From Probiotics to Postbiotics: Key to Microbiome and Health

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Abstract

Humans are consuming probiotic microorganisms through traditionally fermented food since thousands of years, unknowingly. Probiotic microorganisms are usually lactic acid bacteria, are generally recognized as safe, and play a significant role in human health by producing a variety of metabolites. The list of their health benefits is pretty long, but despite of it, probiotics have some limitations to use for therapeutics mainly due to being live. Hence, in the recent past, the focus of health benefits of microorganisms is being shifted from viable live probiotics to nonviable paraprobiotics or probiotic-derived postbiotics. Postbiotics are nonviable metabolic products of probiotic bacteria possessing biological activity in the host. These metabolites are noted to have equivalent health potential as that of probiotics and additionally have advantages over limitations of probiotics that are discussed in this chapter.

Keywords

Human health · Paraprobiotics · Postbiotics · Prebiotics · Probiotic

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18.1 Introduction

Probiotics have been defined as live microorganisms which when administered in adequate amounts confer health benefit to the host (Markowiak and Slizewska 2017). Though the concept of probiotics has been elaborated in modern science lately, humans have been unknowingly consuming beneficial microorganisms since thousands of years through traditionally fermented foods, which are main sources of probiotic microorganisms (Linares et al. 2017). Probiotic microorganisms are lactic acid bacteria (LAB) and belong to the genera *Lactobacillus*, *Bifidobacterium*, *Pediococcus*, etc. There are many evidences indicating that LAB play a vital role in human health by producing various metabolites (Xu et al. 2019). They are generally recognized as safe and hence important not only in the food sector but also in the pharmaceutical industry.

Thus, LAB are functional components for foods; moreover, their metabolic products like lactic acid and bacteriocins offer property of natural preservative and antimicrobials against contaminating microorganisms (Chuah et al. 2019). Their benefits are reported and include prevention of various infections, immunomodulation, and amelioration of clinical conditions like irritable bowel syndrome (IBS), hypercholesterolemia, various types of cancers, etc. These effects are intervened through mechanisms like alteration of gut microflora, boosting immune response, antiproliferative, anti-oxidative, apoptosis, modulating gut microbiome, etc. The list of health benefits is still incomplete, and despite of it, probiotics have some drawbacks due to their viability status that imparts main limitations for their applications in food and pharmaceutical industries (Nataraj et al. 2020). The limitations include (1) unknown or poor mechanisms at a molecular level, (2) strain-specific effect, (3) threat of antibiotic resistance through horizontal gene transfer, (4) maintaining viability, (5) threat of opportunistic infections, (6) inflammatory responses, and (7) systemic infections (endocarditis, sepsis, etc.). Consequently, though probiotics are nonpathogenic microorganisms offering beneficial effects, carefulness is required when administering in patients with inflammation and severe pancreatitis, and some probiotic strains may result harmful in irritable bowel syndrome (Cicenai et al. 2014).

Fermented foods are important for the gut health, even though the benefit does not characteristically result from the colonizing microbes, but the ferment itself. During fermentation, bacteria form many biomolecules/metabolites (postbiotics) that are beneficial to the gut and immune mechanism (Maguire and Maguire 2019).

Probiotics also maintain and restore the skin microbiota as in the gut, but the use of live bacteria on skin poses some limitations (Majeed et al. 2020). Though since the last four decades or so, the use of probiotics found place in reducing load of common infections in children, scientific community does not hold up probiotic involvement in pediatric diseases due to case findings of probiotic-associated infections like necrotizing enterocolitis, pneumonia, meningitis, bacteremia and their rising trend of adherence, invasion, and cytotoxicity, etc. (Rojas et al. 2020).

In addition to the above-stated disadvantages of probiotics, many physicians are still doubtful in the use of probiotics for pediatric practice because of unusual cases of probiotic unpleasant effects. On the contrary, more reports suggesting that the probiotic strains need not be live to offer benefits to the host, a report indicated inactivated strains can adhere better to the mucosa of the intestine than viable one (Mantziari et al. 2020).

Therefore, recently, the focus of health benefits is progressively displacing from viable probiotic bacteria in the direction of nonviable paraprobiotics or probiotic-derived postbiotics. Postbiotics known to be physiologically rich, with defined chemical structures, safety dosing, and extended shelf life (till 5 years) make them therapeutically appealing. Also, their features include suitability in absorption, synthesis, excretion, and sharp signaling potential with host tissue responses (Puccetti et al. 2020).

18.2 Postbiotics: Definition and Concept

Although, viability is an integral part of definition to label the microbe as probiotics, it is not all the time obligatory to pursue health benefits. The nonviable probiotics that retain their health benefits are generally termed as paraprobiotics, while the term postbiotic is applied for soluble bioactive factors secreted by probiotics or freed after rupture of their cell (Anderson 2019). In recent years, there is emergent attention in probiotic effects shown by these microbial metabolites, also called bioactive postbiotic metabolites (PM), especially in intestinal health and general immunity (Chuah et al. 2019). These metabolites (PM) are reported to be of equivalent potential with probiotics and encompass soluble or secreted factors, metabolites, cell-free supernatant, bacteriocin, etc. The role of these PM in intestinal health and being safer alternative in contrast to live bacteria is well documented (Chuah et al. 2019).

Postbiotics being nonviable bacterial products from probiotic organisms are nontoxic, nonpathogenic, and resistant to hydrolysis by mammalian enzymes (Kerry et al. 2018). The various metabolites of microorganisms claimed for their postbiotic status are shown in Fig. 18.1.

Though several researchers have proposed various terminologies to express postbiotics and paraprobiotics with the relatively similar perception about these terms, as mentioned by Nataraj et al. (2020), the widely accepted definitions are as follows:

- Paraprobiotics (also called as ghost probiotics or inactivated probiotics): nonviable microorganisms (either intact or broken) or crude cell extracts which when administered in adequate amounts confer benefit to the host.
- Postbiotics: Nonviable bacterial metabolic products having biological activity in the host. As mentioned by Gutierrez et al. (2020), postbiotics (also called as metabiotics, pharmacobiotics, or heat-killed probiotics) are bioactive substances produced by probiotic microorganisms, generally LAB. Moreover, many components present in probiotics that are released before death are also recognized as postbiotics. Rojas et al. (2020) mention postbiotics as bioactive

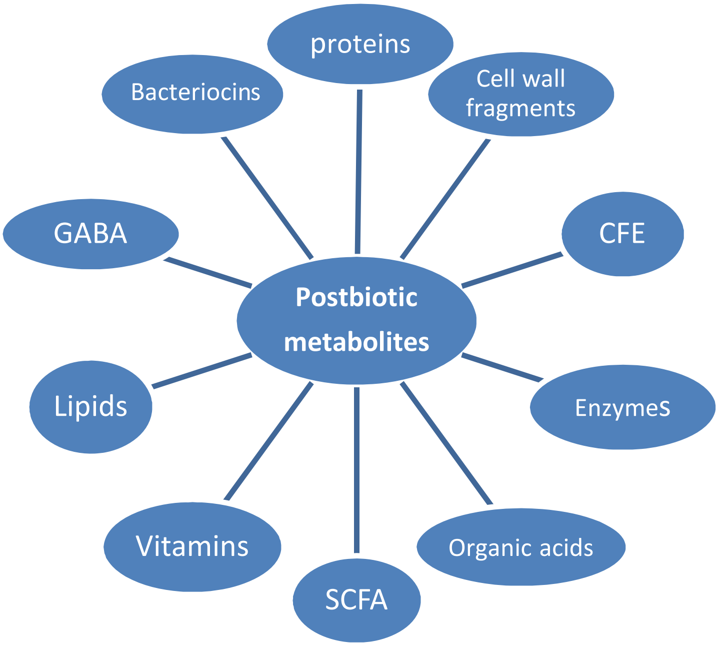

Fig. 18.1 Representative postbiotic metabolites

substances produced during the process of fermentation which maintain health and well-being.

As Rossoni et al. (2020) cited, postbiotics can also be defined as probiotic bacterial products with bioactive property in the host and may include metabolites, cell fractions, fatty acids, proteins, polysaccharides, cell lysates, peptides of peptidoglycan, and adhesion structures like pili.

The recognition of such entities may present an opening to keep away hazards associated with the administration of live microorganisms (Cicenai et al. 2014). Moreover, these things continue offering functional properties to the fermented food those have biogenic benefits resulting from the microbial production of bioactive metabolites during the process of fermentation. Postbiotics comprise extended shelf life safety and hold multiple health benefits (Majeed et al. 2020).

18.3 Sources of Postbiotics

From the discussion above, it is quite clear that postbiotics are products of probiotic microbes, thus the source of postbiotics is probiotics, generally LAB. From these LAB, various cellular components can be the source or origin for postbiotics, as shown in Table 18.1.

Table 18.1 Postbiotics and their location in bacterial cell

Location	Postbiotics	References
Cytoplasm	Enzymes, proteins, vitamins, lipids	Gutierrez et al. (2020)
Cell structure Pili Cytoplasmic membrane	Components of pellicle capsule or cell wall Adhesins Glycerophospholipid	Rojas et al. (2020) Rossoni et al. (2020) Singh et al. (2018)
Secreted products	Organic acids, EPS, SCFA, bacteriocins, polysaccharides, immune modulators, neurotransmitters, etc. Ethanol, diacetyl, acetaldehydes, H_2O_2	Gutierrez et al. (2020) Kerry et al. (2018)

18.4 Forms or Types of Postbiotics

There are varieties of postbiotic biomolecules consisting of secreted metabolic products of probiotic microorganisms like cell-free supernatants (CFS)—vitamins, short-chain fatty acid, organic acid, proteins, bacteriocins, amino acids and their complex or derivatives, etc. Furthermore, the paraprobiotics constituents, i.e., inactivated or dead and nonviable microbial cell preparations containing intact or ruptured cell components like teichoic acids, peptidoglycan, etc., can also be used to evaluate beneficial effects. Usually, paraprobiotics include a broad array of biomolecules like peptidoglycans, surface proteins, and cell wall polysaccharides, whereas postbiotics comprise secreted proteins, peptides, bacteriocins, organic acids, etc. (Teame et al. 2020). Since postbiotics are nonliving entities, their processing and maintenance are easy compared to probiotics. Compiled work out for some representative postbiotic metabolites from source microorganisms with their effects is depicted in Table 18.2.

18.5 Production Methods of Postbiotics

As postbiotics contain inactivated microorganisms or their structures or metabolic products (which are released or secreted during fermentation or poured after rupturing); in many postbiotic preparations used for study, fermented broth is filtered, or heated and the resultant material called cell-free supernatant (CFS) (Mantziari et al. 2020). Alternatively, probiotic cultures are inactivated by heat treatment, filtration (mostly 0.2μm), cell lysis by sonication, followed by centrifugation, and are often exposed to UV. These procedures result in break opening of bacterial cells pouring intracellular biomolecules that can be used as postbiotics. Chuah et al. (2019) mentioned a series of procedures: growth (24 h)—centrifugation (10,000 g, 10 min), CFS—pH adjustment—filtration-storage. Compare et al. (2017) obtained

Table 18.2 Various postbiotic biomolecules and their health benefits

Postbiotic type or form	Example/name	Source organism(s)	Application(s)	References
Amino acids/ derivatives	Selenocysteines and selenomethionines Tryptophan-indoles Gamma-aminobutyric acid (GABA)	*Lactobacillus* spp. Yeasts Mix microbiota *L. plantarum* *L. brevis* *L. paracasei* *L. bulgaricus* *L. bulgaricus* *L. zymae*	Immune modulation, anticancer, oxidative stress, anabolic pathways Intestinal permeability Neurotransmitter inhibitor CVD: hypotensive Epilepsy: gut-brain functionality Anxiety and depressive disorders, diabetes, cancer, asthma, etc.	Singh et al. (2018) Maguire and Maguire (2019) Gutierrez et al. (2020)
Bacteriocins	Ruterin Nisin A Plantaricin PJ4	*Lactobacillus reuteri* *L. lactis* *Lactococcus lactis* *L. helveticus*	Intestinal infections Antibacterial Immune modulator Active against enteric pathogens	Cicenai et al. (2014) Puccetti et al. (2020) Teame et al. (2020)
Cell-free supernatant (CFS)	CFS-PM CFS-PB CFS	*Lactobacillus plantarum* *Lactobacillus casei* DG *Lactobacillus reuteri* *L. acidophilus* *L. casei* *L. rhamnosus*	Anticancer (breast, colon, and cervical) Inflammatory mucosal response LPS-induced liver injury Ant-inflammatory Antioxidant, cancer	Chuah et al. (2019) Compare et al. (2017) Anderson (2019) Jakub et al. (2020)
Cell wall fragments	Lipoteichoic acid (LTA) Peptidoglycan LTA	*Lactobacillus paracasei* D3–5 *L. casei* *Bifidobacterium* sp. *Lactobacillus* sp.	Antiaging Antitumor effect skin mast cell response against bacterial and viral infections	Nataraj et al. (2020) Jakub et al. (2020)

Deoxycholic acid	Bile acids	*Bifidobacterium*, *Lactobacillus*, *Bacteroides*	Inhibition of pro-inflammatory genes, regulates bacterial growth	Puccetti et al. (2020)
Extracellular polymers	EPS	*Lactobacillus plantarum*, *L. gasseri* *L. plantarum*	Antitumor, colon carcinoma Anti-inflammatory Oxidative stress	Chuah et al. (2019) Kwon et al. (2020)
Enzymes	Glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase	*L. fermentum*, *L. plantarum*	Reactive oxygen species (ROS), Crohn's disease, IBS, etc.	Jakub et al. (2020)
Indole/derivatives	5-Hydroxytryptophan, tryptamine, indoleacetic acid, 3-methylindole, indole-3-sulfate	*Lactobacillus*, *Bacteroides*	Antimicrobial peptides, IL-22, epithelial barrier	Puccetti et al. (2020)
Lipid compounds	Glycerophospholipid	*B. animalis* subsp. *lactis*	Down syndrome, antioxidant, Alzheimer disease, etc.	Singh et al. (2018)
Organic acids	Lactic acid, acetic acid	*Lactobacillus plantarum*	Antibiotic replacer in poultry and pig feeds	Chuah et al. (2019)
Polyphenol derivatives or transformed products	Urolithins, equol, and enterolignans	*Bifidobacterium* sp., *Lactobacillus* sp., *Clostridium* sp., *Bacteroides*	Polyphenol bioactivation/ transformations CVD, anticancer Prebiotic effect	Tomova et al. (2019)
Polyphosphates	Polyphosphates	*Lactobacillus brevis*	Colitis, intestinal permeability	Zagato et al. (2014)
Proteins	Protein HM0539 Msp1 and Msp2 (culture supernatant)	*Lactobacillus rhamnosus* LGG (ATCC 53103) *L. rhamnosus* GG	Intestinal barrier injury, colitis, liver injury Intestinal epithelial damage, apoptosis	Gao et al. (2019) Cicenai et al. (2014)
SCFA	Butyrate, acetate, propionate	Bacteroidetes, Firmicutes *Lactobacillus* sp. *Enterococcus* sp.	Mucosal immunity, inhibit pro-inflammatory cytokines, production of IL-18, etc. Diabetes, cancer, obesity	Puccetti et al. (2020) Gutierrez et al. (2020)

(continued)

Table 18.2 (continued)

Postbiotic type or form	Example/name	Source organism(s)	Application(s)	References
Vitamins	Niacin (vitamin B3) Vitamin K B group vitamins Biotin, nicotinic acid, cobalamin, riboflavin, thiamine, pyridoxine, and pantothenic acid	Gut microbiota *Lactococcus lactis*, *L. gasseri*, *L. reuteri* *B. adolescentis* *Propionibacterium freudenreichii*	Intestinal inflammation, colon cancer, colitis, etc. Biofortification Deficiencies	Singh et al. (2015, 2018)

postbiotic preparation for study by growing probiotic culture followed by centrifugation only. Haileselassie et al. (2016) have removed cells from culture broth by centrifugation and the supernatant was filter-sterilized and the preparation stored at pH maintained 7.2−7.5.

18.6 Applications/Benefactions of Postbiotics

One can correlate the benefaction of postbiotics to that of probiotics, since it becomes clear that postbiotics are metabolic products of probiotics. We have enough discussion to convey the limitations of probiotics and how postbiotics can eventually have all those advantages being nonliving. The benefaction of postbiotics has multifaceted coverage as depicted in Fig. 18.2.

Fig. 18.2 Postbiotic effects

18.6.1 Immune Modulation

One of the immune defense responses of the body is inflammation; however, excessive inflammation can harm vital tissues of the organ. Many probiotics are studied to have immunomodulatory effects. Postbiotics are able to fuel the immune system, also involving the intestine, and bowel anti-inflammatory, immunomodulators (Tomasik and Tomasik 2020). Kwon et al. (2020) have shown the immunomodulatory effect of postbiotic EPS isolated from *L. plantarum*. In their study, they found that EPS inhibited pro-inflammatory mediators- NF-8 and MAPK pathways by repressing TLR4 and MyD88 signaling. Diverse postbiotic fractions obtained from *Bacillus coagulans* can provoke anti-inflammatory cytokine production and thus support T helper-dependent immune mechanisms (Jakub et al. 2020). Hence, such properties of postbiotics can bring limitations to TH1-induced immune effects and enhance Th2-arbitrated reactions which are generally seen in persons prone to atopic disease.

18.6.2 Anticancer Properties

Cancer is a global health issue and a chief cause of death affecting many organs by rapidly creating and proliferating transformed cell. GABA (gamma-aminobutyric acid) is one of the postbiotics produced in gut microorganisms, shown to be associated with breast cancer by a prognostic value (Gutierrez et al. 2020). Higher the GABA better is the survival prognosis and GABA was found to restrain colon cancer cells. In the study with PM of *L. plantarum*, Chuah et al. (2019) have noted that apoptosis against cancer cells shows selective toxicity by suppressing proliferation thus indicating potential of anticancer therapeutic value of postbiotics. Induction of apoptosis against cancer cells was observed by SCFA propionate obtained from *P. freudenreichii* (Jakub et al. 2020). The suppression of oncogenes is controlled by these SCFAs.

18.6.3 Luminal and Mucosal Effects

The gut epithelium is considered as the foremost defense line against the huge number of microbes entering the body. A disturbance in this line barrier is called as leaky gut, and the resultant inflammatory reaction poses many clinical conditions of the gut as well as other parts of the body (Anderson 2019). With this concern, a report depicts protein secreted (postbiotic) by *L. rhamnosus* reduced LPS-provoked liver damage through progressing gut uprightness. Gao et al. (2019) observed a promising protective effect on intestinal barrier with a postbiotic protein HM 0539 revealed by stimulating intestinal mucin expression and combating against TNF-α/ LPS-induced gut wound that comprised of disturbed veracity and mucin downward regulation. Haileselassie et al. (2016) have shown a postbiotic CFS of *L. reuteri* influenced retinoic acid forced mucosal like DCs and its effect on regulatory cells with higher IL-10, CD 103, and CD1d expression while suppression of inflammatory genes.

18.6.4 IBS/IBD and Other Conditions

Irritable bowel syndrome (IBS) is one of the commonest GIT problems universally affecting the quality of life of patients. With this concern, postbiotics of *L. casei* have been evaluated and found a promising protective effect in the IBS organ culture model. In the study, TLR4 protein expression and IL-1α, IL-6, and IL-8 mRNA levels were found to be elevated; on the contrary, IL-10 mRNA levels were decreased in both the ileum and the colon (Compare et al. 2017). The postbiotic significantly decreased pro-inflammatory cytokines and provoked the protective effect.

Inflammatory bowel disease (IBD) is a multifaceted chronic inflammatory condition of the GIT, and the intestinal microbiota seems to be the chief etiological factor for its development. Also, studies revealed the role of postbiotics in the reconstruction of impaired interactions of gut microbiota and immune cells. In a mouse model, it was seen that SCFAs and tryptophan postbiotics activated immunomodulatory mechanisms by ordering immune cell generation, trafficking, and functioning (Russo et al. 2019).

18.6.5 Neural Diseases

Experimental reports indicated that metabolites of intestinal microbiota govern the integrity and pathophysiology of the nervous system and thus are associated with neuroimmune clinical conditions. Also, negotiation of integrity of the intestinal tract lining adversely affects the nervous system (Maguire and Maguire 2019). Gutierrez et al. (2020) stated that hypoxic-ischemic actions during fetal development can trigger memory-related shortfall because of neurotransmission disturbance by damage in GABA (postbiotic from *Lactobacillus* spp.) function.

18.6.6 Diabetes

Diabetes has become a great threat to human beings since its occurrence is significantly rising all over. It is due to dysfunctional pancreatic cells that do not produce insulin and result in abnormal glucose levels in the blood. With this connection, it was noted that the therapeutic action of GABA and the found progression of prediabetes and inflammatory response can be inhibited (Gutierrez et al. 2020). This is due to regulatory action of GABA molecule on cells of islets, stressing the depression of insulitis and inflammatory cytokine production. Cavallari et al. (2017) noted that bacterial cell wall-derived muramyl dipeptide (which needs NOD2) is an insulin-sensitizing postbiotic and further showed in obese mice that bacterial cell wall muropeptide can function as postbiotic by improving insulin resistance and metabolic tissue inflammation.

18.6.7 Antimicrobial Potentials

The indiscriminate use of antibiotics for general infections is resulting in antibiotic resistance among pathogens. The surfacing of antimicrobial resistance is alarming and leading to therapeutic failure; hence, there is a need for a new approach to deal with. Many postbiotics from probiotics like bacteriocins, enzymes, organic acids, and small molecules are reported to have antimicrobial activities, for instance, nisin A from *Lactococcus lactis* (Puccetti et al. 2020).

Mantziari et al. (2020) noted important observation: (1) EPS from *Lactobacillus* and *Bifidobacterium* showed protective action against enterotoxigenic *E. coli*, (2) CSF of *B. bifidum* in supplemented medium induced the expression of virulence genes in *E. coli*, (3) postbiotics from *B. bifidum* have shown inhibitory effect against *E. coli*, and (4) CSF from breast milk commensals showed activity to limit HIV infection in vitro. Rossoni et al. (2020) have studied the antifungal activity of postbiotic (crude extract and fraction) of *L. paracasei* and found to inhibit the growth of *Candida auris*.

18.6.8 Miscellaneous Applications

Wegh et al. (2019) reported important findings: (1) a clinical study on postbiotic preparation of *B. breve* revealed that it was well tolerated in infants and decreased the incidence of diarrhea and abdominal distention, (2) postbiotic effect of *L. paracasei* against placebo in adults with atopic dermatitis found better skin severity scores after 12 weeks but not in placebo group, and (3) in old age group study, postbiotics of *L. pentosus* reduce the frequency of common cold compared to placebo on the incidence of common cold. Vandenplas et al. (2020) have also studied in infants (less than 14 days) and found infant formula safe with postbiotics linked prebiotic (ss GOS) from Lactofidus fermentation process.

In a mouse model experiment, infant formula of postbiotics obtained from a specific fermentation process coupled prebiotic study revealed increased functional and morphological intestinal maturation much similar as the mother fed conditions than infant formula lacking postbiotic-prebiotic combination (Salminen et al. 2020).

In addition to the applications and their underlying mechanisms, postbiotics can be exploited vastly with some other areas such as nutrition and health. Postbiotics have potential properties like anti-obesity, antihypertensive, hypocholesterolemic, and many more (Tomasik and Tomasik 2020). Also, in nutrition point of view, food biofortification with postbiotics can be achieved especially for B group vitamins, and this could be an elegant strategy to combat the universal problem of its deficiency-related clinical conditions. Obesity is the chief health concern worldwide that can be dealt with postbiotics through dietary supplements to combat and improve host metabolism (Reynés et al. 2019).

Acne vulgaris is a universal skin disorder generally at peak at puberty and may be now treated with postbiotic formulation LactoSporin as seen in an open-label randomized study (Majeed et al. 2020). It is found that LactoSporin is equally efficient in treating acne lesions in comparison of benzoyl peroxide. The study also revealed the mechanism of amelioration of the condition. The pathology may be associated with the excessive secretion of sebum as the study indicates and LactoSporin could inhibit the 5-alpha reductase enzyme and thus reducing the secretion of sebum.

18.7 Future Prospects as Concluding Remarks

Though the term postbiotics is new compared to the popular terms probiotics and prebiotics, the promising potentials of postbiotics as therapeutics and obvious advantages over probiotics alarm near future pharmaceutical markets to be called for postbiotics. We can find preparations and formulations available easily for probiotics and prebiotics but not for postbiotics. There may be pharmacological, biochemical, and medicolegal aspects to be sorted out for making postbiotics available and useful as therapeutics, but we can certainly expect it in practice to treat a variety of clinical conditions in future.

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