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REVIEW

Beyond probiotics: a narrative review on an era of revolution

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Abstract

Whether knowingly or unknowingly, humans have been consuming probiotic microorganisms through traditionally fermented foods for generations. Bacteria, like lactic acid bacteria, are generally thought to be harmless and produce many metabolites that are beneficial for human health. Probiotics offer a wide range of health benefits; however, their therapeutic usage is limited because they are living organisms. As a result, the focus on the health advantages of microbes has recently shifted from viable live probiotics to non-viable microbes made from probiotics. These newly emerging non-viable microbes include paraprobiotics, postbiotics, psychobiotics, nutribiotics, and gerobiotics. Their metabolites can boost physiological health and reveal the therapeutic effects of probiotics. This new terminology in microbes, their traits, and their applications are summarized in the present review.

Keywords Probiotics · Prebiotics · Synbiotics · Postbiotics · Paraprobiotics · Nutribiotics

Introduction

A balanced gut microbiota has a significant impact on human physiology and nutrition. Bacteria that live inside the human body are given a stable, nutrient-rich habitat in return for conferring health benefits to their host (Żółkiewicz et al., 2020). Recently, the intake of low-quality food and a sedentary lifestyle have contributed to declining human health. This modern lifestyle causes dysbiosis of the gut microbiota, and multiple studies have found that dysbiosis is linked to a variety of prevalent clinical disorders in the twenty-first century (Vyas and Ranganathan, 2012). Improving human health through the modulation of microbial interactions using bioactive components, such as probiotics, prebiotics, and synbiotics, has yielded promising results. In this field, the potential influence of non-viable bacterial cells and their components on probiotic functionality has only recently received some acknowledgement, and moving in this direction has led to the origin of the term 'postbiotics'. Thus, the present review focuses on providing a conceptual basis for the different emerging terminologies used in the probiotic field, and beyond.

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Probiotics

The term probiotic is Greek in origin, with 'pro' meaning 'in favor' and 'biotic' meaning 'life'. Vergin coined the term 'probiotics' when he was researching the negative effects of antibiotics and other microbial agents on the population of bacteria in the gut (Pandey et al., 2015). Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" according to the FAO/WHO guidelines (Araya et al., 2002).

Probiotics are also referred to as "live biotherapeutics" by the U.S. Food and Drug Administration (FDA), and are defined as "living microorganisms with an intended therapeutic impact in humans", which includes "bacteria and yeast employed in disease prevention or therapy, intended for local or regional activity". Probiotics for clinical use are included in this category (Hoffman, 2008). Regardless of the mode of administration (topical, oral, intra-vaginal, etc.), products containing entire live microorganisms (such as bacteria or yeast) with an intended therapeutic or preventive impact on humans are referred to as live biotherapeutic products (LBPs) (Vaillancourt, 2006).

Probiotics are living microbes that harbor useful properties for the host, largely through affecting the balance of intestinal microbiota (Hill et al., 2014). Common lactic acid-producing bacteria (LAB), belonging to genera such as *Lactobacillus* and *Bifidobacterium*, have been isolated from traditional fermented dairy products and from the gut. Acids such as lactic, propionic, and acetic acid, which reduce pH and prevent deadly bacteria from proliferating, are produced by lactobacilli and bifidobacteria. *Lactobacillus*, *Bacillus*, *Streptococcus*, *Enterococcus*, and *Pediococcus*, as well as some fungal and yeast strains such as *Saccharomyces cerevisiae* and *Kluyveromyces*, are examples of probiotics (Markowiak and Śliżewska, 2018). Furthermore, the mechanistic implications of probiotics vary among strains; therefore, different strains of each could have unique health advantages.

The gut microbiota is composed of trillions of bacterial strains per gram of excrement. Their collective genome, commonly referred to as the microbiome, contains 100 times more genes than the human genome (Qin et al., 2010). According to their location of action, probiotics, purporting health-promoting benefits, have been divided into three levels (Rijkers et al., 2010). The first level involves direct communication with gut bacteria or enzymatic activity within the gastrointestinal tract. The second level is via direct interaction with the intestinal epithelium and mucous layer, which affects the mucosal immune system and intestinal barrier function. At the third level, probiotics work with the immune system and bodily organs.

A microbe must meet the following requirements to be categorized as a probiotic (Kolida and Gibson, 2011): (1) Probiotics should be selected based on functionality, safety, and technological usability; (2) Probiotics can be of human or animal origin, and should be isolated from the gastrointestinal tracts of healthy individuals; (3) Probiotics should be granted a generally regarded safety status; (4) Probiotics must be resistant to bile acid toxicity and stomach acidity, and also to the bacteriocins and toxins produced by endogenous bacteria; (5) Probiotics must adhere to mucins and cells of the human intestine, in order to enhance intestinal persistence and growth, and possibly encourage the competitive exclusion of prospective pathogens from mucosal surfaces; (6) Probiotics must produce antimicrobial compounds against gut infections, in order for the makeup of the gut microbiota to return to a healthy state; (7) Probiotics must be safe in both culinary and therapeutic settings, even for individuals with compromised immune systems; (8) Probiotics must be viable and large-scale production must be possible; (9) Probiotics should be genetically stable and, therefore, resistant to bacteriophages; (10) Probiotic efficacy and safety must be assessed in randomized controlled studies.

Probiotics must be safe for both humans and animals, to comply with general food law. In the USA, microorganisms used for human consumption USA should have a generally regarded as safe (GRAS) designation, which is assigned by the FDA. In Europe, the European Food Safety Authority (EFSA) has introduced the concept of qualified presumption of safety (QPS), which includes certain additional safety assessment criteria for bacterial supplements, such as a history of safe use and absence of the possibility of developing antibiotic resistance (Gaggìa et al., 2010).

A wealth of literature has demonstrated the health-promoting benefits of probiotics in humans. These include protective effects against gastrointestinal (GIT) diseases (Acurcio et al., 2017; Fedorak et al., 2015), lactose intolerance (Li et al., 2012), cancer (Legesse Bedada et al., 2020; Sharma et al., 2018), irritable bowel syndrome (Ducrotté et al., 2012), obesity (Kobyliak et al., 2016), type 2 diabetes (Hsieh et al., 2018; Wang et al., 2017), depression (Wallace et al., 2020), and atopic dermatitis (Rather et al., 2016). The proposed health-beneficial effects of probotics mentioned in this review are summarized in Table 1.

Prebiotics

Gibson and Roberfroid initially introduced the concept of prebiotics in 1995 (Gibson and Roberfroid, 1995). Prebiotics are supplements or foods (short-chain carbohydrates) that contain a non-digestible ingredient that is selectively utilized by indigenous bacteria, thus conferring a health benefit (Salminen et al., 2021). A prebiotic is defined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" by the International scientific association for probiotics and prebiotics (ISAPP) in 2017 (Gibson et al., 2017).

Prebiotic components have gained considerable attention in recent years, and have been used in the development of functional foods (Neri-Numa et al., 2020) and dairy products (Rosa et al., 2021). Prebiotics are typically classified as dietary fibers, but not all dietary fibers are prebiotics (Singh et al., 2017). The most popular and widely used prebiotics with health-promoting effects are non-digestible carbohydrates, including galactans [galactooligosaccharides (GOS)] and fructans [fructooligosaccharides (FOS) and inulin], which are GRAS (Gibson et al., 2017; Kumar et al., 2015). Trans-galacto-oligosaccharides, short-chain fatty acids (SCFAs), exopolysaccharides, and peptidoglycans have

Table 1 Proposed health-beneficial effects of probiotics

Probiotic strain	Health beneficial effect	Reference
Lacticaseibacillus rhamnosus D1 *Lactiplantibacillus plantarum* B7	Protective effects against gastrointestinal diseases	Acurcio et al. (2017)
Lactococcus lactis MG1363/FGZW	Decrease in lactose intolerance	Li et al. (2012)
Lacticaseibacillus casei ATCC393 *Lactiplantibacillus plantarum* AS1 *Lacticaseibacillus casei* YIT 9018 (LC 9018) C57BL	Prevention and treatment of cancer	Legesse Bedada et al. (2020) Sharma et al. (2018)
Lactiplantibacillus plantarum 299v	Treatment of irritable bowel syndrome	Ducrotté et al. (2012)
Lactobacillus gasseri SBT2055 *Lacticaseibacillus rhamnosus GG* *Latilactobacillus curvatus* HY7601 *Lactiplantibacillus plantarum* KY1032	Prevention and treatment of obesity	Kobyliak et al. (2016)
Limosilactobacillus reuteri ADR-3 *Lacticaseibacillus casei* CCFM419	Attenuation of type 2 diabetes	Hsieh et al. (2018) Wang et al. (2017)
Lactobacillus helveticus Rosell®-52 and *Bifidobacterium longum* Rosell®-175	Alleviation of symptoms of depression	Wallace et al. (2020)
Lactiplantibacillus plantarum CJLP133	Treatment of atopic dermatitis	Rather et al. (2016)

recently also been considered as prebiotics (Davani-Davari et al., 2019; Salazar et al., 2016). This new definition also allows for the inclusion of compounds such as polyunsaturated fatty acids and polyphenols that have been changed into their respective conjugated fatty acids as prebiotics, where there is sufficient proof of the intended host benefit (Nguyen et al., 2022). Prebiotic oligosaccharides can be prepared by three methods: separation from plant resources, microbial generation or enzymatic synthesis, and enzymatic breakdown of polysaccharides (Gulewicz et al., 2000).

Prebiotics should ideally withstand stomach acids, bile salts, and other hydrolyzing enzymes in the gut, and should be easy for gut microorganisms to ferment. In addition, prebiotics should not be absorbed by the upper gastrointestinal tract (Kuo, 2013), and must provide scientifically-proven health benefits to the host (Brownawell et al., 2012).

Prebiotics have a number of health-maintaining and disease-fighting properties, including beneficial effects on colorectal cancer, irritable bowel syndrome, Crohn's disease, the cardiovascular and neurological systems and the skin, calcium and magnesium absorption, and immunomodulation (Davani-Davari et al., 2019). Prebiotics improve intestinal health by promoting selective growth (composition and function) of beneficial commensal bacteria by acting as an energy source (Flint et al., 2007). Genes for the breakdown of prebiotics have been identified in human gut bacteria using a metagenomics approach (Cecchini et al., 2013).

Synbiotics

The concept of 'synbiotics' was first introduced in 1995 (Kolida and Gibson, 2011). Synbiotics are a mixture of prebiotics and probiotics that can be used to improve human or animal health (Nguyen et al., 2022). The ISAPP has recently defined synbiotics as "a mixture of live microorganisms and substrate(s) that are selectively utilized by host microorganisms and confer a health benefit to the host" (Swanson et al., 2020). This combination leads to the development of beneficial microbiota, maintains the equilibrium of metabolic movement in the gastrointestinal tract, maintains the intestinal structure, and inhibits the growth of pathogenic bacteria present in the intestinal tract (Fazelnia et al., 2021; Nguyen et al., 2022). There is mounting evidence that probiotic microbes become more resilient to atmospheric factors, including pH, oxygenation, and temperature, in the intestine as a result of the usage of prebiotics (Sekhon and Jairath, 2010). However, the precise mechanisms underlying this remain unclear.

Based on these functions, synbiotics can be complementary or synergistic (Swanson et al., 2020). A complementary synbiotic indicates that each component (probiotic and prebiotic) within the symbiotic is independently chosen to confer health-promoting effects on host health. For example, the combination of FOS with *Lacticaseibacillus casei*, in which the functions of both are complementary. In contrast, a synergistic synbiotic contains a prebiotic component (substrate) that supports the activity of a specific probiotic (Swanson et al., 2020). In the case of a symbiotic combination of *Bifidobacterium* and FOS, these two strategies could have various repercussions. For instance, as the complementary method uses probiotics and prebiotics to address host health in various ways, it is necessary to administer each item at a dosage that will allow a desired effect. The encapsulation option is typically eliminated because of the relatively large prebiotic doses (typically > 6 g/day for adults) needed to influence the bacteria in the gut (Kolida and Gibson, 2011). In the synergistic strategy, the synbiotic is viewed as a single product, and the main function of the prebiotic is to increase the viability and implantation of the probiotic. Consequently, the required prebiotic dose may be restricted to this function alone, necessitating a reduced probiotic dose (Kolida and Gibson, 2011).

Some synbiotics have been used in clinical practice. These include FOS/*L. sporogens* and oat fiber/*Lactiplantibacillus plantarum* (Pandey et al., 2015). Synbiotics have positive effects on human health, including improved immunomodulatory capacity, maintenance of gut bacterial dysbiosis, and increased numbers of *Lactobacillus* and *Bifidobacterium*. Increasing the count of *Lactobacillus* and *Bifidobacterium* in the GIT can lead to a reduced number of pathogenic bacteria in the feces (Mofid et al., 2020). In addition, patients with cirrhosis receiving FOS/*L. sporogens* show improved liver function and decreased incidence of nosocomial infections (Zhang et al., 2010). Synbiotic intake by healthy individuals can increase the bioavailability of bioactive compounds (Mofid et al., 2020). In a systematic review and meta-analysis of 167 studies on inflammatory markers, Kazemi et al. found that supplementation with probiotics and synbiotics decreased the levels of several inflammatory markers. The lowering of C-reactive protein and tumor necrosis factor-alpha levels in either a healthy or chronic state was associated with the most successful interventions. Additionally, the symbiotic/probiotic intervention most effectively reduced inflammation in cases of arthritis, irritable bowel syndrome, and fatty liver disease (Kazemi et al., 2020).

Overall, the effects of synbiotics on human health have been demonstrated for obesity, insulin resistance, non-alcoholic fatty liver disease, type 2 diabetes, irritable bowel syndrome, gastrointestinal diseases, atopic dermatitis, reduction of lactose intolerance, different cancer types, and their side effects (Markowiak and Śliżewska, 2017).

Postbiotics

Although not all mechanisms or clinical advantages are directly tied to live bacteria, it is not crucial to have active bacteria to achieve health-promoting effects (Aguilar-Toalá et al., 2018). This recent revelation sparked the advent of the postbiotic research era. The terms 'post', a prefix meaning after, and 'biotic', which means 'related to or coming from living organisms', were combined to form the term 'postbiotic'. Postbiotics were recently defined as a 'preparation of inanimate microorganisms and/or their components that confers a health benefit on the host' by the ISAPP (Salminen et al., 2021). Postbiotics, commonly referred to as metabiotics, are soluble substances secreted by living bacteria or released after bacterial lysis that physiologically benefit the host (Schönfeld and Wojtczak, 2016).

Postbiotics are also defined as "any extracted or secreted molecule that confers physiological benefits to the host", which includes biogenics, cell-free supernatants, metabolic products or byproducts (refers to bioactive soluble components), cell compounds, and substances produced by actions of microorganism on food ingredients. Thus, live probiotics can produce postbiotics (Cicenia et al., 2014; Moradi et al., 2020). Examples of postbiotics include secreted proteins/peptides, enzymes (SOD, GPx, and NADH peroxidase), organic acids, short chain fatty acids, vitamins, cofactors, cell-free supernatants, exopolysaccharides, cell wall fragments, carbohydrates, bacterial lysates, immune-signaling molecules, bacteriocins, metabolites, neurotransmitters, flavonoids, terpenoids, and phenolic-derived postbiotics produced by gut bacteria (Cortés-Martín et al., 2020; Rajakovich and Balskus 2019; Wang et al., 2019; Żółkiewicz et al., 2020). The potential mechanisms of postbiotics include immunomodulation, prevention of infections, anti-tumor and anti-atherosclerotic effects, autophagy regulation, and accelerated wound healing (Żółkiewicz et al., 2020). Aguilar-Toalá et al. (2018) collated the bioactivity of postbiotics using in vitro and in vivo models. Some of the described effects include immunomodulatory, anti-inflammation, anti-proliferative, anti-oxidant, anti-obesogenic, hepatoprotective, and antimicrobial effects. In addition, applications in food and medicines have been addressed. A recent review highlighted the food applications of postbiotics, including biopreservation of food, meat and fish products, dairy products, vegetables, and bread, in situ production of postbiotics in food, manipulation of postbiotic composition for food applications, interaction between postbiotics and food ingredients, application of postbiotics in food packaging (as a mixture or individual postbiotic), prevention and control of biofilms, and degradation of food chemical contaminants, including pesticides, biogenic amines, and mycotoxins (Moradi et al., 2020).

Paraprobiotics

Although probiotics have positive health effects, non-viable microbial cells may offer advantages in terms of safety by lowering the risk of microbial infection, translocation, or inflammation, which have been linked to some probiotics in people with weakened immune systems (Taverniti and Guglielmetti, 2011). A systematic review focusing on studies conducted between 1976 and 2018 found that 93 incidences of infections caused by *Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Escherichia*, and *Pediococcus* occurred after the administration of live probiotics (Costa et al., 2018). Probiotic products also include dead cells, demonstrating that they can be used after their expiration and still elicit a biological reaction similar to their living counterparts. The fact that both live and dead cells can elicit a biological reaction is known as the 'probiotic parado'. Consuming dead microbes might have certain advantages; however, they cannot be referred to as probiotics. As a result, the term 'paraprobiotics' was created (Wilcox et al., 2020).

Paraprobiotics (also called inactivated or 'ghost' probiotics) are non-viable microbial cells (either intact or broken) or crude cell extracts that, when administered (either orally or topically) in adequate amounts, confer benefits to humans and animals. Inactivation of live bacteria can be achieved by various methods, including chemical (acid deactivation and formalin treatment) and physical (heat treatment, sonication, freeze-drying, gamma or ultraviolet irradiation, and high hydrostatic pressure) methods. However, heat treatment remains the method of choice for inactivation (de Almada et al., 2016; Taverniti and Guglielmetti, 2011). A recent review evaluated the use of high-intensity ultrasound (HIUS) for inactivating probiotics (Guimarães et al., 2019). These methods can modify the cellular components and physiological functions of bacterial cells without completely destroying the cell structure. Various cell structures involved in the potential biological activity of paraprobiotics include peptidoglycan-derived muropeptides, cell surface-associated proteins, cell wall-bound biosurfactants, lipopolysaccharides, exopolysaccharides, mannoproteins, lipoteichoic acid, teichoic acid, fimbriae, chitin, and pili (Siciliano et al., 2021).

Paraprobiotics represent an important opportunity for the development of innovative functional foods that are suitable for people with weakened immune systems who may not be good candidates for traditional probiotics. Parabiotics are also characterized by greater stability than traditional probiotics, and can be stored without a cold chain, thereby facilitating industrial handling and wider commercialization.

Although some of the underlying mechanisms are not fully understood, the plausible health benefits of paraprobiotics include immune system modulation (Fujiki et al., 2012), pathogen inhibition (Grześkowiak et al., 2014), and metabolite secretion by dead cells (Shin et al., 2010). In addition, the therapeutic and health-promoting properties of paraprobiotics include anti-inflammatory, anti-allergic, and immunomodulatory effects, treatment of atopic dermatitis, inhibition of cancer growth, effects on respiratory diseases, recovery from intestinal injuries, prevention of tooth decay, anti-aging effects, cholesterol reduction, modulation of dysbiosis of gut bacteria, and protection against ulcerative colitis (Akter et al., 2020). However, further research should concentrate on the precise mechanisms underlying these activities and how they differ from those of viable probiotics. Additional clinical and epidemiological studies are needed to fully understand how paraprobiotics affect human health.

Pharmabiotics

Colin Hill first used the term 'pharmabiotics' in his study on the impact of oral delivery of the gut bacterium *Ligilactobacillus salivarius* UCC118 in *Listeria*-infected mice, where he also provided evidence that pharmabiotics are effective treatments (Hill, 2010). The strain had a powerful effect as a pharmabiotic agent because it secreted a bacteriocin that could eliminate *Listeria* with minimal mouse mortality. The phrase 'pharmabiotics' refers to a broad range of uses for microbes, whether they are dead or alive, parts of organisms, or microbial metabolites that are not included in the traditional FAO/WHO definition of 'probiotics' (Shanahan, 2010).

Pharmaceuticals produced by the gut microbiota can influence a variety of physiological and metabolic processes in the human body. At the local level, they can induce changes in the gut epithelium and enteric nervous system, while at the systemic level they can affect processes such as immune function and central nervous system signaling.

Probiotics utilized as pharmaceuticals in human studies include *B. longum*, *B. bifidum* + *Streptococcus thermophilus*, *Enterococcus faecium* SF68, *Lacticaseibacillus casei* Shirota, *L. acidophilus* + *L. bulgaricus*, *L. helveticus* R0052, *B. longum* R0175 (PF), *Lactiplantibacillus plantarum* 299 V, *Lactiplantibacillus plantarum* DSM9843, *Lacticaseibacillus rhamnosus* GG, *Limosilactobacillus reuteri*, and *Saccharomyces boulardii* (Lee et al., 2018).

Nutribiotics

The term 'nutribiotics' refers to probiotics that also provide nutritional functions by generating vital elements, such as vitamins and minerals, and converting precursors into bioactive metabolites (Chaudhari and Dwivedi, 2022). This source of nutrients is important to provide vitamins that the body cannot produce on its own, and are not obtained through the diet. The nutraceutical properties of probiotics are categorized as 'nutribiotics.' Some microbial species help to produce vitamins, including B1, B2, B3, B5, B6, B7, B9, B10, B11, B12, and K in humans. Because these vitamins are produced by bacteria that grow and multiply in the gut (LeBlanc et al., 2013), individuals with insufficient vitamins in their diet must rely on gut microbial production to meet their nutritional needs.

Psychobiotics

'Psychobiotics' may be defined as beneficial bacteria, or support for such bacteria, which, when ingested in adequate amounts, influence the bacteria-brain relationship and produce health benefits in patients suffering from psychiatric illnesses (Dinan et al., 2013; Sarkar et al., 2016).

Logan and Katzman first proposed the use of probiotics as an adjunct therapy for the management of depression (Logan and Katzman, 2005). Lyte argued that probiotics function mechanistically as delivery vehicles for neuroactive compounds, and that these probiotics have the potential to act as psychotropic agents (Lyte, 2011). The influence of psychobiotics is still not fully understood, and needs to be described more thoroughly. The majority of the literature is centered on rodent models, even though some studies offer mechanistic insights in humans. Investigating the interactions between the microbiome and the brain is an essential first step in understanding these mechanisms (Sarkar et al., 2016).

Notably, some intestinal microbes, such as *B. longum*, *B. infantis*, *B. bifidum*, *L. acidophilus*, *Lacticaseibacillus casei*, *Bacillus*, *Escherichia*, *Saccharomyces*, *Candida*, *Enterococcus*, and *Streptococcus*, can produce neurotransmitters, including norepinephrine, serotonin, and gamma-aminobutyric acid, and can modulate the expression of neurochemical receptors (Akkasheh et al., 2016; Barrett et al., 2012; Selhub et al., 2014).

Although the exact mechanism of the gut microbiota-brain axis is not yet fully understood, it was proposed that it contains five possible communication routes, including the neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis pathway, neuroanatomical pathway of the gut-brain axis, gut immune system, gut microbiota metabolism system, intestinal mucosal barrier, and blood-brain barrier (Misra and Mohanty, 2019). In summary, neurotransmitter production, anti-inflammatory cytokine production, reduction of stress hormones (cortisol), and short-chain fatty acid production by bacteria can lead to improved mental health (Misra and Mohanty, 2019).

Cheng et al. (2019) extensively reviewed the use of probiotics for treating mental health and neurodegenerative illnesses by presenting a cumulative account of several investigations in mice, rats, and humans (Cheng et al., 2019). In a double-blind placebo-controlled trial, consumption of milk containing *Lacticaseibacillus casei* Shirota for 3 weeks improved the mood of 132 healthy participants (Benton et al., 2007). In another double-blind, placebo-controlled, randomized parallel group study, oral administration of the probiotics *B. longum* R0175 and *L. helveticus* R0052 to healthy Caucasian volunteers for a month improved their levels of depression, rage, and anxiety, and reduced their levels of the stress hormone cortisol (Messaoudi et al., 2011). A 4 week placebo-controlled study involving healthy women demonstrated that consumption of a fermented milk product with a probiotic mixture containing *B. animalis* subsp. *lactis*, *S. thermophilus*, *L. bulgaricus*, and *Lactococcus lactis* subsp. *lactis* for one month could influence brain activity (Tillisch et al., 2013).

These results imply that the development of psychobiotics as non-traditional antidepressants is a promising therapeutic strategy that needs to be confirmed by further studies.

Gerobiotics

'Gerobiotics' is a newly coined term that refers to specific probiotic strains that can slow down physiological aging processes, as well as probiotic strains and their postbiotic and para-probiotic offspring that can advantageously slow down the aging processes and prolong the host's healthy lifespan (Tsai et al., 2021). Élie Metchnikoff argued more than a century ago that altering the gut environment with beneficial microorganisms could prevent the development of aging (Mackowiak, 2013). An increasing number of studies have shown that homeostasis and aging of the intestinal microbiome are closely associated (Bana and Cabreiro, 2019; Kim and Jazwinski 2018; Singh et al., 2019). This new field warrants further study because of the massive potential benefits of prolonging health in the elderly.

Future directions

The ingestion of probiotic microbes can improve human health. Probiotic research is advancing rapidly as a result of increased knowledge of the gut microbiota. *Lactobacillus* and *Bifidobacterium* spp. have been utilized in several applications and have GRAS designation. Regardless of the application, it is necessary for researchers to define the efficacy of novel probiotic bacteria and monitor them throughout their application. Probiotics are increasingly being applied as synbiotics, which combine probiotics with prebiotics and may have health benefits. However, the primary concern in the field of synbiotics is establishing selection standards for probiotic and prebiotic combinations to verify their synergistic effects. Numerous studies have used dietary fibers that are not known to be prebiotics. Additional studies under controlled conditions are necessary to fully understand the potential of synbiotics. Future studies should focus on understanding the link between commensal and probiotic microorganisms to aid in the development of disease-specific treatments.

New vocabulary and ideas have developed over time in the field of probiotic research. Postbiotics include metabolites and/or cell-wall components that are secreted by living bacteria or discharged after bacterial disintegration, and have advantageous effects on the host. Although the exact processes involved are not yet fully understood, these characteristics imply that postbiotics may contribute to the improvement of host health. Paraprobiotics or 'ghost probiotics' are non-viable microbial cells or raw cellular extracts that, when administered in sufficient amounts, are advantageous to humans or animals. Further research is necessary to discover and describe new postbiotics and paraprobiotics and their signaling pathways, including randomized controlled studies to support the health claims of probiotic supplements. The potential of proved paraprobiotics and postbiotics can then be exploited in functional food markets with quality-controlled products. The notion that gut microbiomes have a significant influence on pathways in the central nervous system that are connected to mental health has given rise to the unique concept of psychobiotics. The use of single or multiple strains can modulate neuroinflammation, oxidative stress, and the fecal microbiota. However, further research is needed to ascertain the efficacy and underlying mechanisms of psychobiotics as an alternative form of treatment. Finally, gerobiotics is a new concept that proposes that probiotics could be a novel intervention technique to extend human life expectancy and increase health span.

Probiotics with nutritional claims are known as nutribiotics, whereas probiotics with medicinal and pharmaceutical properties are known as pharmaceuticals. Understanding the metabolic products of commensal bacteria and the chemicals that influence them is required to develop the next generation of foods, supplements, and medicinal items that aim to restore and maintain a healthy, balanced gut microbiota. Interprofessional collaboration and coordination are necessary to understand the interactions among gut microbes, probiotics, prebiotics, postbiotics, paraprobiotics, and pharmaceutical agents.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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