Evolutionary concepts in the functional biotics arena: a mini-review

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Received: 5 June 2020 / Revised: 19 August 2020 / Accepted: 24 August 2020 / Published online: 16 September 2020
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Abstract Over the years, the attempts to elucidate the role of beneficial microorganisms in shaping human health are becoming fairly apparent. The functional impact conferred by such microbes is not only transmitted by viable cells or their metabolites but also through non-viable cells. Extensive research to unveil the protective action of such wonder bugs has resulted in categorizing the beneficial microflora and their bioactive metabolites into a variety of functional biotic concepts based on their intended applications in various forms. In the modern era, these are often termed as probiotics, prebiotics, synbiotics, postbiotics, next-generation probiotics, psychobiotics, oncobiotics, pharmabiotics, and metabiotics. Currently, the concept of traditional probiotics is being widened to include microbes beyond lactic acid bacteria. Indeed, this diversification has broadened the functional food portfolio from food to pharmaceuticals. In this context, the present review aims to summarize the existing biotic concepts and their differences thereof.

Keywords Probiotics · Prebiotics · Synbiotics · Postbiotics · Psychobiotics · Next-generation probiotics · Functional food

Introduction

Gut microbiome—the diverse community of trillions of microbes inhabiting our gastrointestinal tract—is often termed as a forgotten organ because of its pivotal role in maintaining the overall health and wellness of the host. Gut microbial eubiosis (homeostatic/balanced microbiome composition) indicates the disease-free state of an individual; however, gut microbial dysbiosis (perturbed microbiome composition) could indicate the onset or existence of several diseases depending on the spectrum of dysbiosis (Glendinning and Free, 2014; Nagpal et al., 2014). Human gut metagenome studies have highlighted the abundance of Firmicutes (including the lactic acid bacteria) and Bacteroidetes phyla in healthy subjects (Zou et al., 2019). In contrast, Firmicutes phylum is often found to be significantly declined in specific disease states, with an abnormally higher proportion of Proteobacteria phylum (Armour et al., 2019) which suggests the probable role of gut microbiome in human health and disease. To overcome disease manifestations, the restoration of beneficial microbes, popularly known as microbial therapy, is being seen as a benign and adjunct approach (Nagpal et al., 2014). Indeed, such microbial therapy starts right from the birth by mother-to-baby translocation of commensal bacteria from mother's birth canal (vaginal and perianal flora) during parturition (Kincaid et al., 2020; Nagpal et al., 2016, 2017), as well as from mother's milk to the infant's gut via the intra-mammary route (Basavaprabhu et al., 2020). On the other hand, the intake of foods containing

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beneficial microbes has evolved through centuries of history with the consumption of ethnic fermented foods to overcome intestinal disturbances without scientific evidence (Beniwal et al., 2019). However, such traditional dietary practices were scientifically conceptualized as probiotics by Russian Nobel laureate Elie Metchnikoff in 1907, who noticed the longevity of elderly Bulgarian people due to the consumption of sour milk products containing beneficial microorganisms (Pandey et al., 2015). Although introduced in the Twentieth century, the science of probiotic remains one of the hot areas of research over the past three decades focusing on comprehending the role of microbial consortia in combating specific diseases with enhanced techno-functional attributes (Nagpal et al., 2012). This intense innovation has expanded the functional product portfolio with probiotics, prebiotics, synbiotics, postbiotics, metabiotics, psychobiotics, next-generation probiotics (NGPs), designer probiotics, pharmabiotics, etc. To best of our knowledge, each of these functional biotics overcomes the limitations exhibited by their immediate previous innovation. For example, the concept of prebiotics was evolved to enhance the survivability of probiotics, while paraprobiotics and postbiotics have been studied to overcome the unknown molecular mechanisms and viability issues of probiotics. Similarly, NGPs have been designed to conquer the generic effects of traditional probiotics. Accordingly, the emerging biotics concepts have intricately woven into the fabric of consumer's health (Fig. 1) as discussed in the below sections.

Probiotics

An internationally agreed definition of probiotics was described by FAO/WHO (2014) as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Hill et al., 2014). However, Zendebood et al. (2020) have recently proposed a new concept of true probiotics and pseudoprobiotics based on their metabolic activity. True probiotics include the viable organism displaying growth with subsequent transformation of the substrate into biochemical metabolites. By contrast, pseudoprobiotics encompass the spores and bacteria that underwent any type of stress (temperature, pH, lack of nutrients, toxins, osmotic pressure, etc.) leading to metabolic dormancy.

To confer the beneficial effects, probiotics should effectively colonize and establish in the human gut (colon) by surviving under harsh hostile conditions such as acid and bile stress (Nagpal et al., 2012). Hence, the viability of probiotics is a paramount factor to be considered while assessing the probiotic phenotypes. A significant decline in the viability of probiotic lactobacilli was observed upon acid and bile exposure for 3 h (Mallappa et al., 2019). Therefore, it is widely recommended to consume probiotic foods containing at least 10^8 – 10^9 viable cells. *Lactobacillus* and *Bifidobacterium* are the major genera of probiotics exploited for human applications as they accorded qualified presumption of safety (QPS) status by the European Food Safety Authority (EFSA) (Pradhan et al., 2020). Microbial

Fig. 1 Interrelation among the various biotics concepts

species isolated from fermented foods, plants, human milk, and stool from breastfed infants have been proposed as potential probiotics. Nevertheless, the probiotics species of human gut origin suite best for human applications with prolonged transit time as they are generally pre-adapted to the human gut niche (Nagpal et al., 2019). Although consumption of conventional lactic acid bacteria (LAB) through fermented products may provide generic health, the confirmation of such LAB as candidate probiotics demands several screening procedures in suitable experimental models. For example, nominating an allochthonous LAB as potential probiotic requires investigation at in vitro (gastric tolerance, absence of antibiotic resistance traits, adhesion to gut enterocytes like Caco-2/HT-29 cells), in vivo (oral acute toxicity tests in rodent models, disease mitigating effects in rodent or other suitable animal models), and the human clinical trials (Mallappa et al., 2019; Pradhan et al., 2019). Hitherto, specific probiotic strains have been found beneficial against various disease including diarrhea, viral infections, cancer, diabetes, Alzheimer's disease, Inflammatory Bowel Disease (IBD), reproductive/urogenital disease, etc. either as prophylactic or therapeutic agents (Basavaprabhu et al., 2020; Kisan et al., 2019; Nimgampalle and Kuna, 2017). Cross-talk between probiotic bacteria and intestinal epithelial lining triggers signal transduction mechanisms to regulate the host immune system. Likewise, several studies have reported the probiotics-mediated expression of tight junction and adherent junction proteins to strengthen the gut barrier intricate (Bhat et al., 2019, 2020; Tursi et al., 2010). Antagonistic activity is another important mechanism of probiotics against a wide range of spoilage and pathogenic microbes. The various antimicrobial compounds secreted by probiotic bacteria include organic acids, hydrogen peroxide, short-chain fatty acids, carbon-di-oxide, diacetyl, reuterin, acetaldehyde, phenyllactic acid, bacteriocins, and bacteriocins-like inhibitory compounds, biosurfactants, and other low molecular weight compounds (Chugh and Kamal-Eldin, 2020).

To date, there have been several probiotic fermented and non-fermented foods (yogurt, cheese, frozen dairy desserts, spray dried milk powder, fruit juices, confectionery, and bakery foods) available in the global market. Amongst different foods, fermented milk products and ice cream have been recognized to be the best delivery matrices of live probiotic bacteria into the human gut (Fenster et al., 2019). Dairy matrix often protects probiotics against various GI stress since they are rich in fat and protein content (Sameer et al., 2020). Moreover, consumer acceptance towards probiotic fermented dairy products is considerably high as traditional fermented milk products have a strong association with gut health in many societies (Behera and Panda, 2020). On the other hand, the addition of probiotic

microorganisms into food products also enhances the quality and aesthetic look of final products besides improving the health status of the consumers (Sameer et al., 2020). Probiotic foods are manufactured either by adding the probiotic strains simultaneously with the standard cultures during fermentation or probiotic bacterial pellet is incorporated into the final product (Fenster et al., 2019). However, it is important to evaluate the strain compatibility before introducing multiple strains into the food system.

Prebiotics

The term prebiotics may be defined as “a substrate that is selectively utilized by host microorganisms conferring a health benefit” (Gibson et al., 2017). Besides augmenting the growth of gut microbes, prebiotics can also support the growth of host microbes in the food products, vaginal tract, skin, etc (Gibson et al., 2017). The prebiotic substances include fermentable/non-digestible oligosaccharides. For example, fructooligosaccharides (FOS), inulin, galactooligosaccharides (GOS), mannan oligosaccharides (MOS), xylooligosaccharides (XOS), isomaltoligosaccharides (IMO), transgalactooligosaccharides (TOS), soybean oligosaccharides (SBOS), lactitol, lactosucrose, lactulose, etc. (Gibson et al., 2017; Holscher, 2017). However, such prebiotic substrates are generally rich in fruits, vegetables, roots, and tubers. Human milk oligosaccharides (HMOs) are the first prebiotics that an individual gets exposed through the mother's milk to selectively stimulate the growth of bifidobacteria and other commensal bacteria in the neonatal gut (Coppa et al., 2004). The fucosylated and sialylated HMOs prevent the adhesion of pathogens to the intestinal epithelium through a competitive exclusion mechanism, ultimately protecting the neonate from infection (Gibson et al., 2017). Notably, a recent meeting held by International Scientific Association for Probiotics and Prebiotics (ISAPP) decided to extend the list of prebiotic substances by including conjugated linoleic acids (CLA), polyunsaturated fatty acids (PUFAs), phenolics, and phytochemicals (Gibson et al., 2017; Holscher, 2017). The utilization of prebiotic substrates by gut microbes may vary from host to host. For example, cellulose cannot be the prebiotics for non-ruminants.

Upon oral administration, the prebiotic molecules resist the gastric digestion and reach the gut (colon) where they get selectively fermented by gut microbes to short-chain fatty acids (SCFAs), majorly acetate (two carbon, C2), propionate (C3) and -butyrate (C4) (Markowiak and Sliżewska, 2017). Fructans and galactans carbohydrates (FOS and GOS) get respectively degraded by the action of gut microbial enzymes viz. β -fructanase and β -

galactosidase. The generated SCFAs interact with free fatty acid receptors (FFAR2/FFAR3) and thus modulate the metabolic activity of gut colonocytes and enterocytes, exhibit anti-cancer effects, maintain gut homeostasis, strengthen the intestinal epithelial integrity, provides energy, modulate the immune system, and alters host epigenetic signature thereto (Holscher, 2017; Mishra et al., 2020). Prebiotics in conjunction with probiotics has been found to show enhanced mineral absorption, cholesterol-lowering ability, pathogen exclusion, and combating metabolic diseases like type 2 diabetes mellitus, obesity, and inflammation (Di et al., 2017; Kotha et al., 2018; Markowiak and Slizewska, 2017).

Despite health-promoting attributes, prebiotics demonstrated considerable control over the sensory profile, physicochemical, and rheological characteristics of foods. Prebiotics interaction with food matrices (casein and other carbohydrates) strengthens the gel structure, decrease the whey syneresis and improve the firmness and cohesive texture of fermented milk products (Ozturkoglu-Budak et al., 2019). Nevertheless, such prebiotics-mediated control of rheological properties certainly depends on the level of prebiotics added during food formulation. Besides, previous reports have also suggested the possible influence of prebiotic components on amplifying the sweetness, creamy mouthfeel, and appearance of fermented milk products. Isik et al. (2011) have observed that the addition of inulin to low-fat frozen yogurt can improve the textural attributes, melting resistance, and decreased fluffiness of yogurt since inulin is widely used as a fat replacer. Similarly, Glibowski and Kowalska (2012) reported enhanced firmness and cohesiveness of kefir upon the addition of inulin. Nevertheless, the water-holding capability of inulin depends on the degree of polymerization. Indeed, short-chain inulin was reported to have better water-holding capacity with superior gel structure over the long-chain inulin and vice versa (Ozturkoglu-Budak et al., 2019).

Synbiotics

The concept of synbiotics was first introduced by Gibson and Roberfroid in 1995 to describe the health benefits of combined probiotics and prebiotics (Maftei, 2019). The concept of synbiotics utilizes an ideal combination of prebiotics and probiotics that magnifies the viability, survivability, and successful implantation or colonization of probiotic bacteria in the gut (Nagpal and Kaur, 2011; Nagpal et al., 2012). However, prebiotics and probiotics must be compatible to derive maximum health benefits from such combinations. Synbiotic combination exhibits a synergistic effect by inhibiting the growth of pathogenic bacteria and enhancing the growth of beneficial organisms

(Grimoud et al., 2010). In a study, honey failed to support the growth of *Lactobacillus helveticus* compared to *Lactiplantibacillus plantarum* (previously known as *Lactobacillus plantarum*) whereas inulin showed better proliferation of *Lactiplantibacillus plantarum*, *Lactobacillus helveticus*, and *Lactocaseibacillus casei* (previously known as *Lactobacillus casei*) (Anand et al., 2018; Zheng et al., 2020). Hence, a careful selection of probiotics and prebiotics for developing synbiotic functional foods is paramount for providing ultimate nutrition and beneficial effects on consumer's health. In this regard, the association of *Bifidobacterium* or *Lactobacillus* with FOS, inulin, and oligofructose has been well studied (Anand et al., 2018; Awasti et al., 2016). Several synbiotic dairy products have been developed comprising probiotic lactobacilli and naturally occurring fruit chicory as putative prebiotic sources (Akrami et al., 2013; Batista et al., 2017; Casiraghi et al., 2007; Nazzaro et al., 2008). In general, the health benefits of synbiotic products are the combined effects of individual health attributes exhibited by probiotics and prebiotics (Anand et al., 2018; Markowiak and Slizewska, 2017).

Postbiotics

The postbiotics are parallelly known as “metabiotics” or “nonbiotics”. Similarly, paraprobiotics have been termed as “non-viable probiotics” or “inactivated probiotics” or “ghost probiotics” (Aguilar-Toala et al., 2018; Sharma and Shukla, 2016). Though there is no internationally agreed definition reported by scientific or regulatory bodies, the paraprobiotics may be defined as “the inactivated (non-viable) microbial cells, which, when administered in sufficient amounts, confer benefits to consumers” (Aguilar-Toala et al., 2018). In this context, a recent opinion article has underscored the emerging terminologies in the current field. Accordingly, (1) Postbiotics may be defined as “non-viable bacterial products or metabolic products from microorganisms that have biological activity in the host; (2) Paraprobiotics are the “non-viable microbial cells (either intact or broken) or crude cell extracts which when administered (either orally or topically) in adequate amounts, confer a benefit on the human or animal consumer” (Langella and Martin, 2019). The concept of postbiotics has emerged to overcome the dark sides of probiotics such as unknown molecular mechanisms, sepsis or bacteremia in immunocompromised subjects, inadequate bioactive compounds at targeted sites, difficulties in viability controls, horizontal gene transfer, etc. (Lerner et al., 2019; Pradhan et al., 2020).

Paraprobiotics constitutes the inactivated/dead/non-viable microbial cells of probiotics (intact or ruptured) containing probiotic cell components upon lysis such as

teichoic acids, peptidoglycan-derived muropeptides, surface proteins, polysaccharides like exopolysaccharides, surface protruding molecules such as pili, fimbriae, flagella or crude cell extracts with complex chemical composition. By contrast, the postbiotic molecules are the complex mixture metabolic by-products of live probiotic bacteria such as vitamins, short-chain fatty acids, extracellularly secreted biosurfactants, secreted proteins or peptides, organic acids, cell-free supernatant, amino acids, and released components after bacterial lysis (Aguilar-Toala et al., 2018; Chugh and Kamal-Eldin, 2020; Zendeboodi et al., 2020). The various treatments viz. ultraviolet rays (5–30 min), heat inactivation (60–121 °C/5–60 min), ionization radiation (10 kGy), and sonication have been used to obtain the different postbiotic components (Zendeboodi et al., 2020).

Since molecular mechanisms exhibited by probiotics are relatively multifaceted due to the complex cell structure, the use of purified postbiotic components in elucidating a particular pathway could be able to rule out the specific underlying mechanisms triggered by individual cell components. For example, the surface proteins of probiotics have been well studied for their anti-inflammatory activity to ameliorate colitis and IBD (Cai et al., 2018). Likewise, various postbiotic molecules have been exploited to overcome inflammation, adhesion of pathogens to GIT, obesity, hypertension, inflammatory diseases, cardiovascular diseases, cancer, and oxidative stress (Kodali and Sen, 2008; Lindstrom et al., 2012; Malashree et al., 2019; Ohara and Mori, 2019; Suzuki et al., 2019; Wang et al., 2020).

Besides pharmaceutical applications, the organic acids, cyclic dipeptides, PLA, and bacteriocins-like inhibitory compounds have found their potential food applications in bio-preservation (Delves-Broughton and Weber, 2011; Gálvez et al., 2014). In contrast, the use of vitamins and amino acids produced by LAB is an efficient and natural way of food fortification or in situ fermentation of foods with bio-protective or specialized cultures makes the food fortified (Xie et al., 2018). On the other hand, bacterial EPS has been shown to improve the rheological properties (viscosity and thickness) of food and dairy products. Therefore, EPS could effectively replace chemical food thickeners/stabilizers. Importantly, the ropy consistency of EPS can, however, replace the fat content (a costly component of milk) of dairy or food products which is responsible for furnishing rich consistency and mouthfeel to the dairy products (Behare et al., 2009, 2010, 2013).

Next-generation probiotics

Next-generation probiotics (NGPs) are parallelly termed as smart probiotics, fourth-generation enhanced probiotics, designer probiotics, and recombinant probiotics (Alvarez-

Calatayud and Margolles, 2016; Martin et al., 2017). NGPs include gut microbes which exhibit a positive association with health irrespective of their phyla. The widely studied NGPs include *Akkermansia muciniphila*, *Eubacterium hallii*, *Faecalibacterium prausnitzii*, *Bacteroides fragilis*, and members of the Clostridia clusters IV, XIVa, and XVIII, etc. (Fig. 2) (Martin et al., 2017; O'Toole et al., 2017). However, earlier attempts were not made to explore NGPs in food applications due to their safety issues. Henceforth, it is important to assess the safety of NGPs before human applications.

Recombinant probiotics or engineered probiotics are another category of NGPs (Kumar et al., 2016). The application of genetic engineering tools viz. conventional plasmid-mediated recombineering or advanced CRISPR/Cas9 gene-editing tool has offered a better platform to construct recombinant probiotics with desired attributes (Koo et al., 2012). Furthermore, the biotechnological intervention has also aided in developing personalized medicine to treat specific diseases or to enhance the function of traditional probiotics by overexpression of specific therapeutic molecules in a desired traditional probiotic strain (Mays et al., 2020).

Of note, NGPs are generally used as a drug rather than food supplements to combat the specific disease or pathogens (US Food and Drug Administration, 2011). Therefore, the genome unmodified NGPs are categorized under the live biotherapeutics (LBPs), and recombinant probiotics are classified under recombinant live biotherapeutics as per US FDA. To date, the EFSA panel has not approved NGPs in the European Union. According to US FDA, LBPs are biological products that (1) contain live organisms, such as bacteria, yeast (except filterable viruses, oncolytic bacteria, or products intended as gene therapy agents), (2) should be aimed at prevention or treatment of a disease condition, (3) is not a vaccine, and (4) is not administered by injection (US Food and Drug Administration, 2011). The major differences between conventional probiotics and NGPs have been presented in Table 1. Hitherto, NGPs have been designed to curb diseases including obesity, cancer, pathogenesis, IBD, etc. (O'Toole et al., 2017). Besides, the advent in patho-biotechnological concept facilitated the expression of specific adhesion protein (*Listeria* adhesion proteins) from a specific pathogen (*L. monocytogenes*) on the probiotic bacterial surface that led to successful prevention of adhesion and colonization of *L. monocytogenes* to Caco-2 cell line (Koo et al., 2012). Besides, NGPs have also found their potential applications as mucosal delivery of vaccines against several bacterial and viral pathogens by expressing a specific immunogenic component on probiotic bacteria surface that can elicit the host immune response against target pathogens (Rosales-Mendoza et al., 2016). However, a major drawback of recombinant probiotics lies

Fig. 2 Emerging members of Next-Generation Probiotics (NGPs)

Table 1 Characteristics of conventional and next-generation probiotics (NGPs)

Conventional probiotics	Next-generation probiotics
History of safe use	No history of safe use
Members of this category include gram-positive microbes	Belong to both gram-positive and gram-negative categories
Generally belong to phyla actinobacteria and firmicutes	Belong to phyla actinobacteria, firmicutes, bacteroidetes, verrucomicrobia, and proteobacteria
These are not genetically modified	These may be genetically modified
Easy to culture	Difficult to culture
Generally microaerophilic to anaerobes	These are extreme oxygen-sensitive (obligate anaerobe) except genetically modified recombinant <i>Lactobacillus</i> probiotic strains
Used as food supplements	Used as both food supplements and drugs
Accorded QPS status from EFSA	No QPS status from EFSA
Effects on the host are generic	Effects on the host are specific due to the intervention of genetic engineering
Do not degrade gastric mucin	Degrade mucin often (Pathogenic trait)
Isolation niche may include dairy and food products, human and animal gut, human milk, plants, etc.	Specifically isolated from the human gut and do not include the bacteria from other human niches

in their regulatory approval procedures as dozens of countries have certainly banned the usage of genetically modified microorganisms as food ingredients.

Pharmabiotics

Pharmabiotics may be defined as “bacterial cells of human origin, or their products, with a proven pharmacological role in health or disease” (LeBegue et al., 2019). In other words, it is a generic term that includes any form of

therapeutic exploitation of the commensal flora, including commensal derived biologically active metabolites or genetically modified commensal bacteria. Of note, these should mandatorily be subjected to clinical trials to measure endpoint efficacy and safety with defined mechanistic action. Pharmabiotics have regulatory approval procedures similar to a drug alike NGPs. Although the term pharmabiotics refers to live biotherapeutics (live bacterial cells), it may also encompass fungi, phages, bacteriocins, or other microbes. The inclusion of fungi and bacteriophages is a remarkable difference between NGP and

pharmabiotics (LeBegue et al., 2019; Patra et al., 2017). On the contrary, bioactive molecules such as bioactive lipids (including SCFA and conjugated linoleic acid), γ -aminobutyric acid, serotonin, catecholamines, acetylcholine, antimicrobial, exopolysaccharides, and vitamins produced by healthy gut bacteria were also classified under pharmabiotics (Patterson et al., 2014). A recent opinion article highlighted another related term Probiocuticals/Probiotaceuticals, which defines probiotic derived factors such as reuterin (3-hydroxypropionaldehyde) from *Lactobacillus reuteri* (Langella and Martin, 2019). Taken together, it can be concluded that pharmabiotics are the beneficial microbes (probiotics or commensal bacteria or yeast, bacteriophages) or their derived biomolecules that have proven efficacy and safety for clinical applications.

Psychobiotics

Psychobiotics may be defined as “live organisms that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness”. In other words, live bacteria (probiotics) which, when ingested, confer mental health benefits through interactions with commensal gut bacteria (Dinan et al., 2013; Sarkar et al., 2016). An in-depth gut microbiome analysis of psychiatric patients displayed a significant shift in colonization pattern in the normal microflora with a characteristic low-grade inflammatory response (Alam et al., 2017). This merely confirms a typical link between the gut and brain, which is widely recognized as a gut-brain axis (Wong et al., 2016). To combat mental depression, intervention with probiotic bacteria (*Lactobacillus* and *Bifidobacterium*) has emerged as a biotherapy to normalize the gut flora which subsequently normalizes the anxiety and depressive symptoms (Pirbaglou et al., 2016). Also, specific probiotic strains have been reported to produce neurotransmitters and proteins such as gamma-aminobutyric acid, acetylcholine, tryptophane, catecholamines, serotonin, and glutamate that overcome anxiety and depression via modulating neural signaling within the enteric nervous system and consequently signal brain function of the host. Additionally, the anti-inflammatory potentiality of probiotics overcomes the low-grade inflammation among mentally abnormal patients (Sarkar et al., 2016; Wall et al., 2014). In a study, *Lactobacillus acidophilus* was reported to modulate the expression of cannabinoid receptors (endocannabinoids are the lipid moieties that act as neurotransmitters in the brain, which contains specific receptors) in the spinal cord (Piomelli, 2003). These evidences suggest the possible influence of probiotic bacteria in ameliorating certain neurological and neurophysiological conditions either as a therapeutic or prophylactic agent. Moreover, the neuro-

active compounds-producing probiotic bacteria may be the effective delivery vehicles for neuroactive compounds.

Oncobiotics

Oncobiotics are the live microbes or their derived metabolites exhibiting ameliorative actions against cancer. So far, probiotics intervention to overcome cancer is largely confined to prevent colorectal cancer, which ranks second for the cause of cancer-related mortality (Eslami et al., 2019). Under the dysbiosis state, pathogenic microflora can activate the enterocyte associated TLR-5 to stimulate the inflammation that promotes genomic instability and DNA damage responses (Rutkowski et al., 2015). Indeed, the abundance of enterotoxigenic *Bacteroides fragilis*, *E. coli*, *Fusobacterium nucleatum*, *Alistipes*, Porphyromonadaceae, Coriobacteridae, Staphylococcaceae, *Akkermansia*, and Methanobacteriales was correlated with epigenetic changes and genotoxicity in colon cells (Parés, 2019). By contrast, LAB and other probiotic strains imbibe immense capability to retard such colon carcinogenesis by possibly modulating metabolic, immunologic and protective functions in the colon and such an emerging field is often also termed as “oncomicrobiotics” (Kumar et al., 2010, 2013). LAB intervention to combat cancer has been reported to lower the activity of xenobiotic-metabolizing enzymes viz. β -glucuronidase, β -glucosidase, nitroreductase, and azoreductase activities in stool samples, which are thought to play an important role in the conversion of procarcinogens to carcinogens. On the other hand, the short-chain fatty acids (butyrate) produced by the anaerobic fermentation of prebiotics by probiotic bacteria stimulate the SCFA-receptors to trigger the proliferation of normal colon cells and suppress proliferation in transformed cells by triggering apoptosis (Wollowski et al., 2001) via COX-2 suppression, caspase-3 activation, the polarization of mitochondrial membrane potential, inflammasome deactivation, down-regulation of NF- κ B, and mitogen-activated protein kinase (MAPK) signaling pathways (Ambalam et al., 2016). Besides, SCFAs have reported modulating epigenetic signatures of colonocytes by inhibiting histone deacetylases (Fellows and Varga-Weisz, 2019; Shimazu et al., 2013).

In conclusion, the benefits of probiotics were originally confined to the prevention and treatment of diseases associated with the gastrointestinal tract. However, modern medicine has found its way to exploit both live probiotics and their molecules beyond the gut. Unraveling the protective action of beneficial microflora and their bioactive metabolites has resulted in the emergence of various functional biotics such as probiotics, prebiotics, synbiotics, postbiotics, next-generation probiotics, psychobiotics,

oncobiotics, pharmabiotics, smart probiotics, and metabiotics. Subtle differences among such concepts are often uncertain to understand. Few bioactive compounds are either used traditionally or developed by modern scientists as the advancements took place in modern science. However, all these bioactive compounds have control over human health and aid in freedom from disease. Furthermore, additional efforts are necessary to evaluate the stability of these biomolecules under different process conditions when produced at a commercial scale. Given that the yield of these molecules is considerably less, it is important to develop economic technologies with optimization of agro-byproduct based medium to cultivate microbes to extract bioactive molecules. Overall, furthermore inclusive and comprehensive well-designed randomized placebo-controlled human clinical trials are paramount to validate the health claims with ensured safety, efficiency, and effectiveness.

Acknowledgements The authors are greatly thankful to the Director, ICAR-National Dairy Research Institute, Karnal, Haryana, India and Science & Engineering Research Board (SERB), New Delhi, Government of India (EMR/2016/001399).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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