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Postbiotics as the key mediators of the gut microbiota-host interactions

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SUMMARY

The priority of the Sustainable Development Goals for 2022 is to reduce all causes related to mortality. In this regard, microbial bioactive compounds with characteristics such as optimal compatibility and close interaction with the host immune system are considered a novel therapeutic approach. The fermentation process is one of the most well-known pathways involved in the natural synthesis of a diverse range of postbiotics. However, some postbiotics are a type of probiotic response behavior to environmental stimuli that usually play well-known biological roles. Also, postbiotics with unique structure and function are key mediators between intestinal microbiota and host cellular processes/metabolic pathways that play a significant role in maintaining homeostasis. By further understanding the nature of parent microbial cells, factors affecting their metabolic pathways, and the development of compatible extraction and identification methods, it is possible to achieve certain formulations of postbiotics with special efficiencies, which in turn will significantly improve the performance of health systems (especially in developing countries) toward a wide range of acute/chronic diseases. The present review aims to describe the fundamental role of postbiotics as the key mediators of the microbiota-host interactions. Besides, it presents the available current evidence regarding the interaction between postbiotics and host cells through potential cell receptors, stimulation/improvement of immune system function, and the enhancement of the composition and function of the human microbiome.

Keywords: postbiotics, gut microbiome, immunomodulation, functional food, COVID-19, public health.

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INTRODUCTION

Trillions of bacteria, archaea, fungi, and viruses with complex connections are embedded in the human gastrointestinal tract (GI) as s unique microbial ecosystem [1, 2]. The formation of this microbial community begins at birth and each stage of life, a particular microbial population prevails that plays a key role in the host physiology. As significant progress has been made, the vital role of the host, the microbiome, the metabolites released in the process, and the activated metabolic pathways is becoming more prominent. The type of cell-cell connection known as quorum sensing (QS) remains undiscovered as far as understanding the intestinal microbiota and its effect on human physiology and nutrition [3, 4]. Recognizing all the advances made in the biological sciences, understanding the true function of bacteria in the gut milieu and their response to interacting with host cells and producing a range of bioactive compounds still needs to be studied to fully elucidate them. Microbial diversity and the relationships between them, the dietary intake, and ultimately the host's health status are among the factors influencing the functional mechanism of the intestinal microbiota. Also, according to studies, inactivated/inanimate microbial cells, their structural-functional parts, and their metabolites can activate specific signaling pathways in host cells and exert certain biological/physiological activities [5]. In this regard, we can refer to bioactive metabolites (postbiotics) produced by intestinal microbiota, which by applying activities such as inhibiting the growth of pathogens, maintaining the integrity and proper function of the intestinal mucosa, and modifying the intestinal microbial population, consider a promising approach to provide therapeutic benefits that in turn play an important role in creating/maintaining the condition of eubiosis. Due to their unique structure, postbiotics interact with host cells and play their cellular and molecular mechanisms by interfering with immune and nervous system control processes. In this case, strengthening the function of the innate immune system, reducing inflammatory responses due to the presence and function of pathogens, and strengthening the function of intestinal barriers are clear examples of this issue [6, 7].

According to the results of studies, the microbiome of each person is unique to him/her and there is growing evidence that the disruption in the composition and diversity of the intestinal microbiome following intestinal dysbiosis, leads to disruption of the normal process of communication between the brain and intestines and causes some physiological, neurological and behavioral disorders. Examples include Autism Spectrum Disorder (ASD), Inflammatory Bowel Disease (IBD), Parkinson's and Alzheimer's diseases, Multiple Sclerosis (MS), and non-communicable chronic diseases such as type 2 diabetes, obesity,

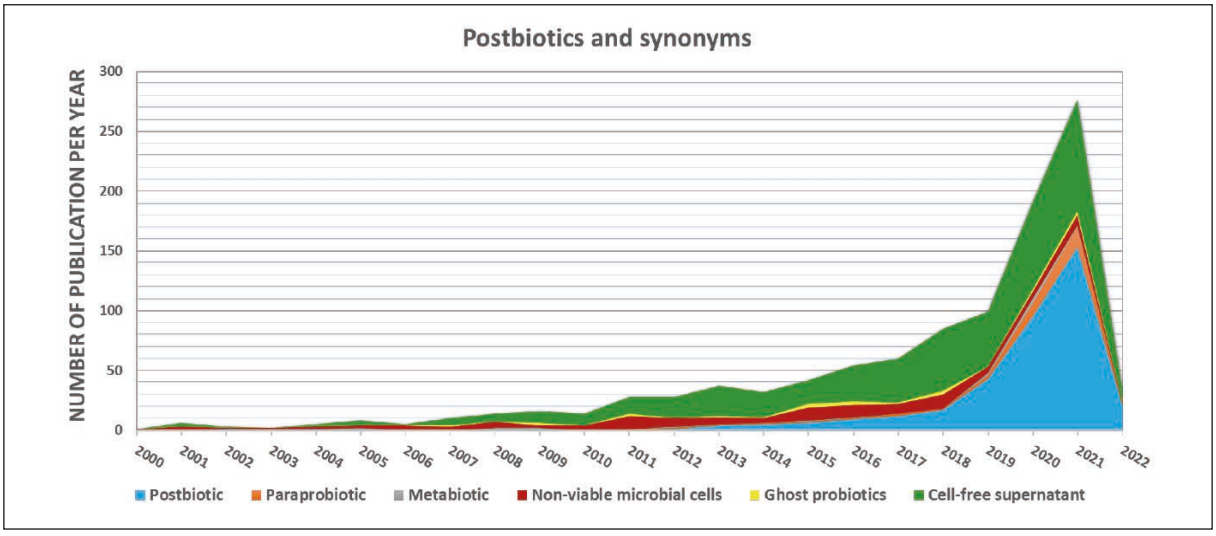

Figure 1 - Increase in the number of papers reporting research in the field of postbiotic.

and cancer [8, 9]. Currently, the evidence for the positive effect of intestinal microbiota on human physiology is increasingly being supplemented and its various dimensions are being studied [10]. Hence, any biological approach aimed at modulating the intestinal microbial population may also have some effect on central nervous system disorders, and therefore it considers an approach with multiple appropriate outcomes.

In this regard, the concept of postbiotics is proposed that can be synthesized during anaerobic fermentation of indigestible food components or even digestible substances (such as complex carbohydrates, lipids, and proteins) as well during the metabolism of bacteria in the gastrointestinal tract (Figure 1). The present review aims to describe the fundamental role of postbiotics as the key mediators of the microbiota-host interactions. Also, it presents the available current evidence regarding the interaction between postbiotics and host cells through potential cell receptors, stimulation/improvement of immune system function, and the enhancement of the composition and function of the human microbiome.

Interaction of postbiotics with their potential receptors on host cells

The positive actions of paraprobiotics or postbiotics are achieved by bacterial metabolites interacting with the host. *Lactobacillus* species have conserved microbe-associated molecular patterns (MAMP) such as peptidoglycan, Lipoteichoic acid (LTA), S-layer protein A (SlpA), exopolysaccharide (EPS), and genomic DNA that may be identified by pattern recognition receptors (PRRs) and initiate downstream signaling cascades, which provide the positive activities [11]. The role of Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs) in facilitating distinct host interactions with paraprobiotics and probiotics has long been recognized [12, 13]. This review summarises four different types of PRRs that play important roles in the regulation of the host's immune response and can bind to certain paraprobiotics or postbiotics of *Lactobacillus* strains.

Toll-Like Receptors (TLRs)

Toll-Like Receptors identify different MAMP families. TLR2 identifies LTA and peptidoglycan; TLR2/TLR4 identifies bacterial EPS through RP105/DM1, and TLR9 responds to unmethylated CpG oligonucleotide (CpG-ODN) [14]. The *Lactobacillus reuteri* DSM 17938 strain inhibited necrotizing enterocolitis via TLR2 [15]. TLR2 identified *L. plantarum* LTA and inhibited Pam2CSK4-induced IL-8 expression [16].

The EPS of *L. delbrueckii* TUA4408L may serve as TLR2 and TLR4 ligands, as well as exert anti-inflammatory activity in porcine IECs via MAPK and NF-κB signaling systems [17]. *L. plantarum* N14 EPS inhibited inflammation in intestinal epithelial cells mediated the RP105/MD1 complex (a member of the TLR family) [18]. Likewise, by altering TLR expressions, *L. rhamnosus* GG and its components (surface layer protein and EPS) suppressed MAPK and NF-κB signaling and relieved LPS-induced inflammatory cytokines in porcine intestinal epithelial cells [19].

Nucleotide-binding Oligomerization Domain-Like Receptors (NLRs)

NLRs are a vast family of PRRs with several subfamilies that may be recognized based on the N-terminal effector domains [14]. NOD1 and NOD2 are two well-studied NLR proteins. NOD1 identifies structures comprising D-Glu-mDAP [20], whereas NOD2 is required for the control of the molecules' NAM-D-Ala-D-Glu unit [21]. NOD2 recognition of muropeptide from *Lactobacillus* can provide anti-inflammatory effects and prevent mice from developing colitis [22]. NODs recognized many types of signaling chemicals from *Lactobacillus* strains, including peptidoglycan components [23], and this sensing resulted in NF-kB activating and antibacterial action [24].

C-Type Lectin-Like Receptors (CTLRs)

CTLRs identify carbohydrates compounds through one or more carbohydrate recognition domains (CRDs) [25]. CTLRs bind to sugar groups present in the glycan backbone of microbial peptidoglycan [26]. With ligand binding, specific CTLRs activate or suppress a broad range of signaling pathways, modulating a variety of immune responses [27]. DC-specific ICAM-3-grabbing nonintegrin (DC-SIGN) is a CLR that is primarily present on dendritic cells (DCs) that detects mannose- and fucose-containing glycans found on numerous *Lactobacilli* bacterial cell surfaces. DC-SIGN has recently been demonstrated *in vitro* to join *L. acidophilus* SlpA [28]. The interac-

tion of SlpA-DC-SIGN enhanced IL-10 release in DCs, which stimulated the development of T cells that produce a lot of IL-4, lowering the Th1/Th2 ratio [28]. In addition, the *in vivo* function of SlpA-induced protective immune modulation was established [29].

G-Protein-Coupled Receptors (GPCRs)
The best-studied GPCRs are GPR41 and GPR43, which are expressed by epithelial cells, adipocytes, enteroendocrine cells, and sympathetic nervous system cells, and are mostly triggered by Short-chain fatty acids (SCFAs) [30, 31]. Butyrate and propionate, which are released from gastrointestinal bacteria, interact with GPR43 and control the formation of $Foxp3^+$ Treg cells [32]. GPR109A has also been found to recognize SCFAs. The butyrate-induced activity of the GPR109A receptor, for example, resulted in the development of regulatory and IL-10-producing T cells, which inhibited colon inflammatory and tumorigenesis by boosting anti-inflammatory characteristics in colonic macrophages and dendritic cells [33]. Moreover, by GPCR signaling, SCFAs generated by gut bacteria may control lipid metabolism, glucose homeostasis, and insulin tolerance [34].

Gut microbiota-derived postbiotics and the host's immune systems
Postbiotics have mostly been related to immunoregulatory actions, as they stimulate the adaptive and innate immune systems, preserve the integrity of the intestinal mucosal barrier, and antagonize microorganisms with antibiotic substances, similar to the activities of probiotics [35, 36].
It is reported that pili and protein p40/p75, which are postbiotics released by *Lactobacilli*, have an immunoregulatory function by inducing aggregation, factor proteins, bacteriocins, and S-layer proteins by demonstrating antagonistic action against pathogens [37]. The immunostimulant action of various microbial species and strains seems to be linked to differences in cell wall components such as lipoteichoic acid and peptidoglycan. It has been proposed that the method by which these bacteria modulate immunity is to raise Th1-associated cytokine levels while decreasing Th2-related cytokines [38]. In the research, peptidoglycans derived from distinct *Lactobacillus species* (*L. acidophilus, L. rhamnosus, and L. casei*) enhanced the ability of macrophage-like cell models to suppress the release of inflammatory cytokines via the LPS-induced TLR-4 pathway [39]. In contrast, in *in vitro* models of the intestinal mucosa (HT29-MTX cells), a combination of heat-inactivated probiotic strains including *L. acidophilus, L. plantarum, L. casei, L. rhamnosus, Bifidobacterium bifidum, Streptococcus thermophilus*, and *Saccharomyces boulardii* protected midgut from *Escherichia coli* infection by reducing paracellular permeable and pathogenic penetration into the intestinal epithelium, restoring tight-junction activity and membrane integrity, and regulating cytokine gene expression [40]. In another investigation, the probiotic strain *S. thermophilus* CRL1190 and its EPS were shown to diminish *Helicobacter pylori* adherence and lower the immune reaction in a human gastric adenocarcinoma epithelial cell line (AGS cells). It has also been proposed that *S. thermophilus* and postbiotics can preserve the stomach mucosa and enhance the anti-inflammatory response by modulating the generation of the cytokine IL-8 [41]. The impact of oral therapy with the parabiotic *S. boulardii* (heat inactivated-10^9 CFU/mL^{-1}) on a murine intestinal obstruction (IO) model was investigated in the research. Heat-killed *S. boulardii* treatment preserved the intestinal barrier ($p < 0.05$) by keeping gastrointestinal permeability at normal levels and minimizing bacterial translocation (to *E. coli* ATCC 10536) and mucosal damages [42].
Similarly, scientists revealed in another research that byproducts (postbiotics) of an infant formula fermented with *L. paracasei* CBA L74 can protect the host against pathobionts and enteric pathogens by reducing immune cell inflammation and having anti-colitis properties [43]. The researchers, on the other hand, investigated the potential of a postbiotic (a new secretory protein called HM0539) produced by *L. rhamnosus* GG in the prevention and treatment of diseases associated with intestinal barrier dysfunction by orally administering it to newborn rats infected with *E. coli* K1. They discovered that HM0539 helps promote the development of newborns' gut defense and is adequate to prevent *E. coli* K1 pathogenic mechanisms. They also showed that HM0539 has the capacity to inhibit dextran sulfate sodium (DSS)-induced colitis, LPS/D-galactosamine-induced bacterial translocation, and liver disease. As a consequence, products lacking live bacteria have been observed to have identical benefits,

eliminating the necessity for probiotic cell viability [44].

Furthermore, it was shown that the immunomodulatory effect of postbiotics derived from probiotic inactivation was greater than that of probiotics. The production of heat shock proteins (Hsp) during the heating phase, for instance, appears to promote immunomodulation function [45]. *Lactobacillus casei* Zhang (LcZ) (heat-inactivated and suspended at 10^6 CFU/mL in PBS) promotes the production of proinflammatory cytokines as well as the transcription of TLR2, TLR3, TLR4, and TLR9, hence boosting the macrophage-mediated innate immunity system [46]. According to the findings of research done using the live and inactive forms of *Bacillus amyloliquefaciens* FPTB16 and *Bacillus subtilis* FPTB13, the inert preparation boosted cellular immune parameter secretion more than the live preparation [47]. Furthermore, mouse research found that combining heat-inactivated (two heat treatments were used: 30 minutes at 100°C and 15 minutes at 121°C) lactic acid bacteria (LAB) boosted immunomodulatory activity in macrophages more than the same combination (*L. acidophilus, L. plantarum, L. fermentum*, and *Enterococcus faecium*) including live strain [48]. In an investigation, it was discovered that *Enterococcus gallinarum* L-1 postbiotics inactivated by ultraviolet (UV) rays (2.5 h) were more efficient than heat-inactivated in increasing phagocyte activity (for 2 hours at 60°C) [45]. *Lactobacillus gasseri* TMC0356, both probiotic and postbiotic, has an immunomodulatory effect *in vitro*. Postbiotic *L. gasseri* TMC0356 causes a greater increase in IL-12 production in macrophages than probiotics, indicating that heat treatment increases the strain's ability to activate IL-12 production in macrophages, and thus the postbiotic form has a higher immunomodulatory effect than the probiotic form [49]. *Lactobacillus acidophilus* A2, *L. gasseri* A5, and *L. salivarius* A6 (heat-inactivated and suspended at 10^6 cells/mL in PBS) are other postbiotics with immunomodulatory action *in vitro*. The non-living microbes altered the Th1-mediated immunity reaction by promoting IL-10 and IL-12 p70 proliferation, IFN-G production in splenocytes, and IL-12 p70 secretion in dendritic cells. Although the mechanisms by which various LAB strains elicit distinct responses in dendritic cells remain unclear, the immunomodulation response appears to be strain-dependent [50]. As a result, postbiotics and parabiotics exhibit immunomodulatory action, which enhances the host's health. As a result, they could be better options for susceptible persons such as the elderly, transplanted patients, and preterm newborns, and they can be able to avoid the many downsides of probiotics.

Effects of postbiotics on microbial community interactions

Postbiotics can have an impact on the composition and function of the human microbiome in both direct and indirect ways. Fermentation products, such as organic acids, may hinder the growth and activity of pathogenic organisms, but they may also be used by particular bacteria species in the intestine, which may produce SCFAs [51] (Figure 2). The direct and indirect impacts of various postbiotic substances will be described more below.

SCFAs are key end products of gut microbial activities, as described before in this review. These SCFAs may be present in postbiotic products, resulting in direct impacts or bacterial cross-feeding. In terms of direct consequences, the most common SCFAs formed are acetate, propionate, and butyrate [52]. The major SCFAs have been shown to boost colonic salt and fluid absorption, as well as to promote colonocyte proliferation [53]. The most abundant SCFA detectable in human peripheral circulation is acetate, as propionate is metabolized by the liver being a major substrate for gluconeogenesis, and butyrate is absorbed and used as the primary source of energy by colonocytes [54]. For this reason, butyrate has received the most attention among these produced SCFAs. Furthermore, butyrate has been linked to a variety of medical benefits. Butyrate, for example, has been shown to improve intestinal barrier function and mucosal immune function, as discussed in detail elsewhere [55, 56]. Besides, butyrate and, to a lesser extent, propionate are identified to inhibit histone deacetylase (HDAC). Histone acetylation is used to improve the accessibility of the transcriptional apparatus in order to stimulate gene transcription; acetyl groups are removed by these HDACs. They produce anti-inflammatory and immunological actions by suppressing lamina propria macrophages and causing dendritic cell development from bone marrow stem cells [57]. SCFAs can also affect extracellular activity via SCFA-specific

G-protein coupled receptors (GPRs) found on intestinal epithelium cells and other cells [58]. SCFAs have also been associated with anti-tumor effects, anti-inflammatory effects on the colonic epithelium, protection from the development of immunological diseases, obesity management, glucose homeostasis control, hunger management, and cardiovascular effects, as thoroughly documented elsewhere [59].

In terms of cross-feeding on SCFAs, the mechanisms for the production of SCFAs from indigestible fiber fermentation support a bacterial cross-feeding complex including various SCFA synthesis pathways to synthesize acetate, propi-

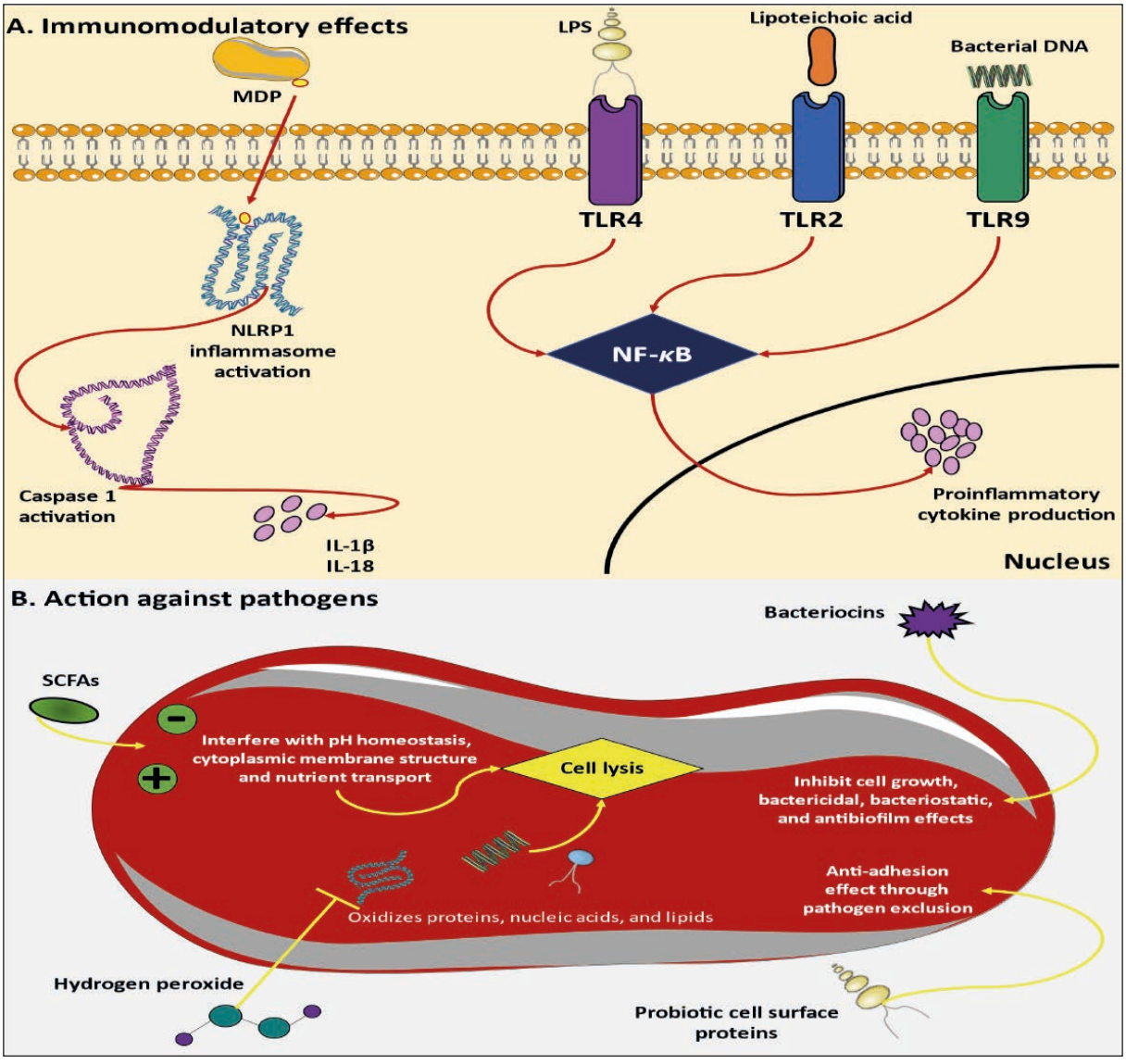

Figure 2 - Possible action mechanisms of postbiotic metabolites. (a) Modulation of the host's immune feedback. (b) Influencing the pathogenic germs. SCFAs: short-chain fatty acids; NF-κB: nuclear factor kappa B; TLR 4, TLR 2, and TLR 9: toll-like receptor 4, 2, and 9, respectively; LPS: lipopolysaccharide; IL-1β and IL-18: interleukin 1 beta and 18, respectively; MDP: muramyl dipeptide; NLRP1: NACHT [NAIP (neuronal apoptosis inhibitory protein), CIITA (MHC class II transcription activator), HET-E (incompatibility locus protein from *Podospora anserina*) and TP1 (telomerase-associated protein)] domain-, leucine-rich repeat-, and PYRIN containing protein 1.

onate, and butyrate [60]. These interactions are only possible because of the enzymatic repertoire of certain intestinal flora species. Acetate is made by bacteria such as *Blautia hydrogenotrophica, Clostridium*, and *Streptococcus* spp. via the fructose-6-phosphate phosphoketolase (F6PK) route, also known as the bifid shunt, and the Wood-Ljungdahl pathway from pyruvate via acetyl-CoA [61, 62]. Propionate can be synthesized in three different ways. *Bacteroides* spp. and *Roseburia inulinivorans*, for example, produce propionate via the acrylate process via pyruvate, after which lactate is reduced to propionate. *Bacteroides fragilis* adopts the succinate pathway', which involves the usage of phosphoenolpyruvate (PEP) or pyruvate to generate succinate and, eventually, propionate. Finally, members of the Lachnospiraceae family, including *R. inulinivorans* and *Blautia* species, may produce propionate and propanol via the propanediol route from the deoxy-sugars rhamnose and fucose via propionyl-CoA [63]. Butyrate is made up of two molecules: acetyl-CoA (which is transformed into butyryl-COA via -hydroxybutyryl-CoA) and crotonyl-CoA [60]. Butyrate-producing gut microbiota members include *Faecalibacterium prausnitzii, Eubacterium rectale, Roseburia intestinalis,* and *Anaerostipes* spp [64, 65].

In addition to SCFA cross-feeding, other research has focused on micronutrient cross-feeding, such as B-group vitamins, which are required in all microorganisms and the mammalian host [66]. Some gut bacteria can generate these precursors of essential metabolic cofactors, but other gut microbes, as well as the mammalian host, are unable to synthesize B-group vitamins [66]. A recent study with humanized gnotobiotic mice and *in vitro* anaerobic fecal culture revealed that B-vitamin interchange and exchange may play an important role in the maintenance of intestinal bacteria populations [67].

Another postbiotic molecule, EPS, has been shown to have direct impacts on the host. Postbiotic EPS-like chemicals may potentially have a function in modulating the makeup and activity of the gut microbiota. Because these carbohydrate polymers are formed of one HePS, two or more HoPS sugars, some EPS polymers can be utilized as fermentable substrates by commensal gut microbes. As a result, the host benefits from the synthesis of metabolites [68]. Some *Bifidobacterium* strains have been characterized as cross-feeding on EPS. *In vivo*, EPS generated by *Bifidobacterium* strains can function as fermentable substrates, causing changes in compound production patterns and interactions amongst gut flora [69]. A study found that EPS generated by a marine LAB called *Weissella cibaria* had a high *in vitro* bifidogenic activity [70]. Similarly, *L. plantarum* EPS has been demonstrated to enhance the growth of beneficial species like *B. longum* and *L. acidophilus* [71]. Yet, no human intervention studies have been conducted to corroborate the impacts on bacterial communities' interaction observed in *in vitro* investigations.

Finally, postbiotic chemicals may have a function in pathogen suppression. Bacteriocins or organic acids are likely to be the postbiotic components responsible for pathogen suppression [72]. Bacteriocins are antimicrobial peptides that are ribosomally produced and have bacteriostatic or bactericidal characteristics [72, 73]. Probiotic products derived from six distinct *L. plantarum* strains, for example, were shown to inhibit both gram-positive and gram-negative infections [72].

Despite the scarcity of adult human intervention investigations revealing changes in bacteria caused by postbiotics, one research found a large rise in propionic acid, butyrate, and valeric acid, as well as a significant increase in *Clostridium* cluster IV [74]. Furthermore, a few research have been published on the effect of fermented formula on the baby's intestinal microbiome [75,76]. In these trials, it was found that supplementing fermented formula reduced fecal pH [74,78]. Furthermore, substantial relative levels of acetate were found [75]. Even though these studies did not explicitly concentrate on the gut microbiota composition, these pH reductions might imply an increase in SCFA synthesis and adjustment of the gut microbiota composition towards SCFA production, which may be favorable to the host. Overall, particular postbiotics may play a role in intestinal flora regulation, so benefiting host health by promoting the proliferation of beneficial bacteria species while suppressing the growth and activity of potential pathogens.

As a result, even if the specific processes are not entirely understood, postbiotics may contribute to the enhancement of host health. To show the health impacts of postbiotics, well-designed randomized placebo-controlled intervention trials are required in addition to the mechanism of action

focused on preclinical and *in vitro* investigations. Furthermore, breakthroughs in assessing the composition and function of the microbiome usher in a new period of '-biotic' study. This has already contributed and will continue to contribute to the expansion of the variety of substances with significant health advantages that may be used in specialized nutrition. Ideally, advancements in gut bacteria research will help to explicitly build individual suggestions for tailored diet or healthcare therapies. Postbiotics can be an effective and reliable way to promote health since they present fewer obstacles in terms of storage and shelf-life than viable probiotics. Furthermore, as demonstrated in this review, multiple trials indicate comparable outcomes for the live probiotic and the postbiotic substance, suggesting that it may be a better option than probiotics in immunocompromised or extremely unwell children [77, 78]. Also, postbiotics and bioactive compounds may be an efficient strategy to boost the efficacy of probiotics, allowing them to be transformed into useful components or medicinal molecules [79].

Bacteriocins as the known postbiotics with antiviral effects

Currently, studies show that lactic acid bacteria can produce several antimicrobial peptides that are considered potential candidates for controlling some viruses. Nisin derived from *Lactococcus lactis* has been the most studied and commercially used of all bacteriocins. Each of the FDA and EFSA authorities have approved its biopreservation and safety profile [80]. In this regard, in the medical sector, the evidence related to the biological activity of bacteriocins is increasing and with the initial implementation in clinical studies, their precise functional mechanism will be determined. Numerous approaches have been suggested for enhancing the bioactivity and *in situ* targeting efficacy of bacteriocins [81]. Applicable strategies include inserting specific mutations into the bacteriocin structural gene and modifying the bacteriocin amino acid sequences, or modifying the translation of peptide sequences [82]. As a clear example, the increase of bacteriocin resistance against gastrointestinal proteolytic enzymes with the specific polar polymers by N-terminal modification of bacteriocins has been shown [81]. Inhibitory activity of bacteriocins against closely related species has typically been investigated in previous studies. However, due to the importance of the effectiveness and safety of novel therapies, research has recently focused increasingly on the growth inhibitory function of bacteriocin against other pathogens, including viruses. The precise functional mechanism of bacteriocins in the inhibition of viral activity is becoming apparent during ongoing studies [83, 84]. Bacteriocins from certain strains of *Lactococcus* spp., *Lactobacillus* spp., *Erwinia* spp., *Staphylococcus* spp., *Bacillus* spp., *Enterococcus* spp., and *Actinomadura* spp. have already been shown to reveal activity versus different viruses including measles virus, poliovirus, Newcastle disease virus, herpesvirus (HSV-1 and HSV-2), HIV-1, HAS, and coliphage [83, 85, 86]. At present, the advanced pathway for bacteriocin-mediated poliovirus control may provide options for developing treatment strategies in the management of SARS-CoV-2 [87]. In this regard, Wachsman et al. proposed mechanisms that inhibit the interaction of enterocin produced by *E. mundtii* CRL35 with the herpes virus to block the replication of viral gamma protein (glycoprotein D) during the virus invasion process [88]. Also, in the study of Serkedjieva et al., it was shown that bacteriocin produced by *L. delbrueckii* has significant antiviral activity [89]. Previously, a significant anti-herpes virus effect of antibiotic ionophore pandavir (nigericin) was demonstrated in the Dundarov and Andonov study. In this study, it was shown that even a concentration of 0.01-0.02 ng/ml pandavir was able to inhibit virus reproduction through specific inhibition of viral DNA synthesis [90]. Monensin and A-23187, as ionophore antibiotics, are also able to inhibit some RNA viruses by blocking viral glycoproteins on the surface of infected cells [91].

The activity of lactic acid bacteria in the matrix of traditional fermented food products leads to the production of a diverse range of bacteriocins that show significant antiviral activity against various viruses, including herpesvirus [92-94]. Modulation in the development of immune system responses is one of the known beneficial effects of consuming traditional fermented products [92]. It should be noted that the health effects of these foods are not limited to the presence of bacteriocins and are directly related to a wide range of biological compounds. These products are inherently rich in bacteriocin-producing microorganisms, but also other biologically active metabolites such

as polysaccharides, polypeptides, short-chain fatty acids, vitamins, inhibitors, and/or activators are formed during the fermentation and processing process that is currently known as "postbiotic metabolites". All these factors together lead to the beneficial effects of each fermented product in the host, so the relative maintenance of production conditions can in turn stabilize the health effects and prevent some side effects in susceptible individuals.

The results obtained from various studies indicate the essential and supportive role of bacteriocins in managing the prevalence of viral diseases [84, 95]. Due to their unique structure and protein nature, bacteriocins are not directly involved in killing the virus, but act as proteinase inhibitors, inhibiting enzymes involved in virus replication, thereby disrupting the virus's life cycle [88]. On the other hand, according to some researchers, other biological processes can be involved in the interaction between bacteriocin and virus, which trigger/promote the growth inhibitory effects of bacteriocin, and future studies in this field can reveal the ambiguities of this issue. On the other hand, the design and widespread utilization of vaccines is considered to be the gold standard in the prevention and control of viral diseases, including COVID-19 in various countries (developed and developing). However, the presence of various mutations and the discovery of new strains of the COVID-19 virus in turn is an important challenge for health systems and requires the use of multiple strategies with an emphasis on the use of natural and safe bioactive compounds to strengthen immune function and promote the immune response to the gold standard (vaccination). Regarding the functional mechanism of bacteriocins, we can point to their interaction with human epithelial cells for exerting therapeutic actions [96]. On the other hand, in most respiratory diseases caused by the virus, including SAR-CoV-2, mucosal epithelial surfaces act as the main route of virus entry [97,98]. Therefore, epithelial surfaces can be one of the potential treatment targeting options to control/reduce viral infections. Strategies related to this hypothesis in the food and pharmaceutical industries can be shaped by the design and development of functional foods or therapeutic products (such as oronasal sprays) containing postbiotics with known antiviral effects. Also, during the metabolic processes of probiotics, a variety of postbiotic metabolites is synthesized in the intestinal milieu that can interact with gastrointestinal epithelial cells, enter the bloodstream (in case of respiratory infection), and reach the invaded organ (respiratory tissues) and exert their antiviral activities [99]. Therefore, it should be considered that maintaining molecular/signaling connections of the gut-lung axis is essential for better interaction of intestinal microbes and the host immune system to respond to infections [99]. Overall, it can be concluded that biological compounds derived from intestinal microbiota can be considered promising tools in microbial biotherapy and there is an urgent need to study the exact functional mechanism and further biological effects in future studies.

Production and characterization of postbiotics

In the production issue of postbiotic compounds, maintaining stable production conditions can be an important factor in exerting the biological effectiveness of postbiotics in various produced batches. In most related studies, a cell-free supernatant is prepared that contains lysed cell structures or active metabolites that generally form under the specific growth condition/metabolism of the probiotic strain in culture media/food matrices and are known as postbiotic metabolites. It is noteworthy that a variety of postbiotics have different production capacities in different amounts depending on the composition of the culture medium, the response behavior of the bacterial strain, and the post-propagation bacterial treatment [100]. Also, the existence of structural heterogeneity has led to the development of various methods to achieve the highest amount of postbiotic. The type of parent microbial strain, the optimal composition of the fermentation matrix, the favorable atmospheric and temperature conditions, the presence of growth stimulants, various extraction, concentration, and storage methods are among the important factors for the production of postbiotic compounds in the laboratory and industrial levels. In this regard, various methods such as heat and enzymatic treatment, solvent extraction, and ultrasound have been developed to extract different types of postbiotics [56].

Depending on the purpose of production and purification, a variety of further techniques such as centrifugation, freeze-drying, column purification, and dialysis can also be used in addition

to the main methods [92]. Mainly for purification purposes to add to specific food and drug matrices, the process of identifying bioactive compounds depending on the type of analytical target (qualitative or quantitative) is done by their unique equipment. Furthermore, chromatography in combination with tandem mass spectrometry and Fourier transform ion cyclotron resonance mass spectrometry with direct transfusion was utilized to identify and categorize metabolites such as glycerolipids, oligosaccharides, fatty acids, sphingolipids, and purines in biological specimens. As a practical example, high-performance liquid chromatography (UPLC) with features such as high efficiency and resolution, high sensitivity and accuracy, and low solvent use in the process of identifying postbiotic (non-volatile) compounds is recommended [100]. Despite the mentioned methods for extraction, identification, and qualitative/quantitative characterization of postbiotics, further research in this regard is required due to the unique nature of each of the different components of postbiotics, unusual interactions, optimization of each culture, extraction and identification methods as well as for describing the functional mechanisms and involved signaling pathways. Therefore, researchers should focus on genetic engineering processes, design, and development of new culture media to produce specific postbiotics, as well as to develop ideal analytical methods.

CONCLUSIONS

Overall, based on the available evidence obtained from preclinical and clinical studies, it can be acknowledged that bio-strategies based on probiotics-derived bioactive compounds can be a promising tool in the prevention and complementary treatment of a wide range of infectious diseases. It is noteworthy that the effectiveness of the proposed strategies largely depends on the tools used in them. In this regard, postbiotics, due to the fact that they are derived from safe sources of probiotics, therefore have a structure and function compatible with host cells and participate in several cellular processes involved in the establishment of homeostasis. The generation of some postbiotics in culture media or/and food matrix is a response of the parent probiotic cells to the presence/absence of some nutrients, pathogens, and undefined agents for the host biological systems. Consequently, by knowing more and more about lactic acid bacteria, and utilizing developed methods in extraction, identification, and characterization, as well as the implementation of metabolomics and proteomics studies, it is possible to achieve certain formulations of postbiotics with special efficiencies (*e.g.*, genetic manipulation of known probiotic strains to produce a specific peptide with anti-cancer effect, etc.), which in turn will significantly improve the performance of health systems (especially in developing countries) toward a wide range of acute/chronic diseases.

Conflict of interest
None.

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