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A Brief Overview on Probiotics: The Health Friendly Microbes

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Probiotics are defined as non-pathogenic live microorganisms that, when administered in adequate amounts, confer health benefits on the host. Association of probiotics with human beings has a lot of history. Well known as 'health-friendly bacteria', they are widely used commercially as a functional food. The popularity of probiotics has gone exponentially high due to an increasing number of clinical trials, supporting their beneficial effects. Several in vivo and in-vitro experimental evidence supports strain-specific and disease-specific probiotic efficacy to prevent and ameliorate antibiotic-associated diarrhoea, traveller's diarrhoea, ulcerative colitis, and many more. Besides, numerous recent studies have reported that probiotics could have a significant effect in alleviating various metabolic, lifestyle and diet-related disorders like obesity, type 2 diabetes, metabolic syndrome, irritable bowel syndrome Strains of Bifidobacterium, Lactobacillus and Saccharomyces boulardii are the most commonly used as probiotics. Safety, efficacy, pathogenicity, infectivity, intrinsic property, virulence factors are to be addressed during probiotic selection. The underlying mechanisms of probiotics effects are still not fully elucidated and have been under intensive research. Numerous diverse, strain-specific probiotic mechanisms have been proposed, which include early colonization of perturbed microbes, competitive exclusion of pathogens, short-chain volatile fatty acid production, alteration of gut pH, immunomodulation and many more. Considering the remarkable influence on human health, probiotics seem to be alluring attractive agents to promote human health conditions and to improve the quality of life against several diseases. This review discusses the current documentation and recent advances on probiotics and their possible health attributes, in scientific literature, focusing on diverse, heterogeneous, and strain-specific mechanisms of action. Randomised human controlled clinical trials are needed to reconfirm its safety and beneficial effects.

Keywords: Bifidobacteria; Health; Lactobacillus; Microorganism; Probiotics; Saccharomyces.

Human beings are a natural habitat for a large, complex, dynamic microbial ecosystem. Bacterial colonization of the gut begins in early life, which imitates that of its mother[1]. In healthy adults, gut microbiota show higher complexity and diversity. Diet, genome, the lifestyle of host, use of antibiotics and ageing process may influence microbiota composition.[2] These microbes form a population density gradient ranging from about 10^2 /ml in the stomach to about 10^{11} - 10^{12} /ml in the colon.[3] Gut microbiota can accomplish metabolic (ferment non-digestible dietary residues) as well as protective function (via immunomodulation).[4,5] Alteration in microbiome diversity (dysbiosis)

and composition are studied to be related to chronic diseases like obesity, type 2 diabetes mellitus, oxidative stress-related diseases, non-alcoholic fatty liver disease, cardiovascular disease and immune-mediated diseases.[6,7] Due to the emergence of bacterial resistance against antibiotics, the therapeutic use of medicines would provide limited efficacy. In this regard, probiotics and their relationship with human health have been an area of interest in recent years. Probiotics can be defined as non-pathogenic live microorganisms that exert health benefits to host upon ingestion. Probiotics exhibit this unique ability to promote human health by s colonization and normalization of a perturbed intestinal microbial community. Moreover, they should be able to express their activities against pathogens and should be able to stimulate the immune system.[8] They are being implicated clinically as co-adjuvants for the elite properties like anti-diabetic, anti-obesity, anti-inflammatory, anti-angiogenic activities.[9,10] Most of the probiotics are available commercially as foodstuff or drugs containing live microbes. Therefore, consideration of the safety assessment of probiotics is of utmost importance before use.[11] Looking at the long list of health benefits, it may be considered as a biotherapeutic agent. A comprehensive review of the relevant literature was performed to reiterate the factual findings. Present review article provides a current understanding of different aspects of probiotics, highlighting the historical prospectus, compliance to the global scientific definition, criteria for safety selection, brief mechanism of action, and its role towards human health. This may result in establishing validation of probiotic therapies in application to human beings.

Origin and Historical perspectives

Etymologically, the term "Probiotic" comes from the Greek word "pro-bios" which means "for life". It has long been integral since ancient times when fermented products had been used for nutritional and therapeutic purposes. A century ago, the journey of probiotics was started when scientist Henry Tessler (1899), Pasteur Institute of Paris, discovered *Bifidobacterium* in the intestine of breastfed infants and found it useful for diarrhoeal episodes in those infants.[12]

However, Nobel laureate Russian scientist Elie Metchnikoff (1907), first introduced the hypothesis of using microorganisms for health benefit by replacement of gut flora with useful ones.[13] In the early 1930s, Shirota reported the survival of intestinal bacteria through the gut passage. He developed fermented milk containing *Lactobacillus acidophilus* Shirota, which is still popular today as Yakult.[14] Lilly and Stillwell (1965) then first introduced the term "Probiotic" to describe a substance which stimulates the growth of other micro-organisms.[15] Next supporting evidence came from Parker (1974), who gave a new definition to probiotics as 'microorganism and substances responsible for intestinal microbial homeostasis.[16] Following which, many scientists widened the definition of probiotics, including health benefits of the host.[17,18,19] Subsequently, Food and agricultural organization of United Nations and World Health Organisation [FAO/WHO,2002], explained probiotics as "live micro-organisms which when administered in adequate amounts, confer health to the host".[20] This recommended definition and guidelines have been popularly adopted and proven to be useful to researchers. Since then, research in the field of probiotics has grown exponentially high, and it has been strengthened considerably to understand the role of a wide range of probiotics in enhancing or preventing chronic diseases.

Microbial species as probiotics

Contemporary probiotics research aims at the characterization and composition of gut microbiota, which functions as a microbial ecosystem. It is worth mentioning here that probiotic effects are strain specific. So health claim is distinctive for each probiotic strain, and probiotic prospective of bacterial strains varies significantly within the same species.[21,22] That is why strain identification is recommended to characterize the functions of each probiotic to the specific strain. This could be achieved by genetic recognition using molecular approaches like DNA-DNA hybridization, 16SRNA sequencing, and pulsed-field gel electrophoresis for strain typing.[23,24] That apart polymerase chain reaction(PCR) method can come up with fast quantitative and qualitative information on the constitution of the intestinal microbiome.[25] It is also reported that several probiotic products contain more than one strain. A single strain may exhibit different benefits when used individually and in combination.[26,27]

Every individual is bestowed with exclusive gut microbiota that take part in distinctive functions like nutrient metabolism, continuance of structural coherence of gut mucosal barrier, and immunomodulation. Traditionally, the term probiotics are more related to most popular strains of Lactobacillus and Bifidobacterium (Table-1), but it can be extended to other microorganisms like Streptococcus, Saccharomyces (yeast strain), Enterococcus and Bacillus.[28,29,30] Many of these probiotics strains have been preferred based on selection criteria.[31]

Some bacterias that do not normally colonize the intestinal tract, may also come under the category of probiotics that include *Lactobacillus bulgaricus, streptococcus thermophilus*, and *Leuconostoc* species. Neither these bacterias colonize nor exert any significant effect on intestinal microbial balance.[32] But they do play an important role in the food industry. There are several studies in progress to recognize the futuristic genre and new strains for probable use as probiotics. These new strains need to be appraised and analyzed based on accepted and confirmed selection criteria before implication.

Requisites for selection of safe and effective probiotics

Eighteen years before, scientific definition of probiotics was conceived, along with the guidelines warranting pertinent use of them. The aim of administering live microbes can assist therapeutic function is achieving precedence. Most of the probiotics are promoted as foodstuff or drugs (tablets, powder, and other formulations) containing live microbes. The variety of food products accommodating probiotic strain is wide such as fermented milk, cheese, ice cream, buttermilk, milk powder, yogurt, and many more. The viability and feasibility of probiotics is a fundamental parameter for developing probiotic food, as probiotics are certainly very fragile to many environmental burdens such as acidity, oxygen, heat, etc.[33] Probiotic food products are widened worldwide due to never ending steady generation of research confirmations, indicating their likely health benefits to consumers. Consideration of safety of probiotics and compatibility of the product with the microbes are very important because of the frequent isolation of widely used bacteria (Table-1) from clinical infection sites. This has raised debate over their infectiveness and safety. However, it is unlikely that they require generalized infectivity as their separation is the result of opportunistic infection, which might be caused by chronic diseases, skin injury, cancer, or drug induced abnormality.[34] Practically, *lactobacillus* and *Bifidobacterium* are an infrequent cause of infection to humans. This lack of pathogenicity perpetuates all age groups and also to the immunosuppressed individual.[35] Assessment of the safety of probiotics from various angles is not a simple task. However, it is relatively easy for an in vitro study of several factors. Several such studies in animal and human beings have been proposed to assess the safety standards of probiotics by studying on an intrinsic property of the strain, the pharmacokinetics of the strain (survival, activity in intestine, faecal and mucosal recovery) and interaction between strain and host.[36] But the values of these parameters are under debate due to discrepancies and lack of standardization of operating procedures.So,the best-proposed approach should be the target population and function-specific studies. Although, many probiotic strains are well described as safe, risk-free and reports of harmful effects to the host are rare, the following factors need to be evaluated to assess its safety and effectiveness:

1. Identified genetically at genus, species and strain level [whole genome strain characterisation][37]
2. Non-pathogenic, non-infective.[38,39,40]
3. Should not carry transferable antibiotic resistance gene.[41]
4. Non toxic [no formation of any harmful substances like ammonia, indole, phenol, amines][42]
5. Able to survive in adequate number during intestinal transit [acid, bile tolerant][43]
6. Bile salt hydrolase activity [deconjugation of biliary salt, prevents carcinogenesis].[44,45]
7. Antimicrobial activity [able to adhere to the mucosal epithelium, able to colonize and competitive exclusion of pathogen][46]
8. Able to antagonize pathogenic bacteria [in vitro culture study depends on microbial cell mass, buffer component, fermentation span, and growth medium][47]
9. Stable and capable of remaining viable under storage condition [potentiates gut adherence, immunomodulation and can lower gut permeability][48]
10. Clinically documented and validated health

effects [strain to be tested in randomized controlled human trial][49]

11. Designated strain-specific for human use and animals[49]

That apart, several other determinants that must be described during the analysis of safety, are Platelet aggregation activity and mucus degradation activity. Harry et al. could isolate different strains of *L. Rhamnosus* from infective endocarditis, which is having higher activity than laboratory strains.[50] This suggests that they may have an infective property in contributing to the progression of endocarditis. Mucous degradation activity is because of the production of enzymes glycosidase and protease, which might break intestinal mucous glycoproteins, so causing infective endocarditis.[51] Ruserler et al. in his study lactobacillus and *bifidobacterium* did not find the efficacy of this proposed mechanism.[52] Therefore, it is critical to establish the infectivity related to the outer layer structure containing glycoproteins and lectins.

Mechanism of action of probiotics

Probiotics are safe microbes that confer beneficial effects to the host when administered in an adequate dose and at an appropriate period. The consequences of probiotics on host well-being have been communicated in many reports, articles, reviews, systematic meta-analysis, though many studies lack insight into the potential mechanism of action.[53,54,55] The underlying mechanism on why and how the bacterial strains work to achieve such effect, has been under intensive study. Numerous probiotic mechanisms have been proposed, which are diverse, heterogeneous, and strain-specific such as modulation of host defence, antagonist to pathogenic bacteria, and effect through microbial toxins.[56] After a thorough comprehensive search of relevant literature, elaborated mechanisms from in vivo and in vitro studies are given below:

1. Colonization and normalization of the perturbed intestinal microbes.[57]
2. Competitive exclusion of pathogens.[58]
3. Enzyme activity [beta galactosidase, beta glucuronidase].[59,60]
4. Production of bacteriocin, mucin and volatile fatty acid.[60]
5. Cell adhesion and cell antagonism.[61]
6. Modulation of immune system.[62]
7. Interaction of brain-gut axis.[63,64,65]

Currently, it is accepted that early colonization of probiotic strain and normalization of the perturbed intestinal microbial community is the key mechanism that confers health benefits to the host. Normally intestinal microflora exhibits colonization resistance or barrier effect, an indigenous mechanism to inhibit colonization of harmful enteric pathogen, which is attained by complex interactions among the bacterial community.[66,67] Adhesion of bacteria to host surfaces prevents mechanical clearing of pathogens. The anti-pathogenic activity of probiotics has been a topic of research as a wide variety of such compounds (bacteriocin, ethanol, organic acid, hydrogen peroxide, acetaldehyde, peptides, etc) are produced by them.[68] Some *lactobacillus* and *bifidobacterium* produce bacteriocin, which prevents proliferation by competitive exclusion of selected pathogen and can increases membrane permeability, that leads to depolarisation of membrane potential.[69] Enzymatic activity of probiotic specifically beta-glucuronidase hydrolyses glucuronidated metabolite in their toxic form, causing intestinal damage. More so it has been linked to an early pre-neoplasticism marker for colon carcinoma.[70] Agreeing with in vitro and in vivo study information, volatile fatty acids have been documented to have numerous biochemical, physiological and molecular effects. It is a useful source of energy for enterocytes and it acts as a key signalling molecule for maintenance of gut health.[25]

Evidence for probiotic effectiveness [in vivo & in vitro studies]

The association between lifestyle, diet, and well-being has increased the requirement for products, which can build up health beyond rendering basic nourishment. The conglomeration of probiotics on human health goes back to the long past when people were using fermented milk for their well-being.[71]The detailed review of literature by WHO/FAO illustrated a comparatively small number of areas in which probiotics have shown their positive effect, which will be presented below.

Probiotics for newborn and children

Intestinal infection in neonates is very frequent and is the leading cause of death in developing countries.[72] Necrotizing enterocolitis is a devastating intestinal condition, mostly seen in preterm infants, where intestinal microbiota will be dominated by many pathogens like Enterococcus faecalis, E.Coli, Staphylococcus epidermidis,

Klebsiella pneumonia etc.[73] However, the study has indicated a low incidence of the said condition if premature infants were given breast milk, which may allow non-pathogens like lactobacillus and bifidobacterium to organize within the premature intestine. Recent meta-analysis has identified the specific strain *Lactobacillus rhamnosus* GG ATCC53103 or combination of *Bifidobacterium infantis* Bb-02, *Bifidobacterium lactis* Bb-12, and *Streptococcus thermophilus* TH-4 in order to reduce necrotizing enterocolitis.[74] This suggests a correlation between the reduction in *Lactobacillus* and the increased risk of necrotizing enterocolitis. That apart, in a review on mucosal immunity starting at birth, Walker outlined a correlation between the normal intestinal microbiome, early intestinal colonisation, and subsequent defence from several disorders.[75] In another meta-analysis, the author briefly discussed the effect of probiotic and conventional oral rehydration therapy, which reduces the extent of acute diarrhoea in one day in the case of little ones under 5 years of age.[76] Cochrane review involving infant and children also reported beneficial effects of probiotics as the reduced duration of diarrhoea and diminished stool frequency.[77]

Probiotics for Antibiotic-associated diarrhoea and Traveller's diarrhoea

There is considerable evidence to encourage probiotic use in GIT illness like acute diarrhoeal disease and amelioration of antibiotic linked diarrhea.[78,79,80] Treatment and improvement of infectious diarrhoea are presumably the most comprehensively accepted health asset of probiotic microorganisms. Rotavirus is the commonest source, which replicates in the highly differentiated absorptive columnar cells of the small intestine. Evidence suggests the effectiveness of *L. Rhamnous, B.animalis, L. Casei Shirota* in diminishing the span of acute rotavirus infection by immunomodulation, competitive hindrance of receptor sites, and by yielding substances that inactivated viral particle.[81] Moreover Rotavirus protein NSP1 may be linked to inhibition of interferon production by stimulating the degradation of interferon regulatory factor.[82] Recent systematic review and meta-analysis explained the positive effect exerted by probiotics *Lactobacillus rhamnosus* GG in reducing the duration of acute rotavirus diarrhea.[83] Randomised control trial by Allen et al. to assess the probiotic efficacy in proven acute infectious diarrhoea showed the reduced mean duration of diarrhoea and reduced stool frequency after the intervention.[84] Several incidents of diarrhoea are the usual after-effects of antibiotic therapy. This is due to suppressing GI microflora that encourages overgrowth of opportunistic infections like clostridium difficile. A meta-analysis by Hempel et al have evaluated the evidence of probiotic administration in reducing the risk of the condition.[85] The majority of traveller's diarrhoea is triggered by bacteria E.Coli and rest by virus and Protozoa. The 2017 guidelines for prevention of traveller's diarrhoea [TD] by International society of travel medicine proposed inadequate affirmation to suggest the use of probiotics for treatment. A meta-analysis of randomised control trials by Jong-Myon Bae showed statistically significant efficacy in prevention of TD [86] Another study by Hilton et al on randomised American tourists with

Table 1. Commonly used probiotic microorganism

Lactobacillus	*Acidophilus, Plantarum, Crispatus Rhamnosus, Paracasei, Fermentum Reuteri, Johnsonii, Breves, Casei Delbrueckii gasseri, Salivarus Gallinarum, Crispatus, Bulgaricus*
Bifidobacterium	*Breve, Bifidum, Infantis, Longum Thermophilus, Animalis Adoloscentis*
Bacillus	*Sereus, coagulans, subtilisLactis, reuteri, rhamnosus Casei, acidophillus Cervisiae,*
Lactococcus	*boulardii Thermophilus, salivarius, sanguis Faecium SF 68, faecalis Acidilactici,*
Saccharomyces	*pentosaceus Uniformis Leuconostoc mesenteroides E.Coli strain Nissle Weissella cibaria,*
Streptococcus	*confusa Pediococcus acidilactici*
Enterococcus	
Pedicoccus	
Bacteroids	
Others	

an intake of a probiotic placebo showed a reduced daily risk of developing diarrhea.[87] Interpreting the details from several blinded, randomised, placebo-controlled trials, sazawal et al. established that the use of probiotics in antibiotic-associated diarrhoea decreases the probability of diarrhoea by 52%, traveller's diarrhoea by 8%.[88] Furthermore, numerous other study results have indicated contradictory findings owing to the difference in the study population and species of probiotic being used.[89,90]

Probiotics for Inflammatory Bowel Disease [IBD]

Ulcerative colitis and Chron's disease are the two important bowel diseases, where a change in normal intestinal flora has been associated with gut microbial genetic susceptibility and its ambience. Change in the normal intestinal flora and subsequent breaking in the uniformity between intestinal immune status and microbiome may lead to IBD.[91] It is worth mentioning here that Probiotics are progressively known for its potentiality to impede and handle intestinal disorders and enhance the immune system in both in vitro and animal model research. Several clinical review articles demonstrated the efficacy of probiotics in IBD.[92,93] Though the exact mechanism of action is not known, probiotics are thought to utilise their effect by modulating and harmonising intestinal flora and intestinal immune response.[93] Enteric bacteria may alter the balance of pro-inflammatory and anti-inflammatory cytokine levels (secreted by T helper cells-1 and T- helper cells-2 respectively) of the intestine that predisposes for intestinal disorders.[94] These two are important in maintaining the homeostasis of the immune system in the intestinal barrier. A preliminary study investigating the efficacy of probiotics suggests that a high dose of a combination of strains may alleviate symptoms of a disease, as compared to placebo.[95] This improvement in the severity of the disease might be due to a decrease in inflammation. But still, there are inadequate confirmations to conclude about the potency as there is the fear of opportunistic by modulating inflammatory status.[96] Several animal trials also conducted to investigate the effects of probiotics on IBD showing its anti colitis effects via downregulation of TNF-alpha, COX-2, and upregulating anti-inflammatory cytokines.[97,98,99] Although probiotic treatment improves the severity of disease by diminishing inflammation; it did not treat the source. So definitely more clinical trials of longer duration studies are required to understand safety, effectiveness and to prove sustainability of the positive results.

Probiotics for Hypercholesterolemia:[100,101,102,103]

Specific strains of Probiotic like *b.adolescentis* have been claimed to exhibit possible therapy for reducing cholesterol levels. The possible mechanisms include:

i. Bile salt hydrolase activity, which is considered by many scientists to be a prerequisite for the selection of probiotics.

ii. Deconjugation of bile salt in enterohepatic circulation that makes it less soluble, so can be excreted via feces. This mechanism exhibited by *Lactobacillus* has drawn attention

iii. The accumulation of cholesterol into bacterial cell membranes. *E.faceium* CRL183 strain has already been experimented to reduce lipid parameters, so it could prevent atherosclerosis development in rabbit with induced hypercholesterolemia[104]

Much work has already been accomplished using bile salt deconjugation by *Lactobacillus* to treat hypercholesterolemia.[105] Another study by Lye et al also reported experimental evidence of cholesterol-reducing property of *Lactobacillus*, where cholesterol was found to get converted into coprostanol with the help of cholesterol reductase produced by the probiotic strain.[106] Probiotics may also produce short-chain fatty acids, which can inhibit HMG CoA activity and subsequently can decrease the transformation of primary to secondary bile acid due to colonic acidification.[100, 107]

Probiotics for Cancer

In vivo and in vitro experimental data supported the anti-carcinogenic effect of probiotics, which may be attributed to pro-inflammatory, anti-inflammatory response.[33,108] *Lactobacillus*, *Bifidobacterium* and *E.Coli strain of Nissle* have shown antimutagenic activity in-vitro due to inactivation of the mutagenic compound.[109] Roller et al. in his animal study on rats could correlate inhibition of carcinogenesis with a change in immune activity on probiotic consumption.[110] Precise mechanism remains unclear due to a lack of human experimental evidence. The proposed

mode of action includes immunomodulation, production of antimutagenic substances, which alter the physicochemical and metabolic effect.[111]

Other health benefits of probiotics

Apart from these conventional beneficial effects, the role of probiotics in diabetes, inflammation, allergy, cardiovascular diseases, and neurodegenerative diseases has been a fascinating area of research. It has been reported that probiotics by improving mucosal barrier function, might help to protect against allergies.[112] They are found to have cardiovascular protection via antihypertensive action.[113] Accumulating pieces of evidence prove the beneficial dermal effects of probiotics such as a wound, scar healing, skin rejuvenation.[114,115] Many other effects include a reduction in body and abdominals mass,[116] lactose intolerance,[117] periodontal infections,[118,119] women's reproductive and bladder health[120, 121] and modulation of the gut-brain axis.[122, 123] Undoubtedly, the current research progress toward healthful effects has been encouraging.

Probiotic: hope or hype

Researchers and clinicians used probiotics in a variety of medical conditions, taking into account safety guidelines and scientific requirements. Different new technologies like microencapsulation, cell immobilisation have been developed to enhance its stability and viability in functional food. That apart, molecular technology is already being tried to manipulate *Lactobacillus* by replacing it with its active ingredient or metabolite to produce new improvised products, which are clinically proven safe. It is suggested that these new ways of handling gut microbe-host interaction offer hope for the therapeutic effects of probiotics. Consumption of probiotics as dietary supplements may potentiate health benefits as human gut microbiome functions like a microbial ecosystem to boost the immune system by preventing the growth of other pathogenic bacteria.[124] A scientific question arises here whether probiotics can modify dysbiosis or not. According to many recent scientific observations, the mode of the impact of probiotics on gut microbiome composition is not significant.[41, 44,47,48] Lerner et al. did an extensive study on several systemic reviews and meta-analysis and concluded that there are limited experimental design, precision, and incomplete reporting with variation in strain, which might lead to lack of safety and transparency in research design.[125] Safety is further complicated by the use of duplicate cultures of original strain by DNA fingerprinting technique which increases the risk of side effects.[125] The common systemic and intestinal side effects of probiotics consumption include Lactic acidosis, brain fogginess, hostile gene transfer, the introduction of specific bacteriophages, virulence factors, intestinal probiotic overgrowth, and many others.[126] Antibiotic resistance determinants question the safety issues, as it can be passed to resident gut bacterial by horizontal gene transfer, which in turn is responsible for opportunistic infection.[126, 127] Use of Polymerase chain reaction[PCR] technique and microarray analysis can detect acquired resistance. Nevertheless, more safety and toxicity-defined study is needed in the future to reveal the sombre side of probiotic use and to highlight the potential detrimental effects. Moreover, consideration of the risk-benefit ratio should be recommended before suggesting the use of probiotics.

CONCLUSION

Probiotics may be considered as a functional food as they provide health benefits beyond the traditional nutritional functions. Safe and health-friendly bacterial species come under the probiotics category. Association of probiotics with human beings has a long history. Probiotics have become increasingly popular as there is documented evidence of health benefits. The capability of probiotics to ameliorate different health aspects with utmost safety is the basis of the selection of probiotics. Safety assessment should be the screening tool to identify potential probiotics. *Lactobacillus* and *Bifidobacterium* genera are reported to be used widely as probiotic food supplements due to their therapeutic benefits. Recent research explorations suggest that probiotics can modify the composition and few metabolic activities of the microbiota. Probiotic clinical effects are still controversial, as several results obtained are heterogeneous. So, sustainability of the desired results is a matter of conflict. Despite the strong scientific evidence of various health benefits of probiotics, further intensive research with well-designed randomised clinical trials is needed to justify the safety and efficacy.

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