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Review

Postbiotics: An evolving term within the functional foods field

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ABSTRACT

Background: It has been recognized that a number of mechanisms mediating the health benefits of beneficial bacterial cells do require viability. However, new terms such as paraprobiotic or postbiotic have emerged to denote that non-viable microbial cells, microbial fractions, or **cell lysates** might also offer physiological benefits to the host by providing additional bioactivity.

Scope and approach: This review provides an overview of the postbiotic concept, evidence of their **health benefits** and possible signaling pathways involved in their protective effects, as well as perspectives for applications in foods and pharmaceuticals.

Key findings and conclusions: Postbiotics refers to soluble factors (products or metabolic byproducts), secreted by live bacteria, or released after bacterial lysis, such as enzymes, peptides, teichoic acids, peptidoglycan-derived muropeptides, polysaccharides, cell surface proteins, and organic acids. These postbiotics have drawn attention because of their clear chemical structure, safety dose parameters, long shelf life and the content of various signaling molecules which may have anti-inflammatory, immunomodulatory, anti-obesogenic, antihypertensive, hypocholesterolemic, anti-proliferative, and antioxidant activities. These properties suggest that postbiotics may contribute, to the improvement of host health by improving specific physiological functions, even though the exact mechanisms have not been entirely elucidated.

1. Introduction

Several studies have provided plausible evidence of several mechanisms underlying the health-promoting effects of desirable gut bacterial cells; these include modification of the gut microbiota, competitive adherence to mucosa and epithelium, improvement of epithelial lining barrier function and modulation of the immune system (Bermudez-Brito, Plaza-Díaz, Muñoz-Quezada, Gómez-Llorente, & Gil, 2012; Vyas & Ranganathan, 2012). It is important to note that such mechanisms are clearly dependent on the viability status of bacteria (Sanders, 2009). However, recent evidence suggests that bacterial viability is not necessary to attain the health-promoting effects, as not all mechanisms nor clinical benefits are directly related to viable bacteria. Research performed by Lee, Zang, Choi, Shin, and Ji (2002) reported significant immunoregulatory abilities of four different *Bifidobacterium bifidum* BGN4 fractions (i.e., whole-cell, cell free extracts, purified cell wall and culture supernatant), where each fraction showed different patterns of immune reactions. Besides, fractions and extracts from *Bifidobacterium* and *Lactobacillus* spp., containing high levels of microbial carbohydrates, have shown profound *in vitro* tumor-suppressing activities (Choi et al., 2006; Raman, Ambalam, & Doble, 2016). Therefore, new terms such as paraprobiotic and postbiotic have emerged which imply that bacterial viability is not an essential requirement for health benefits, providing a potential opportunity in the field of functional foods.

Paraprobiotics, also known as “non-viable probiotics”, “inactivated probiotics” or “ghost probiotics”, refer to inactivated (non-viable) microbial cells, which, when administered in sufficient amounts, confer

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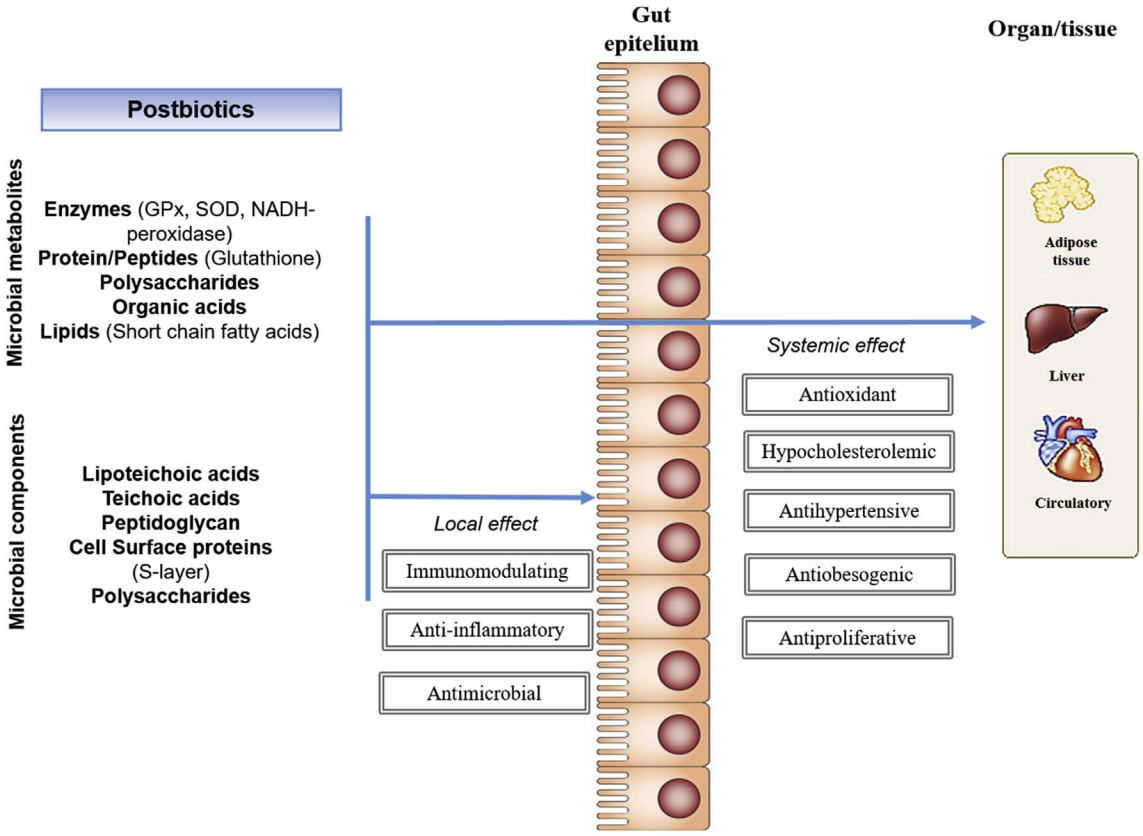

Fig. 1. Some postbiotics and their potential local and systemic positive effects in the host.

benefits to consumers (Taverniti & Guglielmetti, 2011; Tsilingiri & Rescigno, 2013). Despite of proven health benefits of probiotics, non-viable microbial cells may have safety advantages over probiotics by reducing the risk of microbial translocation, infection or enhanced inflammatory responses, shown for some probiotics in consumers with imbalanced or compromised immune systems (Taverniti & Guglielmetti, 2011). Bacterial cell inactivation may be achieved by physical (mechanical disruption, heat treatment, γ- or UV irradiation, high hydrostatic pressure, freeze-drying, sonication) or chemical (acid deactivation) methods which may alter microbial cell structures or their physiological functions; hence, bacteria become incapable of growing and therefore retain the beneficial health effects their viable form provides (de Almada, Almada, Martinez, & Sant'Ana, 2016).

On the other hand, the term postbiotics, also known as either metabiotics, biogenics, or simply metabolites/CFS (cell-free supernatants); refers to soluble factors (products or metabolic byproducts) secreted by live bacteria or released after bacterial lysis. These byproducts offer physiological benefits to the host by providing additional bioactivity (Cicenia et al., 2014; Konstantinov, Kuipers, & Peppelenbosch, 2013; Tsilingiri & Rescigno, 2013). Such soluble factors have been collected from several bacteria strains; examples include short chain fatty acids (SCFAs), enzymes, peptides, teichoic acids, peptidoglycan-derived muropeptides, endo- and exo-polysaccharides, cell surface proteins, vitamins, plasmalogens, and organic acids (Konstantinov et al., 2013; Oberg et al., 2011; Tsilingiri & Rescigno, 2013).

Despite the fact that the mechanisms implicated in the health beneficial effects of postbiotics are not fully elucidated, scientific data have provided evidence that postbiotics possess different functional properties including, but not limited to, antimicrobial, antioxidant, and immunomodulatory. These properties can positively affect the microbiota homeostasis and/or the host metabolic and signaling pathways, thus affecting specific physiological, immunological, neuro-hormone biological, regulatory and metabolic reactions (Sharma & Shukla, 2016; Shenderov, 2013).

Currently there is a vast available literature addressing fundamentals, therapeutic and technological aspects of viable "good" bacteria. Most of this literature has focused on whole cells (alive or heat-killed cells) or its membrane/cell wall components (Sánchez, Ruiz, Guemonde, Ruas-Madiedo, & Margolles, 2012; Reid, 2016; Chua, Kwok, Aggarwal, Sun, & Chang, 2017; Huang et al., 2017), and little attention has been paid for the intracellular soluble fraction (so called postbiotics). Although the importance of postbiotics has relatively been overlooked, scientific evidence of their beneficial health effects is progressively increasing (Compare et al., 2017; Haileselassie et al., 2016; Kareem, Ling, Chwen, Foong, & Asmara, 2014; Lee et al., 2004; Nakamura et al., 2016; Tiptiri-Kourpeti et al., 2016), even though their precise composition and underlying mechanisms are still under investigation. To the best of our knowledge, there are only a few reports summarizing findings on postbiotics, mainly focusing on those from different *Lactobacillus* species (Cicenia et al., 2014; Konstantinov et al., 2013; Patel & Denning, 2013; Shenderov, 2013; Tsilingiri & Rescigno, 2013). Hence, this review contributes with new and novel information regarding other bacterial species and yeast reported as a source of postbiotics, *in vitro* bioactive properties, *in vivo* health effects and potential mechanisms involved in different bioactivities. Additionally, promising analytical tools useful for the detection, identification and quantification of postbiotics, as well as current trends in food and pharmaceutical applications, will be addressed.

2. Classes of postbiotics and their characteristics

Gut bacteria depend fully on their host to provide the necessary nutrients that may promote microbiota growth. However, bacteria produce small molecular weight metabolites during their lifecycle; these compounds play a key role in regulating self-growth, development, reproduction, encourage the growth of other beneficial organism,

Table 1
In vitro and *in vivo* studies of postbiotics, their bioactivity and/or effects.

Bacteria	Components	Type of study	Bioactivity or effect	Method or tool used for identification or isolation of postbiotic	Ref.
Bifidobacterium sp., *L. acidophilus, L. casei, L. delbrueckii* subsp. *bulgaricus, L. gasseri, L. helveticus, L. reuteri, S. thermophiles*	Cell wall components and cytoplasmic extract	RAW 264.7 macrophage cell line	Immunomodulation	N.I.	Tejada-Simon and Pestka (1999)
Faecalibacterium prausnitzii A2-165 (DSM 17677)	Cytosolic fraction	Caco-2 cells	Immunomodulation	N.I.	Sokol et al. (2008)
L. plantarum K8 (KCTC10887BP)	Lipoteichoic acids	Human monocyte THP-1 cells	Immunomodulation	MALDI-TOF Mass spectrometry	Kim et al. (2011)
B. bifidum BGN4,	Cell free extracts, purified cell wall and supernatant	RAW 264.7 cells	Immunomodulation	N.I.	Lee et al. (2002)
L. johnsonni La1, *L. acidophilus* La10	Lipoteichoic acids	Human HT29 cell line	Immunomodulation	Octyl-Sepharose® CL-4B column	Vidal et al. (2002)
L. casei YIT 9029, *L. fermentum* YIT 0159	Lipoteichoic acids	RAW 264.7 macrophages	Immunomodulation	Macro-prepHigh Q and Octyl-Sepharose® CL-4B column	Matsuguchi et al. (2003)
L. paracasei B21060	Cell-free supernatants	Dendritic cells from human peripheral blood monocytes	Immunomodulation	N.I.	Mileti, Matteoli, Iliev, and Rescigno (2009)
L. paracasei B21060	Cell-free supernatants	Human mucosa explant of colon	Anti-inflammatory	N.I.	Tsilingiri et al. (2012)
Bacillus coagulans	Cell wall components	Human polymorphonuclear cells	Immunomodulation and anti-inflammatory effect	N.I.	Jensen, Benson, Carter, and Endres (2010)
L. rhamnosus GG	Cell-free supernatants	Human colonic smooth muscle cells	Anti-inflammatory	N.I.	Cicenia et al. (2016)
L. acidophilus (ATCC 43121, ATCC 4356, 606), *L. brevis* ATCC 8287, *L. casei* (YIT 9029, ATCC 393), *L. rhamnosus* GG	Intracellular content	HeLa, MCF7, U-87, Hep G2, U2OS, PANC-1, HT-29, WiDr, DLD-1 and CX-1 cells	Antiproliferative	N.I.	Choi et al. (2006)
L. casei ATCC 393	Sonicated-cell suspension	Murine CT26 and human HT29 colon cancer cells line	Antiproliferative	N.I.	Tiptiri-Kourpeti et al. (2016)
Strep. salivarius ssp. *thermophilus* ATCC 19258 and *L. delbrueckii* spp. *bulgaricus* ATCC 11842	Intracellular content	*In vitro*	Antioxidant	N.I.	Ou et al. (2006)
L. acidophilus KCTC 3111, *L. jonsonnii* KCTC 3141, *L. acidophilus* KCTC 3151, *L. brevis* KCTC 3498	Intracellular content	*In vitro*	Antioxidant	N.I.	Kim et al. (2006)
L. casei ssp. *casei* SY13 *and L. delbrueckii* ssp. *bulgaricus* LJJ	Intracellular content	*In vitro*	Antioxidant	N.I.	Zhang et al. (2011)
7 *Bifidobacterium,* 11 *Lactobacillus,* 6 *Lactococcus, and* 10 *Strep. thermophilus* strains	Intracellular content	*In vitro*	Antioxidant	N.I.	Amaretti et al. (2013)
B. longum SPM1207	Sonicated-cell suspension	High-cholesterol rat model	Hypocholesterolemic	N.I.	Shin et al. (2010)
L. casei YIT9018	Polysaccharide-glycopeptide complexes	Spontaneously hypertensive rats and renal hypertensive rats models	Antihypertensive	HPLC and ^{1}H NMR	Sawada et al. (1990)
L. amylovorus CP1563	Fragmented cells	Obese mouse model	Antiobesogenic	N.I.	Nakamura et al. (2016)
L. fermentum BGHV110	Cell lysate suspension	Human hepatoma HepG2 cells	Hepatoprotective	N.I.	Dinić et al. (2017)
Enterococcus lactis IITRHR1 and *Lactobacillus acidophilus* MTCC447	Intracellular content	Cultured rat hepatocytes	Hepatoprotective	N.I.	Sharma et al. (2011)
L. plantarum RG11, RG14, RI11, UL4, TL1 and RS5	Cell-free supernatants	*In vitro*	Antimicrobial	N.I.	Kareem et al. (2014)

N.I: Not identified; MALDI-TOF: Matrix-assisted laser desorption/ionization time-of-flight; HPLC: High performance liquid chromatography; ^{1}H NMR: Proton nuclear magnetic resonance spectroscopy.

cell to cell communication and protection against stress factors (Hibbing, Fugua, Parsek, & Peterson, 2010; Netzker et al., 2015; Zhang et al., 2010). Some of these soluble metabolites may be secreted by live bacteria, or released after bacteria lysis, into the host environment, offering additional physiological benefits (Fig. 1) by modifying cellular processes and metabolic pathways in the host. Although beneficial attributes of one specific bacteria (or a cocktail of bacteria) may differ from one another, it is theoretically possible, using bioengineering procedures, to design recombinant probiotics capable to exert a variety of beneficial properties by expressing biologically copies of such bioactive metabolites (Chua et al., 2017; Singh, Mal, & Marotta, 2017). In general, the postbiotics can be differentiated either by their elemental composition, i.e., lipids (*e.g.* butyrate, propionate, dimethyl acetyl-derived plasmalogen), proteins (e.g. lactocepin, p40 molecule), carbohydrates (e.g. galactose-rich polysaccharides, and teichoic acids), vitamins/co-factors (e.g., B-group vitamins), organic acids (e.g., propionic and 3-phenyllactic acid) and complexes molecules such as peptidoglycan-derived muropeptides, lipoteichoic acids (Konstantinov et al., 2013; Tsilingiri & Rescigno, 2013), or by their physiological functions (See Table 1) which include immunomodulation, anti-inflammatory, hypocholesterolemic, anti-obesogenic, anti-hypertensive, anti-proliferative, and antioxidant effects (Nakamura et al., 2016; Sawada et al., 1990; Shin et al., 2010).

In general, postbiotics possess several attractive properties such as clear chemical structures, safety dose parameters, and longer shelf life (up to 5 years, when used as ingredient for foods and beverages or as nutritional supplements) that are greatly sought out (Shigwedha, Sichel, Jia, & Zhang, 2014; Tomar, Anand, Sharma, Sangwan, & Mandal, 2015). In addition, research performed by Shenderov (2013) revealed that postbiotics have favorable absorption, metabolism, distribution, and excretion abilities, which could indicate a high capacity to signal different organs and tissues in the host thus eliciting several biological responses. Moreover, it has been demonstrated that postbiotics can mimic the health effects of probiotics while avoiding the necessary administration of live microorganisms, which may not always be harmless as previously proved by Tsilingiri et al. (2012) who found, on a *ex vivo* assay, that some probiotics can induce a local inflammatory response that resembles the response induced by *Salmonella*. Furthermore, theoretical concern associated with live probiotic bacteria administration (e.g., bloating and flatulence, probiotic-related translocation and bacteremia and fungemia, and possible transfer of antibiotic resistance gene) have been described in case reports, clinical trials and experimental models, in patients with major (e.g., immunosuppression, premature infants) and minor (e.g., impairment of the intestinal epithelial barrier, concurrent administration with broad-spectrum antibiotics to which the probiotic is resistant) risk factors for adverse events (Doron & Snydman, 2015; Williams, 2010). Hence, the use of postbiotics may represent a valid and safer alternative to avoids risk linked to live probiotic bacteria, which confer to postbiotics certain practical applicability and functionality to become a prominent strategy for treating many diseases (Haileselassie et al., 2016; Tsilingiri & Rescigno, 2013; Vieira, Fukumori, & Ferreira, 2016).

3. Methods used to obtain and identify postbiotics

In general, postbiotics have been obtained by using cell disruption techniques, which include heat (Lee et al., 2002; Tejada-Simon & Pestka, 1999), and enzymatic treatments (Li et al., 2012), solvent extraction (Kim et al., 2011), as well as sonication (Amaretti et al., 2013; Choi et al., 2006; Kim et al., 2006; Matsuguchi et al., 2003; Ou, Ko, & Lin, 2006; Sharma, Singh, & Kakkar, 2011; Shin et al., 2010; Sokol et al., 2008; Tiptiri-Kourpeti et al., 2016; Zhang et al., 2011).

Besides, additional extraction and clean-up steps such as centrifugation, dialysis, freeze-dried and column purification have been used to assist obtaining procedures (Matsuguchi et al., 2003; Sawada et al., 1990; Vidal, Donnet-Hugues, & Granato, 2002). For instance, Octyl-Sepharose® CL-4B column was used for isolation of lipoteichoic acid (LTA) from *L. johnsonii* La1 and *L. acidophilus* La10 (Vidal et al., 2002), and a combination of Macro-prep High Q and Octyl-Sepharose® CL-4B column for isolation of LTA from *L. casei* YIT 9029 and *L. fermentum* YIT 0159 (Matsuguchi et al., 2003). On the other hand, dialysis against distilled water in a molecular porous membrane tube for 1 d was used to assist the extraction of polysaccharide-glycopeptide complex obtained from *L. casei* YIT9018 (Sawada et al., 1990); as well as centrifugation in the extraction of intracellular content from various *Bifidobacterium* spp., *Lactobacillus* spp., *Lactococcus* spp., and *Streptococcus* spp. strains (Amaretti et al., 2013; Ou et al., 2006; Zhang et al., 2011).

On the other hand, different analytical approaches have been proposed for postbiotic identification. The selection of instrumental technique depends on the analytical goals and the type of characterization (qualitative and/or quantitative) pursued. Accordingly, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry has been employed to identify LTA produced by *L. plantarum* K8 (KCTC10887BP) (Kim et al., 2011); and HPLC and proton nuclear magnetic resonance spectroscopy (^{1}H NMR) were used to identify and characterize polysaccharide-glycopeptide complexes of *Lactobacillus casei* YIT9018 (Sawada et al., 1990).

Additionally, chromatography coupled with tandem mass spectrometry and Fourier transform ion cyclotron resonance mass spectrometry with direct infusion, have been used to identify and characterize metabolites (e.g. fatty acids, glycerolipids, purines, sphingolipids, oligosaccharides) in biological samples (Antunes et al., 2011; Kok et al., 2013). However, techniques with high efficiency and resolution, low use of solvent and high sensitivity and accuracy such as Ultra Performance Liquid Chromatography (UPLC) are greatly preferred (Dong & Guillarme, 2013). Recent studies show that UPLC will be indicated due to superior separation and identification capacity of postbiotics; this technique was used in the profile identification of compounds (e.g. glutathione reductase, amino acid transport protein) present in intracellular content of *L. plantarum* (Wang et al., 2016) and the intracellular protein profile (e.g. thioredoxin, phosphoglycerate kinase, cysteine synthase) in *L. mucosea* LM1 (Pajarillo, Kim, Lee, Valeriano, & Kang, 2015). Similarly, Carbon-13 and ^{1}H NMR, infrared, and electrospray ionization mass spectrometry techniques have been used to characterize antifungal metabolites (e.g. phenol) produced by *L. brevis* P68 (Arasu et al., 2015). Moreover, changes in the protein profile of intracellular content of *L. plantarum* 423, when exposed to acid conditions (pH 2.5), was determined by gel-free nanoLC-MS/MS proteomics approach (Heunis, Deane, Smit, & Dicks, 2014). Similarly, the protein profile of *L. plantarum,* after bile salt stress, was identified using two-dimensional electrophoresis (2-DE) and liquid chromatography-mass spectrometry analysis (Hamon et al., 2011).

Despite that all these techniques could be used to detect, identify and quantify postbiotics, more research about extraction protocols and analytical tools are necessary to allow discovery and characterization of novel postbiotics, but also to understand the mechanisms of action and the signaling pathway modulation. However, further research is required to optimize media and culture conditions as well as the analytical methods (Anvari, Khayati, & Rostami, 2014). Once laboratory scale optimization is achieved, it must be scaled-up and optimized to ensure maximum postbiotic yield. It is important to note that clinical trials are necessary to define adequate dose and optimal administration frequency (Patel & Denning, 2013). Nevertheless, preclinical studies should be performed prior to initiation of the clinical trial for better selection of the postbiotic candidate. Similar to preclinical testing of the microbial strains, the details of preclinical activities can vary according to the type of postbiotic and the expected mechanism of action (Sorokulova, 2008).

4. Postbiotic bioactivity and/or effects

In recent years, a considerable number of studies using *in vitro* (e.g., diverse cell lines) and *in vivo* (e.g., obese and hypertensive rats) models have been used to assess the potential bioactivity and/or health effects of various postbiotics, including intracellular metabolites and cell wall components, either as isolated structures or mixtures, such as extracts or suspensions (Robles-Vera et al., 2017). A summary is depicted in Table 1.

In the majority of cases, postbiotics are derived from *Lactobacillus* and *Bifidobacterium* strains; however, *Streptococcus* and *Faecalibacterium* species have also been reported as a source of postbiotics (Konstantinov et al., 2013; Tsilingiri & Rescigno, 2013). It has been proven that supplementation with postbiotics reduces blood pressure which confers the antihypertensive capacity to these compounds. The mechanism of this protective effect on the endothelial function has not been elucidated; however, this could be due to changes in the gut microbiota and its metabolic by-products; the restoration of the gut barrier function; and the effects on endotoxemia, inflammation, and renal sympathetic nerve activity (Robles-Vera et al., 2017).

Studies show that the intestinal microbiota also impacts a wide range of functions in the gastrointestinal tract including the development of the immune system, defense against pathogens, and inflammation (Klemashevich et al., 2014). With the recent development of the postbiotic concept, growing data, mainly obtained by the analysis of Lactobacilli strains, support the evidence that these beneficial effects may depend on secreted-derived factors (Compare et al., 2017).

Immunomodulation is influenced by retinoic acid-driven mucosal-like dendritic cells and their subsequent effects on regulatory T-cells *in vitro* using *L. reuteri* 17938, by producing the anti-inflammatory cytokine IL-10 (Haileselassie et al., 2016). In related research, Sokol et al. (2008) reported increased IL-8 levels in Caco-2 cells when exposed to intracellular extracts and the supernatant fraction of *F. prausnitzii*. Additionally, the data suggested that administration of cell-free supernatant, in a TNBS-induced colitis mice model, exerted an anti-inflammatory effect by increasing IL-10 and reducing IL-12, which suggested that secreted metabolites induced this protective effect. The study also revealed that the anti-inflammatory effect was attributed to a butyrate-independent pathway. Moreover, the proposed mechanism was via NF-κB activation blockade; however, the active molecules involved in this protective effect were not determined. Additional evidence has indicated that the culture supernatant from *Lactobacillus paracasei* B21060 can protect healthy tissue against the inflammatory properties of invasive *Salmonella* in a human mucosa explant of colon (Tsilingiri et al., 2012), and that culture supernatant from *Lactobacillus casei* DG can mitigate the inflammatory response in ileac and colonic mucosa cultures obtained from post-infectious bowel syndrome patients (Compare et al., 2017).

On the other hand, Cicenia et al. (2016) reported that supernatants from *Lactobacillus rhamnosus* GG collected at different stages of growth (middle and late exponential, stationary, and overnight) were able to protect human colonic smooth muscle cells (HSMCs) against lipopolysaccharide (LPS)-induced myogenic damage. Maximal protective effect was observed with supernatants of the late stationary phase, which reverted 84.1% of LPS-induced cell shortening, and inhibited 85.5% of acetylcholine-induced contraction and 92.7% LPS-induced IL-6 secretion.

Postbiotics have also been described as pathogenic bacteria inhibitors against pathogens such as *Listeria monocytogenes* L-MS, *Salmonella enterica* S-1000, *Escherichia coli* E−30 and vancomycin-resistant *Enterococci* when using cell-free supernatants culture obtained from *L. plantarum* RG11, RG14, RI11, UL4, TL1 and RS5 strains (Kareem et al., 2014). Furthermore, antioxidant activity in *in vitro* and *in vivo* models exposed to specific exopolysaccharides (EPS) have been reported. Xu, Shang, and Li (2011) observed that EPS from *Bifidobacterium animalis* RH displayed *in vitro* inhibition of lipid peroxidation and radical scavenging activity (hydroxyl and superoxide radicals). Moreover, Li et al. (2014) described that both crude culture extract and purified EPS, from *Lactobacillus helveticus* MB2-1, exhibited strong scavenging capacity of three kinds of free radicals and chelating capacity to ferrous ion.

Among specific examples of intracellular bacterial enzymes found to have beneficial health effects (*e.g.* antioxidant) include glutathione peroxidase (GPx), superoxide dismutase (SOD), nicotinamide adenine dinucleotide (NADH)-oxidase and NADH-peroxidase (Kim et al., 2006; Li et al., 2012). On the other hand, some cell wall components have been associated to *in vitro* immunomodulatory properties including lipoteichoic acids (LTA), and S-layer proteins (Konstantinov et al., 2013). Additionally, several postbiotics exhibit multiple bioactivities and can simultaneously trigger multiple physiological pathways. For example, some cell wall components, such as LTA, have been reported to exhibit a variety of bioactivities including antitumor, antioxidant and immunomodulatory capacities (Lebeer, Claes, & Vanderleyden, 2012; Yi, Fu, Li, Gao, & Zhang, 2009). Besides, microbial membrane sterol-like compounds have received special attention including plasmalogens, known as endogenous antioxidants, which confer resistance to H_2O_2-induced oxidative stress in several *Bifidobacterium* strains (Oberg, Ward, Steele, & Broadbent, 2012; Oberg et al., 2011).

According to other works, SCFAs produced by gut microbiota act as signaling molecules improving regulation of lipid metabolism, glucose homeostasis and insulin sensitivity, through the activation of receptors such as G protein-coupled receptors (GPRs), thus contributing in the regulation of energy balance while maintaining metabolic homoeostasis (Canfora, Jocken, & Blaak, 2015; Kimura et al., 2013). Specific SCFAs (e.g. butyrate, acetate and propionate) have also proven to contribute to plasma cholesterol homeostasis in rodents and humans (den Besten et al., 2013).

The hepatoprotective role of postbiotics has also been described. In this sense, cell lysate suspension from *Lactobacillus fermentum* BGHV110 reduced acetaminophen-induced hepatotoxicity in HepG2 cells by activating the autophagy in HepG2 cells through PINK1 signaling pathway (Dinić et al., 2017). In a related work, Sharma et al. (2011) reported the hepatoprotective effect of intracellular content from *Enterococcus lactis* IITRHR1 and *Lactobacillus acidophilus* MTCC447 against acetaminophen-induced hepatotoxicity in a cultured rat hepatocytes model. Additionally, the authors found that postbiotics have the potential to restore the glutathione levels and to reduce levels of oxidative stress biomarkers.

Additionally, postbiotics may also be produced by yeast metabolic activity. Canocini et al. (2011) reported that culture supernatants, obtained from *Saccharomyces boulardii*, improved wound healing capacity and epithelial cells migration via the activation of α2β1 integrin collagen receptors using *in vitro* models. Moreover, the authors observed that daily oral administration of such culture supernatant to mice for 7 days improved enterocyte migration along the crypt-villus axis in small intestinal tissues, as examined by immunostaining. The data suggested that these supernatants could improve the repair process of intestinal epithelium after damage (intestinal restitution) and possess potential therapeutic applications in a wide variety of gastrointestinal disorders.

Bioactive properties discovered in postbiotics suggest that these compounds may contribute in the improvement of host health by providing better specific physiological effects, through the combined effect of postbiotics, other biological metabolites and the live microorganism. This synergy may result in more effective protective qualities (Thanh, Loh, Foo, Bejo, & Azhar, 2010).

4.1. Potential mechanism involved in postbiotic bioactivity

Despite the previously stated health beneficial effects of postbiotics, the mechanisms of action are not fully understood.

The protective effect of postbiotics could be caused by compounds that mimic the beneficial and therapeutic effects of probiotics, even

though the mechanisms of action may vary. For instance, hypocholesterolemic mechanisms of probiotic bacteria, include the inhibition on intestinal cholesterol adsorption and/or the suppression of bile acid reabsorption (Ogawa, Kadooka, Kato, Shirouchi, & Sato, 2014). On the other hand, postbiotics have been reported to activate peroxisome proliferator-activated receptor which causes fatty acid β-oxidation to reduce triglycerides (Nakamura et al., 2016). Also, postbiotics were found to activate nucleotide-binding oligomerization domain-containing protein 1 that induce cell-autonomous lipolysis in adipocytes (Chi et al., 2014), to decrease the enzyme activity of hepatic 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), and to increase the AMP-activated protein kinase in liver and muscle tissue (den Besten et al., 2013), thus promoting lipid metabolism and dyslipidemia control.

Furthermore, it has been found that muramyl dipeptide-based postbiotics may reduce adipose inflammation and glucose intolerance via a nucleotide-binding oligomerization domain-containing protein 2 and though the activation of transcription factor IRF4 in obese mice (Cavallari et al., 2017). Moreover, this postbiotic reduced hepatic insulin resistance in obesity and low-level endotoxemia.

Postbiotics have also proven an antiproliferative specific activity against colon cancer cells; most likely related to the activation of pro-apoptotic cell death pathways through regulation of immune responses (Tiptiri-Kourpeti et al., 2016). It has been reported that postbiotics obtained from *Lactobacillus* strains might decrease metalloproteinase-9 activity inhibiting colon cancer invasion (Escamilla, Lane, & Maitin, 2012). To elucidate the active compound responsible for this effect, the postbiotic (cell-free supernatant) was fractionated based on molecular weight ranges; it was found that the active inhibitory fraction corresponded to the > 100 kDa and 50–100 kDa compounds, suggesting that the inhibitory compound may be a macromolecule such as a protein, nucleic acids, or polysaccharides.

Some studies (Kullisaar et al., 2002; Lin & Chang, 2000; Saide & Gilliland, 2005) determined that cell-free extracts from lactic acid bacteria may exhibit significantly higher antioxidant capacity than whole cell cultures; suggesting that the antioxidant capacity could be attributed to both enzymatic and non-enzymatic intracellular antioxidants. Furthermore, *Bifidobacterium infantis*, *Bb. breve*, *Bb. adolescentis*, and *Bb. longum* are capable of degrading hydrogen peroxide by producing NADH peroxidase (Shimamura et al., 1992). It has been reported that glutathione peroxidase and glutathione reductase are two important antioxidant enzymes that protect cells from oxidative damage by scavenging reactive oxygen species (ROS). However, the antioxidant capacity and antioxidant enzyme activity could not be positively correlated for all strains, which indicates that other compounds may be involved in the antioxidant effect (Kim et al., 2006). In this sense, it has been proposed that the antioxidant capacity of the intracellular fraction of different strains of *Lactobacillus* positively correlates with the cellular content of reduced glutathione, an important non-enzymatic antioxidant that plays an essential role in maintaining intracellular redox state (Yoon & Byun, 2004). The antioxidant activity of such non-enzymatic postbiotic could be caused by its ROS and reactive nitrogen species scavenging properties (Amaretti et al., 2013; Zhang et al., 2011).

Additionally, exopolysaccharides have antioxidant activity (Pan & Mei, 2010; Xu et al., 2011). Some studies suggest that this activity is attributed to elevated contents of uronic acid. Some authors (Li et al., 2014; Liu et al., 2011; Xu et al., 2011) proposed that uronic acid plays an important role in the antioxidant properties of polysaccharides from *B. animalis* RH and *L. helveticus* MB2-1. Similarly, Li et al. (2014) reported a polysaccharide from *L. helveticus* MB2-1, with a greater proportion of negatively charged uronic acid that produced a higher chelating capacity ferrous ion. Ferrous ions are involved in the formation of free radicals by the Fenton and Haber-Weiss reactions, which generate reactive hydroxyl radicals. In a related research, a direct relationship between uronic acid content and the radical scavenging capacity of tea polysaccharide was reported (Chen, Zhang, & Xie, 2004; Chen, Zhang, Qu, & Xie, 2008).

It has been suggested that the immunomodulatory and anti-inflammatory capacities of postbiotics are mediated by the inhibition and induction of the immune systems in various animal models. It has been found that postbiotics regulate the production of the cytokine response and Th1 pathway inhibition (Jensen et al., 2010; Sokol et al., 2008). The antimicrobial activity of postbiotics may be attributed to the presence of several known and unknown antimicrobial compounds, usually including but not limited to bacteriocins, enzymes, small molecules, and organic acids, which exhibit bacteriostatic or bactericidal properties against both gram-positive and gram-negative microorganisms (Kareem et al., 2014).

All these properties suggest that postbiotics may contribute to the improvement of the host's health status by providing better and specific physiological effects, although the exact mechanisms remain to be elucidated.

5. Food and pharmaceutical potential applications of postbiotics

The increased knowledge of functional foods has led to the development of a new generation of health products, including those containing probiotics. However, one issue related to the application of probiotics is the occurrence of antibiotic resistance genes in some probiotics strains, as they have the potential to pass the antibiotic resistance genes to pathogenic bacteria through horizontal gene transfer (Imperial & Ibana, 2016). Another main concern associated with the probiotic product formulations (i.e., pharmaceutical and commercial food-based products) is maintaining bacteria viability during product manufacturing and storage, since the viability of probiotics organism in a delivery system (i.e., pharmaceutical formulations and commercial food-based products) could be affected by different variables, including interactions with other microbial species present, final acidity of the product, water activity, temperature, availability of nutrients, growth promoters and inhibitors, inoculation level, fermentation time, dissolved oxygen, and formulation process procedures such as freeze drying, spray drying or freeze concentration (Shah, 2016). Furthermore, discrepancies between stated and actual probiotic levels in commercial products for both human and veterinary use have previously been reported (Weese & Martin, 2011). Hence, this lack of probiotic stability may compromise the expected health benefits provided by probiotic products.

In contrast, postbiotics are supposed to be more stable than the living bacteria they are derived from (Venema, 2013). Phister, O'Sullivan, and McKay (2004) reported that peptides with antimicrobial properties, namely bacilysin and chlorotetaine, produced by *Bacillus* sp. strain CS93 are water soluble and active over a wide pH range, which could allow their application in a wide variety of food products. Furthermore, the use of selected phytase-producing lactic acid bacteria as starters for breadmaking have been reported as good alternatives for preparing whole wheat bread with low phytate content (Palacios, Haros, Sanz, & Rosell, 2008). However, previous studies have shown that an advanced hydrolysis of phytate is achieved by increasing the fermentation time and/or decreasing the pH during whole wheat dough fermentation; conditions that not only may affect the sensory attributes of the final products, but also could influence the synthesis of phytate-degrading enzymes by microorganisms (Haros, Bielecka, Honke, & Sanz, 2008). With the use of purified phytate-degrading enzymes, these compounds would not be a serious issue. Another major advantage of postbiotics is their favorable safety profile, as there is no need for the uptake of billions of living microbes (Shigwedha et al., 2014). Additionally, postbiotics can be applied in a controlled and standardized way, whereas, in the case of the application of living bacteria, the level of the active structure in the intestine is dependent on the number and metabolic activity of the respective strain (Gabriele, 2016). Thus, selected soluble factors from specific bacteria may become a class of

bacterial biological strategy for treating many diseases; however, a big challenge is translating scientific knowledge into commercial applications and thus bridging science and industry.

Currently, cell-free preparations obtained from the metabolic products of different beneficial bacteria have been introduced with potential pharmaceutical applications in the prevention or treatment of diseases (Klein et al., 2013). For instance, Colibiogen® (Laves-Arzneimittel GmbH, Schötz, Switzerland) a commercially protein-free filtrate derived from cultures of *Escherichia coli* (strain Laves 1931), containing amino acids, peptides, polysaccharides and fatty acids, has been shown to be effective in inhibiting *in vitro* both antibiotic resistant and sensitive *Salmonella* isolates (Zihler et al., 2009), in the amelioration of murine colitis (Konrad et al., 2003), and to significantly reduce skin lesions in patients with polymorphous light eruptions (Przybilla, Heppeler, & Ruzicka, 1989). Hylak® Forte (Ratiopharm/Merckle GmbH, Germany), a bacteria-free liquid containing metabolic products (*e.g.* SCFA, lactic acid an other non-identified metabolites) from *E. coli* DSM 4087, *Streptococcus faecalis* DSM 4086, *L. acidophilus* DSM 414, and *L. helveticus* DS 4183, has proved to be effective in the management of salmonellosis in infants (Rudkowski & Bromirska, 1991) and in the treatment of intestinal dysbacteriosis of patients with chronic gastritis (Omarov, Omarova, Omarova, & Sarsenova, 2014). Besides, has shown to significantly reduce the incidence and the severity of the radiation-induced diarrhea in radio-oncology patients (Timko, 2010). CytoFlora® (BioRay Inc., Laguna Hills, CA, USA), is a preparation of micronized cell wall lysates of *L. rhamnosus, B. bifidum, L. acidophilus, B. infantis, B. longum, S. thermophilus, L. plantarum, L. salivarius, L. reuteri, L. casei, L. bulgaricus, L. acidophilus DDS-1* and *Lactobacillus sporogenes*, that has been used to correct intestinal dysbiosis, promote a balanced immune response, and improve symptoms in autistic children (Ray, Sherlock, Wilken, & Woods, 2010). Another commercial product is Del-Immune V® (Pure Research Products, LLC, Boulder, CO, USA), a US Food and Drug Administration-registered formulation containing muramyl peptides, amino acids and DNA fragments of *L. rhamnosus* V (DV strain), has shown to significantly reduce the severity of gastrointestinal distress in children with Autism Spectrum Disorder when administrated as blend of Del-Immune V® plus probiotics (West, Roberts, Sichel, & Sichel, 2013).

It has also been reported that probiotic cell lysates may contain hyaluronic acid, sphingomyelinase, lipotechoic acid, exopolysaccharides, peptidoglycan, lactic acid, acetic acid and/or diacetyl, which provide broad biologic activity that can be harnessed to provide skin benefits such as improving atopic eczema, atopic dermatitis, healing of burn and scars, skin-rejuvenating properties, improving skin innate immunity and protecting against photodamage (Kober & Bowe, 2015; Lew & Liong, 2013). According to this, many studies and patents have been published on the use of probiotics extracts to development of personal care products including oral, underarm (deodorants and antiperspirants) and skin products (Callewaert, Lambert, & van de Wiele, 2017; Coronado-Robles, 2016; Holz et al., 2017; Huang & Tang, 2015; O'neill & McBain, 2015; Ouwehand, Lahtinen, & Tiihonen, 2016).

Although several foods are naturally abundant in postbiotics (e.g., yogurt, kefir, pickled vegetables and kombucha) or their precursors (Chaluvadi, Hotchkiss, & Yam, 2016), some postbiotics have been intentionally applied to certain foods rather than considering its *in situ* production by the producer strain. For instance, cell-free supernatant from *L. pantarum* YML007 has been explored as biopreservative on soybeans grains (Rather et al., 2013). EPS containing rare sugars have been investigated for new applications in food industry due to their role in the physicochemical (viscosifying, stabilizing, or water-binding capacities) and sensorial (palatability) characteristics in the final food products; however, with the exception of dextran, EPS from lactic acid bacteria have not yet been commercially exploited as food additives because of their low yields (Torino, de Valdez & Mozzi, 2015). Nisin, a lantibiotic produced by specific *Lactococcus lactis* subsp. *Lactis* strains, is the only bacteriocin approved for use as a food preservative. Examples of food products with Nisin include canned soups, ice for storing fresh fish, baby foods, baked goods, mayonnaise and dairy products, especially cheeses (Chen & Hoover, 2003). With the above in mind, the use of foods as postbiotics delivery system seems to constitute a field with several opportunities, but also with big challenges.

Improving animal health is another promising field of application, since it has been reported that postbiotics may influence growth performance of hens, broilers and piglets (Choe, Loh, Foo, Hair-Bejo, & Awis, 2012; Kareem, Loh, Foo, Akit, & Samsudin, 2016a; Loh, Choe, Foo, Sazili, & Bejo, 2014; Loh, Thu, Ling, & Bejo, 2013; Thu, Loh, Foo, Yaakub, & Bejo, 2011). In this sense, a recent research performed by Kareem et al. (2016a) determined that broilers fed with postbiotics produced by *L. plantarum* developed significantly higher final body weight and total weight gain than broilers fed with a basal diet without postbiotics. Also, postbiotics were found to increase significantly duodenal and ileal villus height. Moreover, the combination of postbiotic and inulin may enhance growth performance, improve the final count of beneficial bacteria and reduce the presence of Enterobacteria and *E. coli* populations (Kareem, Loh, Foo, Asmara, & Akit, 2016b). In a similar study, Loh et al. (2014) found a significantly daily higher egg production of hens when treated with a postbiotic supplement.

Some reports proposed that the administration of postbiotics from *L. plantarum* exerted a positive effect on growth performance and protein digestibility, as well as reduced diarrhea incidence. Given the collected data, authors suggested that postbiotics altered the mucosal architecture in terms of longer villi and enhanced animal growth performance. Also, the use of postbiotics modified the intestinal microbiota, improved the population of protective bacteria (*e.g., Lactobacillus* and *Bifidobacterium*) and enhanced the health status of test animals. In addition, postbiotics could contain antimicrobial substances produced by *Lactobacillus* strains, which may provide nutrients and enhance physiological activities in the animal gut, resulting in absorption improvement and decreased intestinal pathogenic bacteria. Postbiotics can be considered potential contributors as feed additives to achieve higher productivity and better animal health (Loh et al., 2014).

Postbiotics may be useful as microbial-free food supplements, fermented functional foods, and prophylactic drugs, as complementary treatment for several diseases (Chaluvadi et al., 2016). Postbiotics research represents an opportunity not only to understand their mechanisms of action in detail but also to develop new therapeutic strategies for health improvement (Klemashevich et al., 2014; Shenderov, 2013).

On the other hand, the advent of modern techniques for genetic manipulation has created opportunities for the development of novel bioengineered probiotic strains capable to produce metabolites targeted to the prevention and treatment of several diseases (Paton, Morona, & Paton, 2012; Sola-Oladokun, Culligan, & Sleator, 2017). For instance, genetically modified lactic acid bacteria has been used for intestinal delivery of antimicrobial peptides (Amalaradjou & Bhunia, 2013), angiotensin-converting enzyme inhibitory peptides (Yang et al., 2015), cancer-suppressing peptide KiSS1 (Zhang et al., 2016), fusion protein of HSP65 with tandem repeats of P277 (Ma et al., 2014) and glutamic acid decarboxylase and IL-10 cytokine (Huibregtse et al., 2012; Robert et al., 2014), thus providing promising strategies for the treatment of enteric infections, hypertension, colon carcinoma and intestinal inflammatory and autoimmune diseases such as Type 1 diabetes mellitus. Despite of promising biomedical application of recombinant probiotic metabolites, important safety and regulatory aspects still need to be addressed in depth.

6. Conclusions

Postbiotics comprise metabolites and/or cell-wall components, secreted by live bacteria or released after bacterial lysis, with demonstrated beneficial activities in the host. Postbiotics may induce anti-inflammatory, immunomodulatory, anti-obesogenic, anti-hypertensive,

hypocholesterolemic, anti-proliferative, and antioxidant activities. These properties suggest that postbiotics may contribute to the improvement of host health by providing specific physiological effects, even though the exact mechanisms have not been fully elucidated. Additional efforts are necessary to allow discovery and characterization of new postbiotics; which may contribute to the understanding of the signaling pathway modulation. Novel research will allow the generation of detailed information to insure stability during the manufacturing processes of postbiotic products and their efficacy. Special attention should be paid in the development of uniform and stringently defined culture procedures in order to eliminate possible variability of postbiotics production, since uncontrolled environmental factors can well change metabolism and undergo unexpected transient variability. Beside, well-designed randomized placebo-controlled human/clinical intervention trials along with metabolomics studies must be conducted looking to support health claims of postbiotics supplementation.

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