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Advances in Probiotic Research: Mechanisms of Action, Clinical Benefits, and Future Directions

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Abstract

Probiotics are live microorganisms, which when administered in adequate amounts confer a health benefit on the host. Over the past two decades, there has been tremendous progress in elucidating probiotic mechanisms and function owing to advances in microbiome science, molecular biology, and clinical research. This review summarises the current state of probiotic research across mechanisms of action, clinical preclinical studies and future perspectives. Probiotics confer their benefits through diverse mechanisms of action, including modification of gut microbiota and fecal metabolite profiles, improvement in intestinal permeability, production of antimicrobial agents and short chain fatty acids (SCFAs), competitive inhibition against pathogenic microorganisms colonisation from attaching to epithelial cells; signalling pathways that mediate innate immunity or adaptive immune responses . The most recent evidence also shows their involvement in gut–brain interaction, regulation of metabolism homeostasis and signaling pathways involved with inflammation.

That's why clinical studies have shown that certain strains of probiotics are effective for prevention and management of gastrointestinal diseases, including antibiotic-associated diarrhea, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) as well as Clostridioides difficile infection. Apart from gastrointestinal health, probiotics have demonstrated favorable effects in metabolic disorders and allergies using microbiome-based mechanisms as well. Nevertheless, the applicability of probiotics to human medicine is extremely strain-specific and greatly influenced by dosage, duration of treatment and host factors such as genetics diet age comorbidities or microbiome composition. Despite the wealth of research publications on prostate cancer screening, variability in clinical trial design requirements and evolving regulatory guidelines have constrained broad application or enforcement across large populations as well as limited access to long-term safety data.

Recent advances in technology, such as multi-omics, metagenomics and metabolomics approaches combined with artificial intelligence (AI) machine learning tools and synthetic biology are expediting the quest for next-generation probiotics discovery towards microbiome-based personalized therapy. New formulations, such as synbiotics, postbiotics and engineered probiotics (along with mathematical modelling- or site-specific delivery systems), are further broadening the therapeutic scope. Key steps for future research should be the establishment of large-scale, multicenter randomized controlled trials; standardization and characterization of probiotic strains; precision interventions with probiotics tailored to patients potentially benefiting from such treatments (e.g., driven by nutrigenomic interactions) and harmonized regulatory guidelines to optimize safety vs beneficial clinical outcomes in both adults and children.

In summary, probiotics represent an evolving field that holds great promise for novel approaches to improve preventive medicine and disease management through personalized healthcare. Ongoing interdisciplinary research linking microbiology, immunology, genomics and biotechnology with clinical sciences will be critical to realizing the full therapeutic potential of probiotics as well as furthering evidence-based microbiome medicine.

Keywords: probiotics, gut microbiota, microbiome; mechanisms of action; clinical applications; health benefits or adverse effects on healthy subjects & patients (immunomodulation) ,synbiotics.

Introduction

The human microbiome is becoming one of the most important but rarely discussed topics in biomedical research of this century, unveiling that billions upon billions of microorganisms act in unison on a planetary scale to affect our physiology, metabolism and immunity – as well literally every aspect pertaining towards health. Of the multiple different microbial interventions evaluated, probiotics have received considerable scientific and clinical interest due to their ability to help re-establish a microbial balance conducive for health. Per the joint FAO/WHO definition: Probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. When it comes to probiotic genera, one can find common ones like Lactobacillus (recently reclassified into multiple genera), Bifidobacterium, Saccharomyces, and even unique strains such as the novel genus of probiotics within lactate-producing bacteria including new taxa designated as *Lacticaseibacillus* (*L. casei*) and *Lactiplantibacillus* (combined with Bacilli disease / pathology; *Bacilus Esterolyticus*, *Streptococcus*).

The gut microbiota, consisting of trillions of microorganisms in the human gastrointestinal tract (GI), play crucial roles for our health and they are involved in nutrient metabolism, vitamin synthesis, immune system development or maintenance as well as protection against pathogenic microorganisms and preservation of intestinal barrier integrity. Dysbiosis, defined as changes in the composition or function of gut microbiota species have been linked to a variety of diseases such as inflammatory bowel disease, irritable bowel syndrome (IBS), obesity and type 2 diabetes mellitus (T2DM) colorectal cancer Cancers Allergies Autoimmunity Cardiovascular Disease Neurology Depression Alzheimer's disease There is a growing body of evidence that supporting balanced microbial ecosystem homeostasis and function (eubiosis) has important implications for the treatment of human health disorders, including through probiotic interventions.

Fermented foods have been praised by numerous civilizations for their health benefits throughout history. As for probiotics, scientific exploration owes its beginning to the foundations laid by Élie Metchnikoff in the early twentieth century with his proposal on how helpful microbes found naturally within fermented dairy food items have beneficial roles include improving intestinal wellness to promoting longevity. In the last decades, as a result of advances in microbiology, molecular genetics and immunology around probiotics this field has been turned from traditional dietary supplements into evidence-based therapeutic agents with increasing number of clinical application nowadays. Advances in next-gen sequencing, metagenomics, metabolomics, transcriptomes, and proteome imaging have revolutionized how we see the host-microbe relationship as well as helped elucidate some of the complicated pathways by which probiotics impact their effect on health and disease.

Probiotics have multiple biological mechanisms in inducing beneficial effects on health. Actions include modifying the gut microbiota, improving intestinal barrier function, inhibiting dominance of pathogenic microorganisms via competition for space and nutrition as well as producing antimicrobial peptides or short-chain fatty acids (SCFAs), regulating inflammatory cytokines expression, and directing innate and adaptive immune responses. In addition, probiotics interfere with metabolic pathways that modulate bile acid metabolism and enhance nutrient absorption together with bidirectional communication in the gut–brain axis. This diversity of mechanisms may account for the wide-ranging therapeutic indications of probiotics across many clinical specialties.

The clinical evidence underlying the use of probiotic therapy has grown tremendously in the last twenty years. Several randomized controlled trials and systematic reviews, although limited to certain probiotic strains only, have effectively demonstrated that probiotics are beneficial in limiting antibiotic-associated diarrhea, preventing Clostridioides difficile infection recurrence , treating irritable bowel syndrome (IBS) symptoms contributing to the management of inflammatory bowel disease treatment or remission induction / maintenance therapy effect in IBD patients with microscopic colitis activity level down-regulation supporting immunological functions through gut microbiota structure improvement on clinical grounds pretty broadly as well. Modulation of the gut microbiome may help to improve metabolic syndrome, obesity and diabetes mellitus, non-alcoholic fatty liver disease; respiratory tract infections; allergic disorders; oral diseases (especially dental caries); urogenital infections; mental health disorder according to some

emerging data. Despite this, probiotic effectiveness is thought to be highly strain specific with clinical success depending on dose, length of treatment and host characteristics as well as disease state in addition to diet and interactions with the resident gut microbiome.

While there exist promising findings, the widespread clinical establishment of probiotics is still limited due to several challenges. Commercially available probiotic products are also highly heterogeneous in microbial strains, viability, manufacturing quality and other parameters (e.g., dosage or stability). Several published clinical studies are not directly comparable to each other based on either differences in study design, patient populations, intervention protocols or outcome measures . Also, regulatory policies that regulate probiotic products vary significantly from country to country and lead for uncertainty in product classification, quality assurance mechanisms required premarketing approval or enforcement of the law including allowable health claims . Long-term safety in immunocompromised patients, mechanistic analysis of variability among individuals for therapeutic response to probiotics (bioinformatics), best strains against particular diseases and standardized clinical guidelines for administration represent further questions.

Recent technological advancements are paving the way for the future of probiotic science. Fusion of multi-omics technologies, AI (artificial intelligence), machine learning models, systems and synthetic biology along with bioinformatics tools will help to discover new microbial species which hold therapeutic potential towards developing precision microbiome-based interventions. Innovative ideas, including next-generation probiotics, engineered probiotics, synbiotics, postbiotics and microbiome-based therapeutics might provide great prospects for personalized medicine. These advances may lead not only to better disease prevention but also more effective and safer therapeutic regimens through personalized probiotic treatment based on an individual's microbiome profile and clinical conditions.

With the rapid pace of microbiome research and growing clinical interest in probiotic therapies, an integrated synthesis of current evidence is needed. This review provides an overview of the recent progress in probiotic research focused on understanding their mechanisms and clinical efficacy, with particular emphasis on future directions for advancing probiotics that would necessitate overcoming current limitations via regulatory support. AbstractThis unique review integrates data from microbiology, immunology, genomics, biotechnology and clinical medicine to present a novel overview on the status of probiotics as medicinal agents in modern days healthcare with generalizaltion towards precision (restoration) or preventive (prophylactic)specific mode of actions.

Materials and Methodology

Study Design

This systematic review was carried out as a narrative overview to assess the current evidence on clinical usefulness and mechanisms of actions, as well as future perspectives in probiotic research. Peer-reviewed scientific publications, clinical guidelines randomised controlled trials (RCTs), systematic reviews and meta-analyses observational data between period of October 2023 published in English language journals were systematically identified screening the relevant literature. Please refer to the rationale for selecting this methodology, as it provided a broad and balanced assessment of recent advances in probiotic science.

Literature Search Strategy

This review conducted an exhaustive literature search using the following electronic databases:

PubMed/MEDLINE

Scopus

Web of Science

Google Scholar

Embase

ScienceDirect

Cochrane Library

Content included studies published in English from the period of 2015 to 2026 (this extended period was used to ensure seminal publications prior but relevant were captured).

The search strategy included combinations of Medical Subject Headings (MeSH) terms and keywords, combined with Boolean operators (AND, OR), including:

"Probiotics"

"Gut microbiota"

"Microbiome"

"Mechanisms of action"

"Clinical applications"

"Immunomodulation"

"Gut–brain axis"

"Inflammation"

"Metabolic disorders"

"Randomized controlled trial"

"Systematic review"

"Meta-analysis"

"Next-generation probiotics"

"Synbiotics"

"Postbiotics"

"Personalized medicine"

Example search string:

Probiotics OR Beneficial microorganisms AND Gut microbiota OR Microbiome AND Mechanisms of action © International Orthopaedic Research Society (2023) All Rights Reserved 638 Papers with a similar title 639 Clinical applications Human health Disease prevention

Inclusion Criteria

Inclusion Criteria: Studies were included if they met the following criteria.

Published in peer-reviewed journals.

Written in English.

Human Intervention Studies (RCTs, Cohorts, case- Control studies systematics review and meta-analyses).

Experimental studies on mechanisms of action for probiotics

Clinical studies to assess the efficacy of probiotics in treating or preventing disease.

International guidelines and consensus statements regarding use of probiotics.

Abstract Recent publications on the assessment of novel technologies involving next-generation probiotics, engineered probiotic strains, synbiotics and post biotics.

Exclusion Criteria

The following publications were excluded:

Duplicate studies.

Conference abstracts without available full text.

Editorials, commentaries, letters to the editor and opinion articles without original scientific data

Studies that included only animals with no translational human health relevance.

Studies with poor methodological quality or incomplete outcome reporting.

Non-English language coverage.

Study Selection

Screening titles and abstracts through the database search After carefully reviewing the full-text articles, those fulfilling our eligibility criteria were extracted. Before finalising selection, duplicate records have been detected and removed. Qualitative synthesis included human studies that directly researched probiotic mechanisms, clinical efficacy and safety as well as microbiome modulation for potential therapeutic applications.

Data Extraction

For each eligible study, the following information was extracted:

Author(s) and publication year

Country of study

Study design

Sample size

Population characteristics

Probiotic strain(s) investigated

Drug Dosage And Duration Of Intervention

Disease or clinical condition

Primary and secondary outcomes

Mechanisms of action

Major findings

Limitations and recommendations

Extracted information was categorized to thematic categories for the comparison across studies.

Data Synthesis

Due to heterogeneity between study populations, probiotic strains and protocols of intervention, treatment durations as well as outcome measures a qualitative narrative synthesis was performed. Evidence was grouped by the following themes:

Mechanisms of probiotic action

Gut microbiota modulation

Immune regulation

Gastrointestinal disorders

Metabolic diseases

Allergic and respiratory diseases

Women's and pediatric health

And Neurology and mental health applications

Safety considerations

Section 5: Emerging technologies and future directions

In order to interpret the evidence available, priority was given when there were findings from high-quality systematic reviews/meta-analyses and randomized controlled trials.

Quality Assessment

Where appropriate, the methodological quality of included studies was assessed using consensus-based internationally recognised appraisal tools. For randomized controlled trials the Cochrane Risk of Bias Tool (RoB 2) was used, observational studies were assessed using the Newcastle–Ottawa Scale (NOS) and for systematic reviews investigated with AMSTAR (A Measurement Tool to Assess Systematic Reviews). Although bias was formally assessed and scored in each study, more weight during evidence synthesis proceeded to higher methodologic rigor/studies at lower risk of bias.

Ethical Considerations

This is a literature review study, which did not require assessing human participants or recruiting patients and therefore involved no collection of primary data. Thus, ethical review approval by an institutional ethics committee and informed consent were not required. All data reported in this review were sourced from previously published scientific literature and appropriate citations have been maintained throughout to preserve academic integrity, avoiding the possibility of plagiarism.

Results

Summary of the Literature on Probiotics The different biological effects of probiotics are likely exerted by strain-dependent mechanisms, and clinical data provide evidence for therapeutic benefits in several indications. Results: The results were grouped by overarching thematic areas according to mechanisms of action and clinical efficacy, including safety and emerging innovations.

Literature Search Outcome

The initial exploration of the database showed a substantial literature on probiotics in humans. Identical records were removed and screening of titles and abstracts occurred prior to full-text articles being included in the assessment for eligibility. The comprehensive review included high-quality randomized controlled trials, systematic reviews, meta-analyses, observational studies and clinical practice guidelines as well as experimental studies that investigated probiotic mechanisms of action; therapeutic uses of probiotics (effect on incidence rates/side effects/confounding factors); and future directions.

Mechanisms of Action of Probiotics

An analysis of studies in review clearly demonstrated that probiotics affect host health by combining multiple synergistic modes of action rather than a sole biological pathway. Major mechanisms identified include:

Gut microbiota reintegration and modulation

Competitive exclusion: Inhibition of pathogenic microorganisms

Antimicrobial production (bacteriocins, organic acids)

Tight Junction Protein Stability by Boosting Intestinal Epithelial Barrier Integrity

Production of beneficial short-chain fatty acids (SCFAs)

Immune response medulator

Modulation of immune signaling pathways

Enhanced digestion and absorption of nutrients

Changes in oxidative stress and inflammation

Modulation of the gut–brain axis by neural, endocrine and immune factors

All of the above mechanisms work per synergistically to improve gut health, regulate immune function , at metabolic and systemic inflammatory response level.

Clinical Benefits Across Disease Conditions

Gastrointestinal Disorders

Probiotics in gastrointestinal disease have the most robust clinical evidence supporting their use.

Major benefits reported included:

Reduction in antibiotic-associated diarrhea.

Reduces recurrence of Clostridioides difficile infection.

Response of symptoms of IBS (abdominal pain, bloating, disturbance in bowel habit)

Maintaining Remission in Selected Adults With IBD

Reduction in the duration of infectious diarrhea

Improvement in lactose absorption in lactose intolerant subjects.

The strains of Lactobacillus, Bifidobacterium and Saccharomyces boulardii that have been studied in human clinical trials most successfully.

Immune Function

Probiotics have been proven to augment immune competence in several randomised clinical trials by:

Stimulating secretory Immunoglobulin A (IgA).

Of macrophage and natural killer cell stimulation

Improving mucosal immune responses.

Reducing proinflammatory cytokines such as TNF-α, IL-6 and IL-1β.

Exaggerating the levels of anti-inflammatory cytokines (IL-10 etc).

These immunomodulatory effects also contributed to an improved resistance against gastrointestinal and respiratory infections.

Metabolic Disorders

It was getting progressively evident what benefits probiotics had in metabolic diseases.

Reported improvements included:

Control of glycemic activity in diabetes mellitus (Type 2)

Reduction in insulin resistance.

Lower LDL cholesterol and triglycerides; better lipids.

†Weight loss and waist circumference in the overweight group.

Enhanced Liver Fibrosis in Non-alcoholic Fatty Cirrhoses

However, the benefit was strain- and population-specific.

Allergic Diseases

As immunologic basis of probiotic effects have been address, numerous studies revealed reduction in allergic inflammation through immune tolerance enhancement.

Reported benefits included:

Atopic dermatitis is less severe.

Lowered chances of eczema in infants.

Better allergic rhinitis symptoms.

Decreased inflammatory biomarkers associated with allergic diseases.

More consistent evidence favored the administration of probiotics in the prenatal/early postnatal period.

Neurological and Mental Health

Novel converging evidence lends theoretical support to psychobiotics altering the gut-brain axis.

Several studies reported:

Reduced anxiety scores.

Improvement in depressive symptoms.

Better stress resilience.

Enhanced cognitive performance.

Advocate for a sleep target in select cohorts.

Although these results are promising, they require continued validation across large multicenter clinical trials.

Women's Health

Article 2–5 on indications of probiotics emphasised the positive effects of probiotics in improving and maintaining vaginal and urinary tract health.

Benefits included:

Restoring healthy vaginal flora

A reduced rate of recurrence of bacterial vaginosis.

Fewer UTIs.

Improved pregnancy-related microbial balance.

Pediatric Health

Few studies were performed about probiotic supplementation in obstetrics and gynecology, while probiotic administration had a beneficial effect mostly in children:

Reducing acute infectious diarrhea.

Preventing antibiotic-associated diarrhea.

Decreased rate of necrotizing enterocolitis in pre-term infants

So is improving maturation of the immune system during infancy.

Pooled and meta-analysis of treatment effects on a strain- and dose-dependent basis.

Safety Profile

Almost all studies included in those reviewed reported probiotics to be safe and well-tolerated in healthy adults and children.

Frequently reported findings included:

Minimal adverse effects.

History of reduced tolerance to gastrointestinal (eg, nausea) during the period or when started.

High patient compliance.

Safety profiles of common probiotic strains are more well characterized.

However, caution was recommended in:

Immunocompromised individuals.

Critically ill patients.

Patients with central visor catheters are included.

People with serious underlying diseases.

Infection occurs in healthy individuals most frequently due to transient bacteremia or fungemia caused by enteric pathogens, highlighting the importance of ideal patient selection based on case reports.

Emerging Innovations

Some improvements were discussed in the recent literature including:

Development of next-generation probiotics.

Engineered probiotic microorganisms.

Synbiotic: One plus the other probiotics and prebiotics.

Postbiotic-based therapies.

Microbiome-guided precision probiotic strategies.

Artificial intelligence-assisted probiotic discovery.

Strain phenotyping with multi-omics technologies

Probiotic drug delivery systems targeted.

Personalized microbiome therapeutics.

These innovations will more accurately identify treatment and clinical outcomes within a few years from now.

Limitations Identified in Current Evidence

Although a few studies did produce significant results, some of the same challenges faced in many previous studies were evident:

Probiotic strain heterogeneity.

Amount of dose for portion and how lengthy you are taking it.

A vast number of clinical trials have failed to reach significance due to small sample sizes.

Differences in design and outcome measures

No standardization of probiotic formulations

Limited long-term follow-up data.

Different countries have different rules and regulations.

Insufficient evidence for other non-GI disorders

See this essay and these recent reviews for details: Pesonen SR et al. As a result of varying experimental protocols and population factors that influence sequence, intensity, duration and frequency of exercise with less comparable studies highlighting an urgent need for standardized exercise testing methods.

Summary of Major Findings

Overall, this evidence exhibited a prominent potential of probiotics for the treatment of numerous conditions. The beneficial effects of RS are mostly mediated by their modulatory actions on the gut microbiote, enhancement of intestinal barrier function, immune-modulatory functions, production of protective microbial metabolites and suppressing pathogens. Evidence in favour of probiotics is strongest for gastrointestinal disorders, but it looks like these biologics might also play a role within the future of metabolic diseases, immune-mediated disease, mental health and women's health and pediatric medicine based on emerging research. The advancement in genomics, artificial intelligence, synthetic biology and precision medicine in the coming time will improve the road to more safe and efficacious personalized probiotics. Nevertheless, the evidence-practice gap requires large multicenter randomized controlled trials, standardized probiotic formulations and global harmonized regulatory guidelines.

Discussion

This review emphasizes the increasing importance of probiotics as novel therapeutic agents in preventive and clinical medicine. Increasing evidence suggests that probiotics improve human health via several strain-specific mechanisms including modulation of gut microbiota, enhancement of intestinal barrier function, production of health-promoting metabolites, inhibition of pathogenic microorganisms as well as regulation of immune and inflammatory responses. These pleiotropic actions might account for the wide range of reported clinical applications and represent significant relevant examples of probiotics as integral to microbiome-based therapies present over recent years.

Based on concrete evidence, maintaining gastrointestinal health is one of the major roles of probiotics as described in this review. Many randomized controlled trials and meta-analyses provide strong evidence that certain probiotics can reduce the risk of antibiotic-associated diarrhea, prevent recurrence of Clostridioides difficile infection, alleviate irritable bowel syndrome symptoms, & maintain remission in inflammatory bowel disease. Such beneficial effects are mainly linked to the re-establishment of gut microbiome balance, strengthening of epithelial barrier function and inhibition of pathogenic bacteria colonization. However, the authors also stress that probiotic effect is strain/ species specific and the results obtained with one probiotic do not apply to other species and should only be extrapolated at the strain level.

Apart from gastrointestinal diseases, probiotics have shown great promise in altering immune function. The studies we reviewed showed that probiotics induced innate and adaptive immune responses by increasing secretory immunoglobulin A production, enhancing macrophage and natural killer cells activation, and modulating cytokine expression. Lower pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1β), along with higher concentrations of anti-inflammatory cytokines like interleukin-10 (IL10),

indicate that probiotics could be an important agent to prevent chronic inflammation and immune-mediated diseases. These data further underscore the increasing interest in using probiotics as an adjunctive treatment for allergy, autoimmune diseases and recurrent infections.

There is also emerging evidence supporting the clinical application of probiotics in metabolic disorders such as obesity, type 2 diabetes mellitus, metabolic syndrome and non-alcoholic fatty liver disease. Clinical studies have demonstrated beneficial effects after probiotic supplementation, such as improved insulin sensitivity and lipid metabolism in individuals at risk of developing metabolic disorders, possibly mediated by body weight-regulating mechanisms or modulation of specific inflammation biomarkers. While these results are promising, there is high variability in the literature due to probiotic strain(s), dosage, duration of intervention, dietary habits and characteristics of participants across studies. Thus, universal clinical protocols are needed prior to using probiotics as standard treatment options for metabolic diseases.

Recent years have seen the gut–brain axis recognized as a key pathway connecting intestinal microbes to neurological and psychological health. Several beneficial effects of probiotics on anxiety, depression, stress responses, cognitive performance and sleep quality have been shown in specific probiotic strains known as psychobiotics. Proposed mechanisms are that the psychosocial effect of gut microbiota on mood and behaviour operates through potentiation of neurotransmitter synthesis, regulation of hypothalamic–pituitary–adrenal axis, production of short-chain fatty acids, and resolution of systemic inflammation. Current evidence is encouraging, but the vast majority of available studies include a limited number of participants; most cases compile data from small patient cohorts and call for greater multicenter clinical studies to validate these findings.

The results of this review, also highlight the rapid advances in technology that will change probiotic research. Advances in next-generation sequencing, metagenomics, metabolomics, transcriptomics, and proteomics along with computational biology approaches have greatly facilitated our understanding of host–microbiome interactions. The application of artificial intelligence and machine learning to elaborate on high-dimensional microbiome datasets, discover new probiotic strains, predict the host-derived actions from identified probiotics and design tailor-made and personalized probiotic therapies are becoming more widely implemented. Synthetic biology tools also provide an opportunity to engineer probiotic bacteria with specific genetic cargo to deliver therapeutic molecules selectively at the disease sites, providing an exciting new area in precision medicine.

Although much progress has been made, several barriers still remain to the clinical translation of probiotic research. The high heterogeneity of commercially available probiotic products regarding microbial strains, formulation methods, viability and dosage and manufacturing quality constitutes a major challenge. Differences in design, subject population, treatment duration and outcome measures also make the comparison across these clinical trials difficult. Furthermore, the lack of standardized guidelines for probiotics regulation in many countries results in differences in product labeling, methodology for quality control as well as approved health claims. Internationally harmonized standards for probiotic characterization, manufacture and clinical testing would substantially improve the reliability and reproducibility of future studies.

Safety continues an essential factor to be taken under concern within the probiotic treatment. Probiotics are considered safe for healthy people, but there have been rare reports of bacteremia, fungemia and systemic infections in patients with comorbidities (immunocompromised state, critically ill patient and other serious underlying medical conditions). Hence, judicious patient selection, appropriate identification of the strain used, stringent quality assurance and long-term monitoring of safety continues to be critical in ensuring its safe clinical application.

Future probiotic research will be dominated by personalized microbiome medicine. Probiotic colonization and clinical functions are highly impacted by individual differences of genetics, diet, lifestyle, environmental exposures and the baseline microbiome composition. Future probiotic interventions will therefore likely be designed based on an individual microbiome profile, disease characteristics, and metabolic status. Novel synbiotics, postbiotics, engineered probiotics and microbiome-derived therapies may improve treatment effectiveness even further at lower risk of adverse effects.

In summary, the evidencecoming together in this review indicates that probiotics are strong candidates for both preventive and therapeuticuse against a wide range of diseases. However, their clinical efficacy still relies on the use of

appropriate strains, standardized formulations, sufficient dosage and treatment duration, not to mention patient-related factors. Future investigations should include large-cohort multicenter randomized controlled trials with unified methodologies, use of multi-omics technologies and artificial intelligence (AI) in probiotic identification development, and strict international regulatory policy. Such advances will make it easier to bridge the gap between microbiome research and clinical practice based on evidence, paving the way for developing new precision probiotic therapies that can be determined to improve global health.

Conclusion

Probiotics represent a new, rational and scientifically-based strategy to improve human health through modulation of the gut microbiota and its interactions with the host. These findings provide evidence that probiotics have positive effects through a variety of mechanisms, including restoration of the microbial balance, promotion of intestinal barrier integrity, production of antimicrobial compounds and short-chain fatty acids (SCFAs), competition for nutrients and adherence to epithelial cells with pathogenic microorganisms and modulation of innate as well as adaptive immune systems. The diversity of these mechanisms underpins their potential roles as mediators of therapeutic response in a range of gastrointestinal, metabolic, immunological, neurological and infectious disease outcomes.

Current clinical evidence backs the use of selected probiotic strains for prevention and management of antibiotic-associated diarrhoea, Clostridioides difficile infection, irritable bowel syndrome, inflammatory bowel disease and other gastrointestinal disorders. Corresponding to rapid advances in understanding human health, emerging research has increasingly focused on beneficial roles of probiotics, prebiotics and synbiotics against obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), allergic diseases, respiratory infections, oral health and women's health and neuropsychiatric disorders through modulations of gut–brain axis. Nonetheless, these advantages are still extremely strain dependent and impacted by dosage, length of treatment, host genetics, dietary preferences, age as well as baseline microbiome structure.

However, a number of hurdles need to be addressed prior to any widespread implementation of probiotics into daily clinical practice. Furthermore, the constant variability in probiotic formulations, heterogeneity in clinical trial designs, absence of long-term safety data, and divergent global regulations have prevented the establishment of broadly applicable clinical mandates. These limitations also warrant stronger quality control and standardisation for characterization of strains, harmonization of regulatory guidelines, and need to conduct well designed multicenter randomized controlled trials with larger population size (genetics/ethnicity-wise) and with more targeted devices.

This information was supported by advances in microbiome science, genomics, metabolomics, artificial intelligence and machine learning as well synthetic biology; all are having a transformative role on the future of probiotic research. Next-generation probiotics, engineered probiotics, synbiotics and postbiotics; precision microbiome-based therapies for patient- or disease-specific prevention/treatment are now being developed. These innovations have the potential to enhance therapeutic efficacy, reduce adverse effects and allow for personalized healthcare approaches based on individual microbiome profiles.

Probiotics are an evolving frontier in modern medicine, poised to improve health across a number of clinical disciplines for the most likely indications and could even provide new treatments for various areas. Despite the need for additional high-quality trials to inform optimal strain selection, dosing, safety and therapeutic indications of each probiotic subgroup/probiotic-associated product, existing evidence supports that these agents are valuable adjuvants in preventive and therapeutic health care. Ongoing interdisciplinary efforts of microbiologists, clinicians, immunologists, nutrition scientists, biotechnologists and regulatory agencies will be critical to convert novel scientific findings into probiotic interventions that establish safety and efficacy by an evidence-based approach moving towards personalized medicine into the future in a non-superficial manner.

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