Nature's Medicine: Probiotics and Prebiotic

Rakhshinda Sadiq[1,*], Monazza Serwar[2], Anam Saleem[1], Naseema Bibi[1], Kainat Arzo[1], Saba Gul[1] and Kashmala Asghar[1]

[1]Women University Mardan, Faculty of Science, Department of Biotechnology, Mardan, Khyber Pakhtunkhwa, Pakistan
[2]Department of Chemistry, Faculty of Science, Women University Mardan, Mardan, Khyber Pakhtunkhwa, Pakistan
*Corresponding author: rakhshinda_sadiq@wumardan.edu.pk

Abstract

Numerous types of bacteria can be found in the human gastrointestinal tract. Despite being commensal, these bacteria evolve together with the host in a way that benefits both parties. A healthy intestinal microbiota is very important because it produces vital nutrients, inhibits bacterial infections, and boosts immunity. In order to attain, restore, and preserve a favorable balance in the ecosystem, the intestinal microbiota must be modified. Additionally, the activity of bacteria in the gastrointestinal tract is essential for the host's enhanced health. By adding prebiotics, probiotics, or symbiotics to the human diet, the microbiota in the intestines can be improved. These are present in foods including raw fruits and vegetables, fermented pickles, and dairy products. Other helpful sources could include pharmaceutical formulations and functional foods. This chapter reviews previous studies and gives a summary of what is currently known about how symbiotic, probiotics, and prebiotics affect human health. Along with an examination of the mechanisms underlying these substances' advantageous effects, it provides validated research data demonstrating their efficacy in human nutrition.

Keywords: Probiotics, Prebiotics, Symbiotics, Bacteria, Human Health

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Introduction

1.1 History, Definitions and Microorganisms uses as Probiotics

Elie Metchnikoff, a Russian scientist and professor at the Pasteur Institute, located in Paris, was the first to propose more than a century ago that lactic acid-producing microorganisms (Table 1) would provide health benefits that could enhance longevity (Anukam & Reid, 2007) .

According to his theory, "intestinal auto-intoxication" and the aging resulting from it could be prevented by modulating the bacteria that live in the digestive tract. and substituting saccharolytic microorganisms for proteolytic microbes, which break down proteins to produce harmful compounds like phenols, indoles, and ammonia (Mackowiak, 2013).

The German researcher Alfred Nissle identified a nonpathogenic strain of *Escherichia coli* from the feces of a First World War soldier who did not get enterocolitis during a severe outbreak of shigellosis in 1917, before to Sir Alexander Fleming's discovery of penicillin. Nissle 1917, the resulting strain of *Escherichia coli*, is a representation of a non-LAB probiotic (Wassenaar, 2016).

In order to treat infants with diarrhea, Henry Tissier (of the Pasteur Institute) separated a *Bifidobacterium* from a breastfed baby. He postulated that it might displace the diarrhea-causing proteolytic bacteria. Dr. Minoru Shirota identified the *Lacticaseibacillus paracasei* strain Shirota in Japan to combat diarrheal epidemics. Since 1935, a probiotic product containing this strain has been offered for sale (Ayivi et al., 2020).

Table 1: Definitions. Acknowledging these widely recognized definitions will result in uniformity in the words' usage on products and in scientific contexts. Although other terminology like para probiotic, immunobiotic, and ghost probiotics have appeared, use of them is discouraged since they lack precise, well-thought-out concepts and could cause confusion.

Concept	Definition
Probiotics	Live microorganisms that provide the host with health benefits when given in sufficient numbers (Hill et al., 2014).
Prebiotic	A substance that undergoes selective fermentation and produces certain alterations in the gut microbiota's composition and/or activity, which benefits the host's health (Gibson et al., 2017).
Synbiotic	A synbiotic relationship is a combination of organisms that are alive and substrate(s) that the host microorganisms selectively use to benefit the host. Synbiotic relationships can be either complementary (probiotic and prebiotic mixtures) or synergistic (live microbes chosen to use a co - administered substrate for the health effect) (Swanson et al., 2020).
Postbiotic	A mixture of inactive microorganisms and/or their constituents that benefits the host's health (Salminen et al., 2021).

These were early pioneers in a current thriving scientific sector. A review of PubMed's human clinical trials today reveals that more than 1500 probiotic experiments have been published. Despite the diversity of these studies in terms of the strains and populations they involve, the collection of available information supports the idea that benefits are quantifiable across a wide range of evaluated outcomes (Tremblay et al., 2021).

Probiotics are live bacteria that help the host's health when provided in appropriate doses (Hill et al., 2014). Historically, *Bifidobacterium* species and lactobacilli have been widely used probiotics. To better handle the diverse range of bacteria allocated to the genus, the genus *Lactobacillus* underwent a significant reorganization in 2020. Researchers have reorganized the genus *Lactobacillus* into 25 genera, which include 23 new species and the emended genus *Lactobacillus* (*L. delbrueckii* group and *Paralactobacillus*): *Acetilactobacillus, Agrilactobacillus, Amylolactobacillus, Apilactobacillus, Bombilactobacillus Companilactobacillus, Dellaglioa, Fructilactobacillus, Furfurilactobacillus, Holzapfelia, Lacticaseibacillus, Lactiplantibacillus, Lapidilactobacillus, Latilactobacillus, Lentilactobacillus, Levilactobacillus, Ligilactobacillus, Limosilactobacillus, Liquorilactobacillus, Loigolactobacilus, Paucilactobacillus, Schleiferilactobacillus*, and *Secundilactobacillus*. The species that tend to be more closely associated or based on similar physiological and metabolic characteristics are grouped together under the new Lactobacillus taxonomy classification. Consequently, this could help us understanding common processes that may regulate the health advantages of probiotics (El-Saadony et al., 2021).

Some species of *Bacillus*, *E. coli,* and the yeast *Saccharomyces boulardii* are also utilized. One of the newest probiotics is *Clostridium butyricum*, which the European Union just authorized as a novel food. LAB, which have been utilized for thousands of years to ferment food and preserve it (Table 2), may also have beneficial health effects.

The word "probiotic" should only be used to refer to living microorganisms that have been demonstrated to have positive health effects in carefully conducted human trials (Figure. 1). Around the world, fermentation is used to preserve a variety of unprocessed agricultural products, including cereals, roots, tubers, fruit, vegetables, milk, meat, and fish.

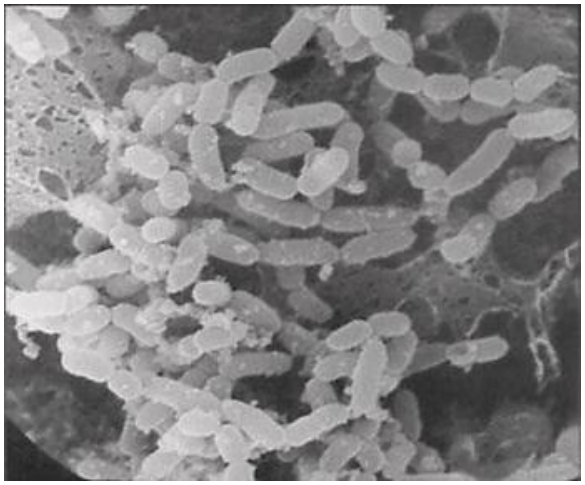

Fig. 1: An electron image showing Caco-2 cells adherent to *Ligilactobacillus salivarius* 118. (Reproduced from the journal via the Copyright Clearance Center; with consent from Blackwell Publishing Ltd.)

1.2 Prebiotics and Synbiotic

Compared to probiotics, the prebiotic idea was first put forth by Gibson and Roberfroid (1995). The main characteristics of a prebiotic are that it is not digested by the host and that it improves the resident beneficial microorganisms, which enhances the consumer's health.

Non starch polysaccharides and oligosaccharides are the most common prebiotics. Many fruits and vegetables, as well as breast milk, naturally contain prebiotics (Salvin, 2013). Additionally, they are added to infant food and other foods like grains, sweets, beverages and milk products. Prebiotic chemicals are usually oligosaccharides of different compositions (Roberfroid et al., 2010).

Initially, synbiotics were defined as suitable blends of probiotics and prebiotics. In more recent times, the notion of synbiotics has expanded to encompass both synergistic and complementary synbiotics. In short, a complementing synbiotic is a combination of probiotics and prebiotics that satisfy the requirements for each, such as accurate characterization, and are taken at a dosage that has been demonstrated to have positive health effects (Figure 2). On the other hand, a synergistic symbiotic is defined as a combination of a living microorganism chosen to use a jointly administered substrate, that, when combined, has a recognized health benefit. It is not necessary for the constituents of a synergistic symbiotic to individually satisfy the requirements for a probiotic or prebiotic.

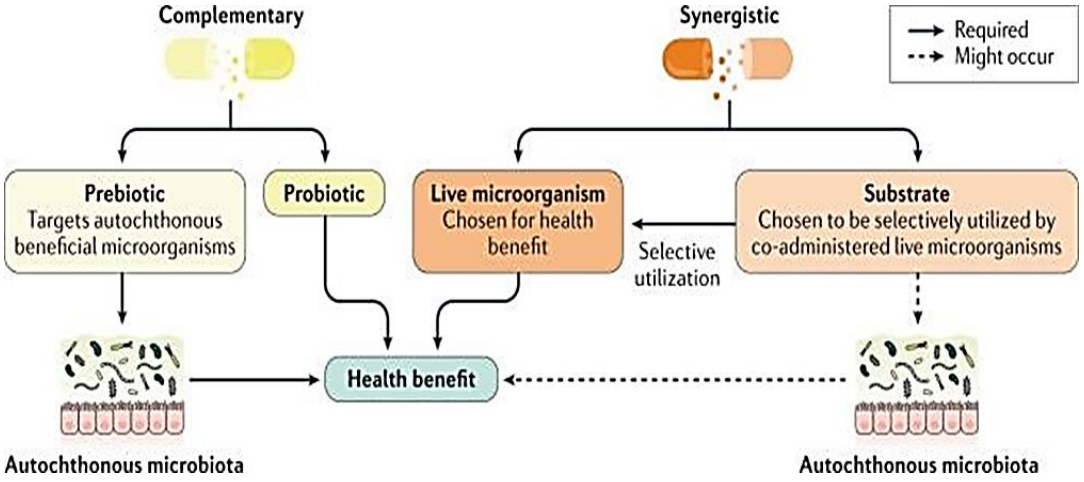

Fig. 2: A complementary synbiotic combines a prebiotic and a probiotic, which work independently to elicit one or more health benefits. The prebiotic functions by modulating the resident microbiota to elicit a health benefit. The synergistic synbiotic is composed of a substrate that is utilized by the co- administered live microorganism, enhancing its functionality. Components of synergistic synbiotics work together (not independently) to bring about the resulting health benefits. Swanson et al. (2020). CC BY 4.0. (Reproduced from the journal via the Copyright Clearance Center; with consent from Nature Portfolio Ltd.)

1.3 Genera, Species, and Strains used as Probiotics

Probiotic strains are identified using the accepted genera, species, and subspecies designations as well as numerical recognition (Table 3). The scientific community has no authority over trade names, product names, or strain designations. Newly identified probiotic strains can be found in a globally approved culture collection, as advised by the World Health Organization (WHO) and the Food and Agriculture Organization (Food and Agriculture Organization, 2006). These depositories will provide strains with another designation. A few commercial strain samples and their names are displayed in Table 2.

Table 2: Nomenclature used for probiotic microorganisms (Fabiano et al., 2021) ATCC, American Type Culture Collection (Manassas, Virginia, USA); CNCM, Collection Nationale de Cultures de Microorganismes (Institut Pasteur, Paris, France); NCIMB, National Collection of Industrial, Food and Marine Bacteria (Aberdeen, Scotland).

Genus	Species	Subsp.	Strain designation	International strain depository designation	Strain nickname	Product name
Lacticaseibacillus	*rhamnosus*	None	GG	ATCC 53103	LGG	Culturelle
Bifidobacterium	*animalis*	*lactis*	DN-173 010	CNCM I-2494	*Bifidus regularis*	Activia yogurt
Bifidobacterium	*longum*	*longum*	35624	NCIMB 41003	*Bifantis*	Align

Probiotic strain designations are significant because the most reliable method of evaluating probiotic data is relating the advantages (For example, the specific gastrointestinal problems this book discusses) with particular probiotic strains or combinations of strains at the right dosage.

Probiotic recommendations, particularly in a clinical context, need to link particular strains to the stated benefits derived from human research (Sanders et al., 2018) Certain strains will possess distinct characteristics that could explain specific antibacterial, neurological, and immunological effects (Hill et al., 2014). Recognizing that certain pathways of probiotic activity are probably shared by various strains, species, or even genera is a new idea in the field of probiotics. In terms of their capacity to promote colonization resistance, control intestinal transit, or restore disturbed microbiota, many probiotics may work similarly (Markowiak & Śliżewska, 2017). For instance, a key advantage shared by many probiotic strains may be the capacity to lower luminal pH in the colon or increase the production of short-chain fatty acids. Therefore, multiple methods may be used to offer some probiotic advantages (Simon et al., 2021).

Multiple strains are now frequently included in systematic reviews and meta-analyses in the probiotics sector. Such a strategy is appropriate if it can be demonstrated that the benefit under consideration results from a common course of action among all the strains taken into consideration. Otherwise, the primary focus of such efforts should be strain-specific evidence (McFarland et al., 2018).

1.4 Microbiological Colonization

The bacteria that live in the human gut are closely associated with the roles of prebiotics and probiotics for gastrointestinal endpoints. One important way to affect the host's health is through crosstalk between probiotics and resident bacteria or probiotics and host cells (Yoo et al., 2024).

The two bacterial genera *Firmicutes* and *Bacteroidetes* make up more than 90% of the microorganisms found in the human gut. The remaining bacteria include Fusobacteria, *Verrucomicrobia, Proteobacteria*, and *Actinobacteria* (Aggarwal et al., 2023).

Human gut symbiotic microbes have long been valued for the advantages they offer the host, including the provision of vital nutrients, the metabolism of indigestible substances, protection from opportunistic pathogen colonization, and even involvement in the construction of the intestinal architecture (Hooper & Gordon, 2001). The human gut microbiota is also essential for immunity (Macpherson & Harris, 2004.)

The populations of colonizing microorganisms in healthy people and those in sickness or unhealthy situations are different, according to numerous research. Nevertheless, scientists are unable to identify the components of a healthy human microbiome. The potential benefits of supplementing with certain commensal bacteria, including *Faecalibacterium prausnitzii*, *Roseburia, Akkermansia,* and *Bifidobacterium*, are still being studied. However, there is a growing correlation between these microorganisms and favorable health consequences (Lloyd-Price et al., 2016).

1.5 Probiotics' and Prebiotics' Modes of Action

Prebiotics work by increasing the quantity or activity of good bacteria in the intestines. As a result, the number of potentially harmful microorganisms may decline, or the host microbiota's potentially harmful metabolic activity may decrease. Prebiotics may have an effect on immunological function as well.

There are a number of known methods by which probiotic strains may mediate health effects. (Table 3). These processes have the ability to strengthen the intestinal barrier, improve the intestinal environment, antagonize possible pathogens, reduce inflammation, and boost the immune system's response to antigenic assaults (Javanshir et al., 2021). One of the most well-known applications of probiotics is to lessen the frequency and intensity of diarrhea, and they are believed to be important in providing the majority of these advantages (McFarland, 2007).

2 Products, Health Advantages, and Economic Factors

2.1 Getting Knowledge about the Market

In multiple regions of the world, probiotic-containing products have been effectively provided. Commercially, a variety of product types are offered, ranging from prescription medications to traditional food. Depending on the regulatory monitoring in the area, different claims can be made about various kinds of items (Hill et al., 2014). The majority of probiotics as well as prebiotics are advertised as dietary supplements or food items, usually claims are generic, no reference to disease or illness is permitted, and the products are aimed at the population that is typically healthy (Fusco et al., 2022).

From scientific viewpoint, the following are appropriate label descriptors of a probiotic product:

- Using names that are now accepted by scientific standards to identify the genera, the species (as well as subspecies, if applicable), and nomenclature

- Strain designation
- Strain's remaining viable cells beyond the end of its shelf life.
- Appropriate storage parameters
- It is important to base the recommended dosage on the onset of the desired physiological impact.
- A detailed description of the physiological impact, as permitted by regulations
- Information about the post-purchase surveillance contact (Fenster et al., 2019; Jackson et al., 2019).

Table 3: Modes through which prebiotics, probiotics, and the host interact.

Probiotics	
Immunologic benefits (Mazziotta et al., 2023)	• Increase secretory IgA synthesis both locally and systemically to enhance B cell presentation of antigen • Modify cytokine profiles • Strengthen the immune system's reaction to dietary antigens
Nonimmunologic benefits (Petrariu et al., 2024)	• Digest food while competing with pathogens for nutrients. • Modify local pH to make the environment hazardous for infections • Generate bacteriocins in order to avoid infections. • Reduce the amount of superoxide produced • Accelerate the formation of mucin by the epithelium. • Improve the function of the intestinal barrier • Compete with pathogens for adherence • Modify the toxins that bacteria produce.
Prebiotics	
Metabolic benefits (Green et al., 2020)	• Short-chain fatty acid synthesis and ion (Ca, Fe, Mg) absorption
Immunologic benefits (Shokryazdan et al., 2017)	• Improving the host's immunity (production of IgA, regulation of cytokines etc.)

2.2 Products: Dosages and Quality

In 2013, the Grand View Research report estimated that the probiotics market was worth US$ 32.1 billion. The global probiotic market is expected to increase at a rate of 8.1% per year, reaching US$ 85.4 billion by 2027 (Shahbandeh, 2023).

It can be hard to sort among the vast array of foods, dietary supplements, and drugs available on the market. Typically, medical associations make prescriptions using strains rather than item names, which may vary by location. Matching probiotic strains to particular items can be challenging, and not all products have appropriate labels. The manufacturer determines the efficacy of a probiotic product (Arora & Baldi, 2015). Regulatory agencies might not be able to guarantee adherence to quality requirements because the majority are not manufactured in accordance with pharmaceutical standards. The overall effectiveness of probiotics is mostly dependent on the efficacy, identity, and quality of the live microorganisms (Merenstein et al., 2023).

Depending on the strain and product, different probiotic dosages are required. Some products have been demonstrated to be effective at lower levels, while others require far higher levels, even though many over-the-counter medications offer between 1 and 10 billion cfu/dose (Anwer & Wei, 2024).

A general dosage for probiotics cannot be determined; instead, it should be established through human studies that demonstrate a positive impact on health. Since probiotics are living organisms, they may die off while being stored in a product. In order for the product to maintain the efficacy stated on the label at the end of its shelf life, manufacturers usually incorporate overages. Competent producers will specify the anticipated dosage at the use-by date, not at the point of manufacturing (Boyte et al., 2023). In many instances, it has been demonstrated that probiotic products on the market do not live up to label claims about the quantity and kinds of live microorganisms included. Therefore, buying products from reputable manufacturers is important (Elshaghabee et al., 2017).

2.3 Product Safety

Probiotics have been utilized in products for decades and are mostly obtained from fermented foods or the bacteria that colonize a healthy individual. Experts in the field believe that lactobacilli have a very low pathogenic potential due to their ubiquity in fermented foods, their status as normal human body invaders, and the low amount of infection they are linked to. Species of *Bifidobacterium* have comparable safety records. The requirements of at-risk individuals should be satisfied by microbiological quality standards, according to Sanders et al. (2016). The use of recently discovered or already existing probiotics for novel disease indications must be reviewed and approved by an independent ethics council. Conventional LAB, which have been linked to food fermentation for a long time, are generally regarded as safe to take orally at quantities customarily used in meals and supplements for the general public (Khushboo et al., 2023).

3. Clinical Applications

An outline of what is now known about the broad picture of therapeutic effectiveness of prebiotics and probiotics in gastroenterology is provided below.

When assessing clinical efficacy, meta-analyses are thought to offer the best quality of evidence. However, the diversity of study plans, the variation of probiotic therapies, the variety of the groups considered, and comparatively limited number of participants included in each clinical trial make applying meta-analysis to probiotic clinical trials problematic (Rondanelli et al., 2017).

3.1 Preventing Colorectal Cancer

Despite the fact that colorectal cancer is believed to be influenced by food. It has been demonstrated that in animal models, both probiotics and prebiotics affect colorectal cancer Indicators, there is little evidence that either supplementation can prevent colorectal cancer in humans (Shang et al., 2020).

3.2 Preventing and Treating Diarrhea

Acute infectious diarrhea in children can be lessened in severity and duration with the use of specific microbial strains as probiotics (Huang et al., 2021). In children, oral administration of probiotics reduces the duration of acute diarrheal disease by around one day. According to meta-analyses of the findings of multiple published clinical trials, probiotics are probably safe and beneficial and can help patients (children, adults, and the elderly) on antibiotics avoid diarrhea linked to *C. difficile* with a moderate degree of certainty (Goldenberg et al., 2017; Guo et al., 2019; Goodman et al., 2021; Zhang et al., 2022).

3.3 Eradication of *Helicobacter pylori*

Instead of directly targeting *H. pylori*, probiotics seem to increase the efficacy of *H. pylori* eradication by lowering the side effects of the eradication medications, in accordance to the 2022 Maastricht VI/Florence Consensus Report on the control of *H. pylori* infection (Malfertheiner et al., 2022).

3.4 Protection and Management of Hepatic Encephalopathy

A specific probiotic blend has been found to reverse mild hepatic encephalopathy. However, a 2017 Cochrane meta-analysis concluded that probiotics may improve recovery, quality of life, and ammonia plasma levels, the researchers concluded, even if the death rate remained unchanged (Dalal et al., 2017).

3.5 Immune Response

Evidence suggests that a number of probiotic strains and the prebiotic oligofructose may improve immunity. Improved immune responses have been shown in studies looking at antibody responses to vaccinations and initiatives to prevent acute infectious illnesses such as winter flu or diarrhea that is nosocomial in children (Mazziotta et al., 2023).

3.6 Long-term Inflammatory Bowel Conditions

3.6.1 Pouchitis

In children and adults with slightly active pouchitis, probiotic blends have been demonstrated to successfully decrease the development of the illness as well as the recurrence of relapses following antibiotic-induced remission (Su et al., 2020).

3.6.2 Ulcerative Colitis

According to a number of studies and a 2020 Cochrane meta-analysis, some probiotics may be equally safe and beneficial as traditional treatments for those with mild to moderately severe ulcerative colitis (Kaur et al., 2020).

3.6.3 Crohn's Disease

Research on the effects of probiotics on Crohn's disease has shown no evidence that they are helpful in causing or sustaining remission (Vakadaris et al., 2023).

3.6.4 Functional Bowel Problems

Probiotic therapies have been shown in published trials to reduce abdominal gas and bloating. Additionally, some strains could aid in pain reduction and overall comfort (Rau et al., 2024).

3. 7 Colic

It has been demonstrated that *L. reuteri* DSM17938 and *B. animalis spp. lactis* BB12 shorten the amount of time that breastfed newborns with colic cry (Chen et al., 2021).

3.8 Intolerance for Lactose

The bacterium *Lactobacillus delbrueckii* and the *thermophilus* strain of *Streptococcus* are two examples of bacteria that help break down lactose and lessen the symptoms of an intolerance to lactose. Several controlled tests in which subjects ate yogurt containing living cultures served to verify this (Savaiano & Hutkins, 2021).

3.9 Necrotizing Enterocolitis

The risk of necrotizing enterocolitis in premature newborns is reduced when probiotics are added to their diet. Although a few probiotic formulations are effective, meta-analyses of tightly controlled randomized investigations have shown a decreased risk of dying among populations that took probiotics (van den Akker et al., 2020).

3.10 Nonalcoholic Fatty Liver Disease

Probiotics are beneficial and have been shown to improve a number of factors, such as levels of cholesterol in the blood, TNF-α, tests for

liver function (e.g., the ALT and the AST), and the homeostasis designs assessment (HOMA). Several randomized clinical investigations have demonstrated that certain probiotics can be useful in decreasing steatohepatitis in adults as well as children (Cao et al., 2023).

3.11 Preventing Invasive Infections

Probiotics have been shown in numerous trials to help lower oral infections, periodontal cavities, vaginosis due to bacteria, respiratory s illnesses and atopic eczema among kids who are young. Because of the general advantages of probiotics in reducing allergy disorders in the postpartum period, the world's Allergy Organization advises people at elevated risk of allergic reactions to use them during pregnancy, nursing, and weaning (Zhang et al., 2016).

Conclusions

The research supporting the acute and chronic roles of the microbiome and microbiota in human health is now significant. However, it should be noted that the impact of our microbes extends beyond the stomach to include the immune system, metabolism, and brain. Although aging and genetics influence the microbiome's variety and composition, other factors that can be changed, like nutrition, exercise, exposure to exogenous bacteria, and the use of antibiotics, may be more important in establishing a balanced microbiota. Although this gives people the opportunity to live more customized lives, there are a number of obstacles to overcome, such as obtaining sufficient data to determine which microbes' interventions are suitable for which demographics, knowing the mechanisms underlying these processes, and designing novel powerful probiotic products. Probiotics are the materials that offer a successful method for preventing or treating a variety of illnesses. Future studies should, however, gather data on the best matrix and the ideal dosage for each unique strain. Further studies need to ascertain whether probiotic strains whether they are ancient or modern colonize our intestines, or they are just beneficial microbes that are transient.

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