.¹² In repeated trials, patients treated with FMT for recurrent CDI demonstrated an efficacy rate of 80-90%.¹³

The regulatory framework for FMT therapy is constantly shifting, with ongoing research into its benefits and risks. Currently, it is not approved by the United States Food and Drug Administration (FDA) for the treatment of Crohn's disease or irritable bowel syndrome, though researchers are permitted to use FMT to treat CDI in patients who are not benefitting from standard therapies.¹⁴ This is a change from the previous guidance, which only allowed FMT if clinicians submitted an investigational new drug (IND) application, which limited patients from being able to receive FMT and led to dangerous self-treatment attempts.¹⁵ In June 2022, the European Union published a regulatory framework for FMT, classifying it as a "biological medicinal product", regulating it similarly to the United States.¹⁶

Although FMT has demonstrated beneficial outcomes, there are still several risks and negative consequences that underscore the need for further investigation before widespread approval. Firstly, there are safety concerns associated with FMT, especially for immunocompromised patients, because of the possible spread of infectious pathogens due to a specific donor or manufacturing processes.¹⁷ In 2019, two patients were infected with *Escherichia coli* bacteria after receiving FMT in separate trials and developed invasive disease. The sample was from the same donor, and one of the patients died as a result.¹⁸ Therefore, FMT centers added criteria to screen for these organisms in donors. However, with emerging infections such as COVID-19 and monkey pox, it is increasingly difficult to predict new pathogens to screen.¹⁹

¹⁰ <https://doi.org/10.1093/gastro/goab046>

¹¹ <https://doi.org/10.1093/cid/ciad639>

¹² <https://doi.org/10.3748/wjg.v28.i23.2546>

¹³ <https://doi.org/10.14309/ajg.0000000000002167>

¹⁴ <https://doi.org/10.14309/ajg.0000000000002167>

¹⁵ <https://doi.org/10.2147/idr.s419243>

¹⁶ <https://doi.org/10.20517/mrr.2023.80>

¹⁷ <https://doi.org/10.2147/idr.s419243>

¹⁸ <https://doi.org/10.1056/nejmoa1910437>

¹⁹ <https://doi.org/10.2147/idr.s419243>

Additionally, this method is difficult to standardize, and the effectiveness depends on the health of the donor. New FMT strategies include developing non-invasive techniques such as oral medication alternatives and involve further investigation into treating other diseases.²⁰

Live Biotherapeutic Products

Live biotherapeutic products (LBPs) are newer treatments. They are similar to prebiotics and probiotics, as they are biological products that contain live organisms, but their intent is to prevent, treat, and cure diseases.²¹ Similarly, the FDA's definition of live biotherapeutic products is composed of three factors: 1) contains live organisms; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine.²² This definition is very broad and encompasses LBPs containing a single species of bacteria or spores to an entire diverse microbial community. The methods of delivery could also include enema or oral delivery.

Currently, there are three live biotherapeutic products worldwide that have been granted regulatory approval. Two LBPs have been approved by the FDA: Rebyota™ and VOWST™ produced by Ferring Pharmaceuticals Inc. and Seres and Nestle, respectively. Biomictra™, produced by BiomeBank, was approved by the Australian Therapeutic Goods Administration in 2022, and was the world's first donor-derived microbiome drug to receive regulatory approval.²³ All three of these therapies were approved in 2022 and 2023 and are intended to be taken for recurrent *C. difficile* infection (CDI).²⁴ Biomictra and Rebyota contain fecal microbiota as the active ingredient and are rectally administered, whereas VOWST is comprised of fecal microbiota spores and is orally administered. These products have demonstrated high efficacy in clinical trials. The ECOSPOR IV trial proved the safety and efficacy of VOWST, where 88% of patients receiving VOWST had a sustained clinical response at 8 weeks.²⁵ In the clinical trials with Rebyota, 70.6% of patients at 8 weeks were recurrence-free.²⁶

Although these products have a high cost - \$17,500 USD for VOWST and \$9100 USD for REBYOTA – the cost of hospitalization for recurrent CDI remains much greater. In addition, the availability of these medications in the market provides greater options for patients to consider in treatment.²⁷

Difference Between FMT and LBPs

Due to the similarities with sourcing and method of administration, FMT and LBPs can be easily mistaken for each other. The key differences between FMT and LBPs are the mode of manufacturing and the method of obtaining them. Both undergo rigorous testing to verify that there are no pathogens. The manufacturing of LBPs includes an additional process after deep-freezing. In addition, production of LBPs must follow Good Manufacturing Policy

²⁰ <https://doi.org/10.20517/mrr.2023.80>

²¹ <https://assets.kpmg.com/content/dam/kpmgsites/ch/pdf/kpmg-ch-whitepaper-microbiome.pdf.coredownload.inline.pdf>

²² <https://www.fda.gov/files/vaccines,%20blood%20%26%20biologics/published/Early-Clinical-Trials-With-Live-Biotherapeutic-Products--Chemistry--Manufacturing--and-Control-Information--Guidance-for-Industry.pdf>

²³ <https://www.biomebank.com/news/biomebank-announces-world-first-regulatory-approval-for-donor-derived-microbiome-drug/>

²⁴ <https://www.nixonpeabody.com/insights/alerts/2023/05/15/fda-approves-microbiome-based-therapies>

²⁵ <https://doi.org/10.1056/nejmoa2106516>

²⁶ <https://doi.org/10.1093/cid/ciad639>

²⁷ <https://doi.org/10.2147/idr.s419243>

(GMP) guidelines and have undergone rigorous clinical trials to prove they are safe and effective.²⁸ FMT, on the other hand, is not standardized and shows variability with collection procedures and storage processes.

Another key differentiation is the modification of the donor sample. For fecal microbiota transplantation, the donor sample is not modified before transplanting to the recipient, whereas live biotherapeutic products undergo several methods of processing before being administered. This can include selecting for certain strains of bacteria or enhancing metabolic properties of microbiota.

Genetically Modified Bacteria

Another therapeutic method being developed is genetically modified bacteria, which are engineered to perform specific tasks in the gut. Specific bacterial strains can be modified to treat several diseases, including gastrointestinal diseases, cancer diabetes, obesity, and hypertension. Bacteria can also be modified to degrade antibiotics in the gut, which mitigates the adverse effects of antibiotics and is beneficial for the balance of the microbiome.²⁹

A significant advantage of using genetically modified bacteria in the microbiome is their potential for therapeutic functions with minimal side effects. This makes them a good candidate for replacing medications like antibiotics, which cause dysbiosis. However, current regulations make it difficult to develop these treatments. These mandate that clinical trials utilize bacteria without genetic modifications.³⁰

Phage Therapy

Phage therapy is an innovative approach that uses viruses, called bacteriophages, to precisely identify and destroy harmful bacteria. These phages can be naturally occurring or genetically engineered to enhance their precision, ensuring they selectively attack pathogenic bacteria while protecting beneficial strains.³¹

Unlike antibiotics, which can indiscriminately harm both beneficial and harmful bacteria, phages are very specific and do not harm human cells. Because of this, phage therapy is a promising alternative to antibiotics.

There are several challenges with the adoption of phage therapy. Regulation and policy issues complicate clinical approval, since phages are considered biological agents and not pharmaceuticals. In addition, high production costs and the need for personalized treatments also limit accessibility. Further studies are needed to verify the therapeutic effects of phage therapy, as there are possibilities that extensive use of phages might also lead to resistance.³²

Microbiome-Derived Metabolite Therapy

Microbial metabolites play a vital role in the connection between diet, the gut microbiome, and host health, with two key classes—short-chain fatty acids (SCFAs) and tryptophan (Trp) metabolites—being known to influence inflammation, immunity, and metabolism. Since many diseases are linked to an imbalance in the gut microbiome

²⁸ <https://www.pharmacytimes.com/view/clinical-overview-fecal-microbiota-transplantation-vs-live-biotherapeutic-products-for-management-of-recurrent-c-difficile-infection>

²⁹ <https://pmc.ncbi.nlm.nih.gov/articles/PMC9606703/#:~:text=Microbial%20genetic%20engineering%20uses%20genetic,the%20bacteria%20with%20new%20phenotypes>

³⁰ <https://pmc.ncbi.nlm.nih.gov/articles/PMC10367592/>

³¹ [https://www.pharmabiotic.org/microbiome-based-medicinal-products/#:~:text=Non-living%20biotherapeutic%20products%20\(as,will%20have%20to%20be%20defined](https://www.pharmabiotic.org/microbiome-based-medicinal-products/#:~:text=Non-living%20biotherapeutic%20products%20(as,will%20have%20to%20be%20defined)

³² <https://pmc.ncbi.nlm.nih.gov/articles/PMC9550173/>

and a decrease in microbial metabolite production, providing these metabolites offers a direct, multi-targeted treatment approach.

While numerous preclinical studies highlight the therapeutic potential of SCFAs and Trp metabolites, they often require high doses and frequent administration to achieve systemic effects, limiting their clinical use. To overcome these challenges, several pharmaceutical strategies have been developed to enable targeted, delayed, or sustained delivery of microbial metabolites. These strategies, such as enteric encapsulation, esterification with dietary fiber, prodrugs, and nanoformulations, are setting the stage for the next generation of microbiome-based therapeutic approaches.³³

Dietary Supplements

According to the European Food Safety Authority (EFSA), food supplements are defined as concentrated sources of nutrients (such as vitamins and minerals) or other substances with a nutritional or physiological effect, which are marketed in "dose" form. These may include, but are not limited to, pills, tablets, capsules, or liquids in measured doses. Food supplements may contain a wide variety of ingredients, including vitamins, minerals, amino acids, essential fatty acids, dietary fiber, as well as various plant and herbal extracts.

Within the European Union (EU), food supplements are regulated as foods. Harmonized legislation governs the use of vitamins, minerals, and their respective sources in the production of food supplements. For substances other than vitamins and minerals, the European Commission has established specific regulations aimed at safeguarding consumer health. This includes maintaining a list of substances known or suspected to pose adverse health risks, thereby controlling their use in food supplements.³⁴

The following sections review dietary supplements related to the microbiome sector:

Probiotics

The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host".³⁵ Probiotics can be found in yogurt, other fermented foods, dietary supplements, and even beauty products.³⁶ As dietary supplements, they are available in various forms, including capsules, powders, and liquids, often containing mixed cultures of live microorganisms.³⁷

The most commonly used probiotic bacteria are *Lactobacillus* and *Bifidobacterium*, which are naturally found in the human gastrointestinal tract and various dairy products. Other EFSA-approved species include *Streptococcus*, *Bacillus*, and the yeast *Saccharomyces*. EFSA regularly updates a list of QPS (qualified presumption of safety) recommended microorganisms for safety assessments every six months.³⁸ However, certain fungi, bacteriophages, and bacterial taxa, such as *E. coli*, are excluded from QPS assessments due to potential risks and require specific evaluation.³⁹

³³ <https://www.sciencedirect.com/science/article/abs/pii/S0163725824000251>

³⁴ <https://www.efsa.europa.eu/en/topics/topic/food-supplements>

³⁵ <https://doi.org/10.20517/mrr.2023.80>

³⁶ <https://www.nccih.nih.gov/health/probiotics-usefulness-and-safety>

³⁷ <https://ods.od.nih.gov/factsheets/Probiotics-HealthProfessional/>

³⁸ <https://www.efsa.europa.eu/en/topics/topic/qualified-presumption-safety-qps>

³⁹ <https://doi.org/10.20517/mrr.2023.80>

Probiotics play essential roles in human health by maintaining gut balance, supporting the immune system, and protecting against certain pathogens. Numerous studies have explored their general health benefits and their role in various diseases.⁴⁰

However, any health claims related to probiotics must be authorized by the European Commission following an evaluation by the European Food Safety Authority (EFSA). Despite a wealth of scientific literature supporting the health benefits of probiotics, EFSA has rejected all health claims for probiotics submitted so far, except for the effect of standard yogurt cultures on lactose digestion.⁴¹ The FDA has also not approved any probiotics for treatment or prevention of disease.⁴²

On the commercial side, according to Statista, North America currently leads the global market for probiotic supplements, followed closely by Europe.⁴³ By 2027, the global market for probiotic supplements is projected to reach 3.28 billion,⁴⁴ with a significant portion of this market focused on supporting gastrointestinal health.⁴⁵

Prebiotics

Prebiotics are substances that are selectively used by host microorganisms and provide health benefits through microbiota-mediated mechanisms. This includes the substance itself, its physiological effects, and the mechanisms by which these effects occur. Prebiotics can be naturally occurring or synthetically produced. Common examples of naturally occurring prebiotics include inulin, oligosaccharides, dietary fibers, and resistant starches, and synthetic prebiotics include lactulose and pyrodextrins (and sometimes oligosaccharides or resistant starches when processed).

Prebiotics are crucial for human health, serving as an energy source for certain gut bacteria. These bacteria metabolize prebiotics and produce byproducts that influence other microbial species in the gut. This process, known as substrate cross-feeding, can significantly affect the composition of the gut microbiome.

Prebiotics have shown therapeutic potential for various conditions by modulating the gut microbiome. In inflammatory bowel disease (IBD), they can improve gut microbiome composition and reduce inflammation. Research into the gut-brain axis also suggests that plant-derived prebiotics, such as inulin and resistant starch, may help manage Parkinson's disease by promoting beneficial gut bacteria and reducing neuroinflammation. Additionally, prebiotics have been linked to improved management of diabetes and obesity.⁴⁶

Synbiotics

The term "synbiotic" refers to nutritional supplements that combine probiotics (live bacteria) and prebiotics (the food components they rely on) to create a synergistic effect.⁴⁷ Initially, synbiotics were developed to enhance the functionality of probiotics by pairing them with prebiotics.⁴⁸

⁴⁰ <https://doi.org/10.20517/mrr.2023.80>

⁴¹ https://foodsupplementseurope.org/wp-content/themes/fse-theme/documents/publications-and-guidelines/FSE-Probiotic_Report-April2021.pdf

⁴² <https://doi.org/10.1016/j.jff.2021.104718>

⁴³ <https://www.statista.com/statistics/1198117/forecast-of-the-global-probiotic-supplements-market/>

⁴⁴ <https://www.statista.com/statistics/1197251/forecast-of-the-global-probiotic-supplements-market/>

⁴⁵ <https://www.statista.com/statistics/1198131/forecast-of-the-global-probiotic-supplements-market/>

⁴⁶ <https://doi.org/10.20517/mrr.2023.80>

⁴⁷ <https://doi.org/10.15740/has/fsrj/7.2/327-334>

⁴⁸ <https://doi.org/10.20517/mrr.2023.80>

The primary reason for using synbiotics is that a probiotic, without its prebiotic 'food source', struggles to survive in the digestive system. Without this necessary food, probiotics become more intolerant of oxygen, low pH, and temperature. Additionally, without a specific food source, probiotics must compete with other bacteria, which can take over.

The health benefits associated with synbiotic consumption include:

- 1) Increased levels of *Lactobacilli* and *Bifidobacteria* and a balanced gut microbiota
- 2) Improvement of liver function in cirrhotic patients
- 3) Enhanced immunomodulatory effects
- 4) Prevention of bacterial translocation and reduced incidence of nosocomial infections in surgical patients.⁴⁹

Postbiotics

According to the definition proposed by Salminen *et al.*, postbiotics refer to a "preparation of inanimate microorganisms and/or their components that confers a health benefit to the host".⁵⁰ Postbiotics are primarily derived from *Lactobacillus*, *Bifidobacterium*, and yeasts like *Saccharomyces cerevisiae* through fermentation processes. The resulting metabolites or polysaccharides often possess antioxidant, anti-inflammatory, and immunomodulatory properties. Short-chain fatty acids (SCFAs), which are produced by bacterial fermentation of dietary fiber, are a key example of postbiotics.

Novel postbiotics, such as inactivated bacterial cells, can be approved as novel foods. For example, pasteurized *Akkermansia muciniphila* has shown promise in reducing obesity, improving diabetes, and enhancing cardiovascular health. It has also been linked to improvements in insulin resistance and glucose metabolism.

Compared to probiotics, postbiotics offer several advantages. They pose a reduced risk of bacterial translocation and infections, making them safer—especially for vulnerable populations. Postbiotics also have a longer shelf life and are more effective in topical formulations, which is beneficial for the cosmetic industry.

While many probiotics report health benefits, their effectiveness is often limited due to the complexity of the gut microbiota and varying strain efficacy. Many probiotics fail to establish stable colonization in the gut after treatment ends. To overcome these challenges, significant efforts are being made to develop more effective therapies, such as live biotherapeutic products (LBPs) and fecal microbiota transplants (FMT), both of which have demonstrated benefits and are recognized as medical products.⁵¹

Psychobiotics

Psychobiotics are a class of probiotics that provide mental health benefits by modulating the gut-brain axis. They stimulate the production of neurotransmitters such as serotonin and gamma-aminobutyric acid (GABA) and promote anti-inflammatory cytokines, which support mental health.⁵² They also enhance microbial diversity and increase the production of metabolites, including short chain fatty acids (SCFAs). These metabolites play a critical role in regulating brain function and have shown promise in alleviating symptoms of central nervous system (CNS) disorders such as depression, insomnia, Parkinson's disease, and multiple sclerosis.⁵³

⁴⁹ <https://pmc.ncbi.nlm.nih.gov/articles/PMC4648921/#CR77>

⁵⁰ <https://doi.org/10.1038/s41575-021-00440-6>

⁵¹ <https://doi.org/10.20517/mrr.2023.80>

⁵² <https://doi.org/10.1007/s00284-020-02289-5>

⁵³ <https://doi.org/10.3390/medicina60040601>

Microbiome-based treatments are becoming increasingly favorable, and the market for psychobiotics is currently experiencing significant growth since they offer alternative solutions to address antidepressant resistance.

Food

Diet is one of the most influential factors in shaping the composition and function of the microbiome.⁵⁴ Given its significance, this topic will be explored in more detail in the following section.

Dietary Interventions

A microbiome dietary intervention refers to dietary changes designed to modulate the gut microbiota to improve human health. Various diets—such as the Mediterranean diet, high-fiber diets (rich in fruits, vegetables, and whole grains), ketogenic diets, and gluten-free diets—have been linked to specific gut microbiome compositions.

These dietary interventions can reduce inflammation, improve insulin sensitivity, promote weight loss, enhance cognitive function, and boost immunity. They may also help manage chronic diseases such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), Crohn's disease (CD), and Type 2 diabetes, and even improve the effectiveness of cancer treatments like immunotherapy and chemotherapy.

However, the effectiveness of these interventions depends on an individual's baseline physiological state and gut microbiome composition. While many studies suggest that diets can influence microbiome composition, the specific factors that predict microbiome responses remain unclear. Future research should focus on identifying diet-responsive microbiota profiles and accounting for recent dietary patterns to enhance the success of these interventions.⁵⁵

Functional Foods

Incorporating more functional foods into one's diet can help diversify and enrich the gut microbiome. A functional food can be a natural food or a food that contains one or more specific ingredients, which positively impact the health and well-being of the consumer. These components can be added, removed, or naturally enhanced or modified in the food to deliver health benefits.⁵⁶

One important category of functional foods is fermented foods, which are especially rich in probiotics. These foods are created through the activity of live microbial cultures, which can help diversify and support the gut microbiome. However, not all fermented foods contain live cultures by the time they are consumed. For example, sourdough bread and many commercial pickles lack live cultures after processing, while certain yogurts contain beneficial probiotics like *Lactobacillus bulgaricus* and *Streptococcus thermophilus*. Other fermented foods that may contain live cultures include kimchi, kombucha, sauerkraut, miso, pickles (if unpasteurized), and raw apple cider vinegar. It's important to note that not all these foods are proven probiotics.

Additionally, some unfermented foods, such as certain milks, juices, and nutrition bars, may have added microorganisms. However, whether these foods offer true probiotic benefits depends on factors such as microorganism levels, survival through digestion, and the specific strains involved.⁵⁷

⁵⁴ <https://doi.org/10.1016/j.bpg.2023.101828>

⁵⁵ <https://doi.org/10.20517/mrr.2023.80>

⁵⁶ <https://doi.org/10.1016/B978-0-12-384947-2.00340-8>

⁵⁷ <https://ods.od.nih.gov/factsheets/Probiotics-HealthProfessional/>

Future Trends

Technologies in the microbiome sector are advancing rapidly, with promising developments in personalized medicine, non-live microbiome-derived drugs, targeted phage therapy, and CRISPR-based gene editing.

Personalized Medicine

The microbiome is increasingly significant in personalized medicine, especially in oncology. The microbiome can serve as a diagnostic tool by aiding in the early detection of disease and the development of targeted therapies for several conditions, including inflammatory bowel disease and colorectal cancer.⁵⁸

Non-Live Microbiome-Derived Drugs

Non-living biotherapeutic products are an emerging class of drugs containing dead or inactivated microorganisms and are intended to treat or prevent disease.⁵⁹ An advantage of these products compared to live biotherapeutic products is their stability.

CRISPR in Microbiome Modulation

CRISPR is a powerful technology that offers transformative possibilities for editing bacterial genomes to optimize the microbiome. CRISPR stands for “clustered regularly interspaced short palindromic repeats”, and it is a gene editing tool that is able to target and cut specific DNA sequences. This allows scientists to change the genetic code in any organism.⁶⁰

In microbiome research, CRISPR is being tested to selectively eliminate harmful bacterial strains in patients while retaining beneficial ones. A recent breakthrough demonstrated the application of CRISPR technology to target certain strains of *E. Coli* in the gut, preserving the strains that contribute to health.⁶¹

CRISPR is being used to develop synthetic probiotics. Researchers are able to modify beneficial bacteria to create strains that perform enhanced functions or produce specific metabolites.⁶²

The Use of AI in Microbiome Research

Recent advancements in artificial intelligence (AI) and machine learning have revolutionized microbiome research by enabling the analysis of complex datasets. These tools are instrumental in uncovering relationships between genes and disease outcomes. By identifying microbiome-based biomarkers, AI facilitates the development of targeted therapeutics tailored to an individual’s unique microbiome composition. It is also used to determine the physical and chemical interactions between components of the microbiome.⁶³ AI in microbiome research holds immense potential for accelerating discoveries and translating them into real-world solutions.

⁵⁸ <https://doi.org/10.1016/j.mayocp.2017.10.004>

⁵⁹ <https://www.microbiometimes.com/non-living-microbiome-therapeutics-european-organisation-strives-to-bring-regulatory-challenges-for-these-drug-products-into-focus/>

⁶⁰ <https://www.synthego.com/learn/crispr#:~:text=CRISPR%20stands%20for%20Clustered%20Regularly,directed%20by%20a%20customizable%20guide>

⁶¹ <https://www.dtu.dk/english/newsarchive/2023/05/scientists-create-the-first-crispr-based-drug-candidate-targeting-the-microbiome>

⁶² <https://doi.org/10.35248/2329-8901.23.11.322>

⁶³ <https://www.nature.com/articles/s43705-022-00182-9>