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Postbiotics and their role in healthy life

Haben FESSEHA[1], Tadelech YILMA[2], and Endale MEKONNEN [1]

[1]*School of Veterinary Medicine, Wolaita Sodo University, Wolaita Sodo, Ethiopia*
[2]*College of Veterinary Sciences, Mekelle University, Mekelle, Ethiopia*

Corresponding author's Email: tseyon.h@gmail.com

ABSTRACT

Introduction. Postbiotics refer 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, long shelf life, safety dose parameters, and the content of various signaling molecules which may have anti-inflammatory, immunomodulatory, anti-obesogenic, antihypertensive, hypo-cholesterolemic, 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. It has been recognized that several mechanisms mediating the health benefits of beneficial bacterial cells do require viability. However, new terms such as para-probiotic 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. Aim. 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.

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INTRODUCTION

Postbiotics are functional bioactive compounds, generated in a matrix during fermentation, which may be used to promote health. The term postbiotics can be regarded as an umbrella term for all synonyms and related terms of these microbial fermentation components [1]. Postbiotics are soluble factors secreted by living bacteria or released after bacterial lysis. Currently, the application of postbiotic in pharmaceutical products, commercial food-based products, and terrestrial agriculture has been reviewed [2].

Several studies have provided plausible evidence of several mechanisms on the extraction of probiotics and underlying health-promoting effects including modification of the gut microbiota, competitive adherence to mucosa and epithelium, improvement of epithelial lining barrier function, and modulation of the immune system [3, 4]. It is important to note that such mechanisms are dependent on the viability status of bacteria [5]. 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 [2].

New terms such as Para-probiotic 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. Para-probiotics, also known as "nonviable probiotics, "inactivated probiotics" or "ghost probiotics", refer to inactivated (non-viable) microbial cells, which, when administered in sufficient amounts, confer benefits to consumers [6, 7].

Even though 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 [8, 9].

Currently, there is a vast available literature addressing the fundamentals, therapeutic and technological aspects of viable "good" bacteria. Most of this literature has focused on whole cells (alive or heat-killed cells) or their membrane/cell wall components [10-13], and little attention has been paid to 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 [14-18] 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 [7, 9, 19-21].

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.

What are postbiotics and how do they benefit?

Postbiotics are the "waste" of probiotics and are defined as "non-viable bacterial products or metabolic products from microorganisms that have biological activity in the host. Postbiotics are also found in any food which has been fermented by live bacteria such as kefir, sauerkraut, tempeh, yogurt, and certain pickles [22].

The word "postbiotics" is currently used to refer to bioactive compounds, which did not fit the traditional definitions of probiotics, prebiotics, and para-probiotics. Therefore, the definition for postbiotics can be expanded to (a) bioactive soluble factors (products or metabolic byproducts) produced by food-grade micro-organisms during the growth and fermentation in complex microbiological culture (in this case named cell-free supernatant (CFS), food, or gut, which exert some benefits to the food or host, (b) cell compounds, and (c) substances produced by the action of microorganism on food ingredients [23].

The term postbiotics, also known as either metabiotic, biogenic, 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 [7, 19, 20]. 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 [7, 20, 24].

The various postbiotic molecules include metabolic byproducts of live probiotic bacteria such as cell-free supernatant, vitamins, organic acids, short-chain fatty acids, secreted proteins/peptides, bacteriocins, neurotransmitters, secreted biosurfactants, amino acids, flavonoids derived postbiotics (desaminotyrosine, equol daidzein, daidzein, norathyriol), terpenoids derived postbiotics (genipin, paeoniflorin, paeoni lactone glycosides, paeonimetabolin I, II, III), phenolic-derived postbiotics (equol, urolithins, valero-lactones, enterolactone, enterodiol, 8-prenylnaringenin), etc [25].

Since the specific action of postbiotics relies on definite dosage levels, most studies have failed to fix a specific dose of postbiotics/para-probiotics to ensure the beneficial effects like probiotics at 109 viable cells. To investigate the effectiveness of postbiotics, currently, there have been a handful of comparative studies conducted at the in vitro and in vivo levels, and such studies suggest the similar potentialities of postbiotics over the probiotics and live bacteria in terms of demonstrating various health benefits and exert several pharmacodynamic features on the host including [26-28] i. No risk of bacterial translocation from the gut lumen to blood among vulnerable and immunocompromised subjects, ii. No chances of acquisition and transfer of antibiotic resistance genes, iii. More natural to extract, standardize, transport, and store, iv. Loss of viability by cell lysis can produce further beneficial effects, v. Enhanced interaction of every released molecule from the disrupted cells with the epithelial cells more directly [25].

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 [29]. 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 [7, 20].

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 [29].

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 [30]. 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 [16].

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 to the regulation of energy balance while maintaining metabolic homeostasis [31].

Moreover, several in vitro studies have shown that heat-treated Bifidobacterium cells induce cellular immune and anti-inflammatory responses by inhibiting IL-8 secretion in intestinal epithelial cells obtained from patients with UC [32, 33]. It was suggested that these effects in UC patient-derived cells are induced by released microbial soluble anti-inflammatory factors that inhibit IL-8 secretion in intestinal epithelial cells. This was not caused by one single factor [32]. Furthermore, it is hypothesized that postbiotic compounds from Lactobacilli spp. can exert immunomodulation activity by increasing levels of Th1-associated cytokines and reducing Th2-associated cytokines [34].

Mouse experiments with fermented infant formula containing postbiotics derived from *Bifidobacterium* breve C50 and Streptococcus thermophilus 065 have demonstrated prolonged dendritic cell survival and maturation, and induced high IL-10 production through TLR-2, suggesting immune regulatory functions. Moreover, postbiotics from these strains have been shown to improve the epithelial barrier function and stimulate Th1 response in mouse models highlighting the involvement of postbiotic components in host immune function [35, 36]. Another study using mouse models showed that metabolic products of fermented infant formula by Lactobacillus paracasei CBA L74 could act via the inhibition of immune cell inflammation and protect the host from pathobionts and enteric pathogens and have protective effects against colitis [37].

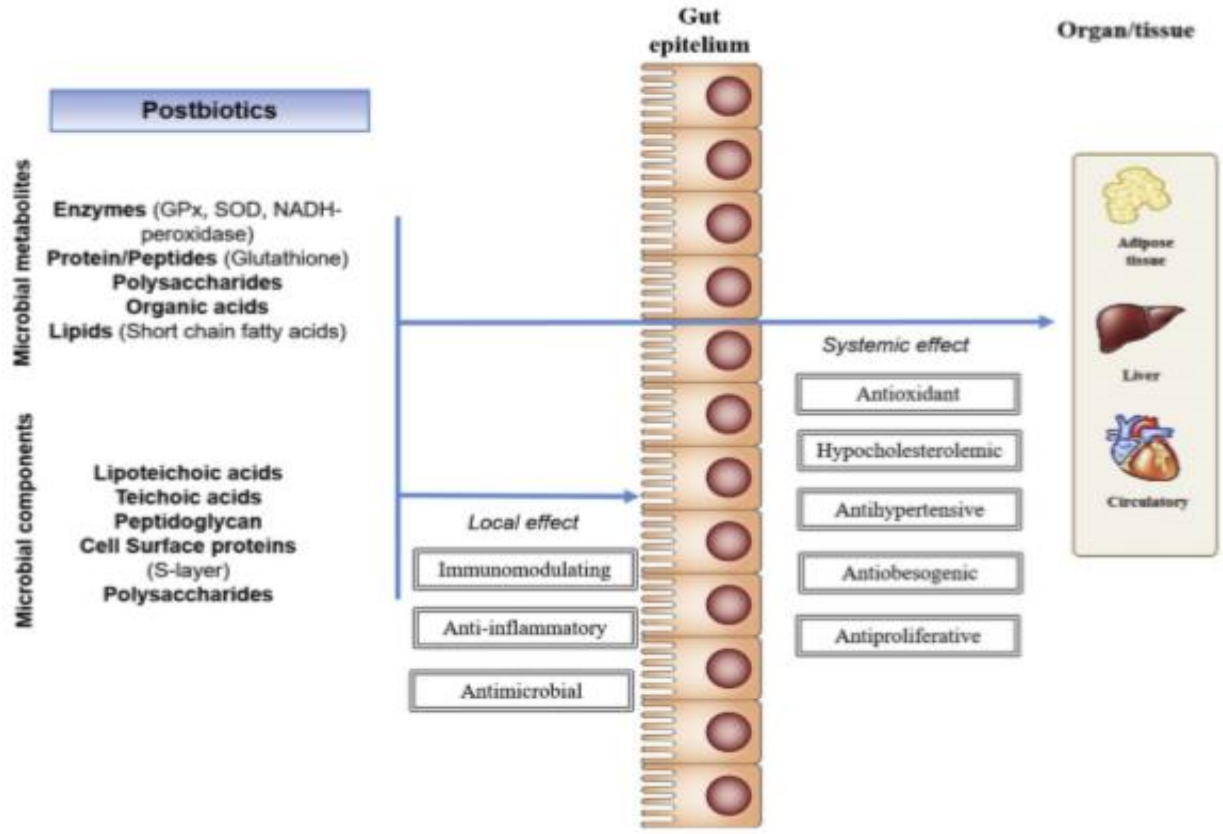

Figure 1. Some postbiotics and their potential local and systemic positive effects in the host [2].

DISCUSSION

The role of postbiotics on immune health

The interactions of the host with the microbiota are complex, numerous, and bidirectional. The gut microbiota is supposed to significantly regulate the development and function of the innate and adaptive immune system [38]. Intestinal commensals secrete antimicrobial peptides, compete for the nutrients and the habitat site thereby aiding in the state of homeostasis [39]. The gut microbiota and immune homeostasis seem to have a back-and-forth relationship and are also a field of great interest and intense research investigation in the field of infectious diseases. Also, gut microbiota-derived signals are known to tune the immune cells for pro and anti-inflammatory responses thereby affecting the susceptibility to various diseases [40].

The immune gut homeostasis is orchestrated by the fine-tuning of the regulatory balance of pro-inflammatory responses such as Th17 versus inflammatory regulatory T cells (Tregs) that are ultimately controlled by the commensal microorganisms [41]. In circumventing a response to pathogenic infections like coronavirus, a healthy gut microbiome essentially could be pivotal in maintaining an optimal immune system to prevent an array of excessive immune reactions that eventually become detrimental to lungs and vital organ systems. In such circumstances, it becomes imperative to have a balanced immune response wherein an over-reactive one or an under reactive one can equally be consequential to aggravate clinical complications like pneumonia and ARDS in a viral disease like Covid-19 [42].

Postbiotics play a vital role in the maturation of the immune system, affect barrier tightness, and the intestinal ecosystem, and indirectly shape the structure of the microbiota. As such, postbiotics may be useful in treating or preventing many disease entities, including those for which effective causal therapy has not yet been found (e.g., Alzheimer's disease, inflammatory bowel disease, or multiple sclerosis) [43].

The molecular mechanisms underlying the effects of postbiotics seem to be mediated through an interaction between the host and microbial products. This in turn can trigger the host immune system, and thereby trigger e.g., anti-inflammatory responses [44]. The possible mechanism of immunomodulation by postbiotics in humans could be derived from an *in vitro* experiment showing the innate response of macrophages to non-viable Lactobacillus casei cells. A suspension with heat-killed bacterial cells increased the expression of pro-inflammatory cytokines and enhanced the transcription of Toll-like receptors (TLR-2, TLR-3, TLR-4, and TLR-9) [45].

For people with conditions that result in immunodeficiency (immune system deficiency or weakness) or infants, probiotics may not be tolerable or safe. Postbiotic compounds, however, are much more tolerable and may reduce problematic inflammation. One study examined the role of probiotics and postbiotics in treating Necrotizing enterocolitis, one of the leading causes of death in newborns, and one of the most common gastrointestinal emergencies. While more studies need to be carried out, it was found that postbiotics, together with prebiotics, are potential alternatives, or complements to, probiotics [1, 46].

The gut microbiota plays a key role in health through its protective, trophic, and metabolic actions. While the microbes get a habitat and nourishment from the host, these microbes in turn help the host by regulating various host physiological functions, including dietary digestion, and imparting protective immunity against pathogens. Alterations of gut microbiota sometimes collectively called "gut dysbiosis" be associated with various diseases and disorders like IBD [47], type 2 diabetes [48], depression [49], cardiovascular disease [50].

As for the gut microbiota, there are pieces of evidence now that suggest the presence of distinct microorganisms in the lung [51]. In the gut, Bacteroidetes and Firmicutes are predominant while Bacteroidetes, Firmicutes, and Proteobacteria preponderate in the lung [52]. Interestingly, the gut microbiota has been shown to affect pulmonary health through a vital cross-talk between the gut microbiota and the lungs which are referred to as the "gut-lung axis" [53]. The gut-lung axis is supposed to be bidirectional, meaning the endotoxins, microbial metabolites can impact the lung through blood and when inflammation occurs in the lung, it can affect the gut microbiota as well [54].

Classes of postbiotics and their characteristics

The human gut microbiota consists of 1014 resident microorganisms which include bacteria, archaea, viruses, and fungi [55]. Primarily, the gut bacteria in healthy individuals is dominated by four phyla Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes [56]. The colon harbors an extremely high density of bacteria in the families Bacteroidaceae, Prevotellaceae, Rikenellaceae, Lachnospiraceae, and Ruminococcaceae [57].

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 organisms, cell to cell communication, and protection against stress factors [52, 58, 59].

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-phenyl lactic acid) and complexes molecules such as peptidoglycan-derived muropeptides, lipoteichoic acids [7, 20], or by their physiological functions which include immunomodulation, anti-inflammatory, hypocholesterolemic, anti-obesogenic, anti-hypertensive, anti-proliferative, and antioxidant effects [18, 60, 61].

The most and currently available classes of postbiotics are cell-free supernatants, Exopolysaccharides, Enzymes, Cell Wall Fragments, Short-Chain Fatty Acids, Bacterial Lysates, and Metabolites Produced by Gut Microbiota [43].

Cell-free supernatants

Cell-free supernatants containing biologically active metabolites secreted by bacteria and yeast into the surrounding liquid can be obtained directly from cell cultures. After an incubation period, the microbes are centrifuged and then removed. Finally, the resulting mixture is filtered to ensure sterility [43].

Supernatants produced from cultures of different microorganisms show differing activities. *Lactobacillus acidophilus* and *Lactobacillus casei* supernatants have anti-inflammatory and antioxidant effects on intestinal epithelial cells, macrophages, and neutrophils by reducing the secretion of the pro-inflammatory tumor necrosis factor α (TNF-α) cytokine and increasing the secretion of the anti-inflammatory cytokine interleukin 10 (IL-10) [62]. Meanwhile, supernatants derived from *L. casei* and *Lactobacillus rhamnosus* GG cultures can prevent the invasion of colon cancer cells [63]. As cell-free supernatants can reduce oxidative stress *in vivo* and provide direct antitumor activity, they may be clinically useful in the prevention of cancer [64].

Exopolysaccharides

During their growth, microorganisms produce biopolymers with different chemical properties. These biopolymers can be released outside the bacterial cell wall, forming a heterogeneous group of substances called exopolysaccharides (EPSs). EPSs are currently used in the food industry as stabilizing, emulsifying, and water-binding agents [46]. Nonetheless, the use of EPSs in pharmaceutical products and functional foods has attracted recent interest. EPSs may modulate the immune response by interacting with dendritic cells (DCs) and macrophages and enhancing the proliferation of T and NK lymphocytes [65].

Enzymes

Microorganisms have evolved defense mechanisms against the harmful effects of reactive oxygen species (ROS), which can damage lipids, proteins, carbohydrates, and nucleic acids. In particular, antioxidant enzymes, such as glutathione peroxidase (GPx), peroxide dismutase (SOD), catalase, and NADH-oxidase, play key roles in combating ROS. Indeed, two strains of *L. fermentum* were found to have a high content of GPx [66] and were later documented to possess potent antioxidant properties in vitro [67]. Antioxidant properties of postbiotics derived from *Lactobacillus plantarum* were demonstrated in the study conducted by Izuddin et al. [68].

Cell Wall Fragments

Many components of the bacterial cell wall are immunogenic (i.e., elicit a specific immune response), including bacterial lipoteichoic acid (LTA). LTA is found in the cell walls of Gram-positive bacteria and can be spontaneously released into the environment [69]. Although LTA has been shown to exhibit immunostimulatory effects [70], data on its activity are ambiguous. Some reports indicate that LTA reduces IL-12 production and induces the production of cytokines with immunoregulatory activity [71]. In contrast, others have shown LTA does not alleviate inflammatory processes and causes damage to tissues in the intestine [72].

The use of LTA in dermatological diseases is slightly less controversial. This data suggests LTA may be useful for treating a wide range of skin infections. The topical application of LTA enhances non-specific defense mechanisms, leading to the release of anti-infectious peptides, including human β-defensin and cathelicidin [73].

Short-chain fatty acids

Short-chain fatty acids (SCFAs) are a product of the fermentation of plant polysaccharides by intestinal microbiota. Well-known SCFAs include acetic, propionic, and butyric acids, which can form the corresponding fatty acid salts (i.e., acetate, propionate, and butyrate). Butyrate is one of the most important energy sources for enterocytes, as it helps to renew the intestinal epithelium and can also modulate gene expression by incompetently inhibiting histone deacetylases. Butyrate also shows immunosuppressive effects [74].

Bacterial lysates

Bacterial lysates (BLs) are obtained by the chemical or mechanical degradation of Gram-positive and Gram-negative bacteria commonly found in the environment. Their clinical use is based on the concept of the gut-lung axis, i.e., the functional connection between the immune system of the intestine and the respiratory system [75]. In particular, studies have shown that orally administered lyophilized BLs reach the Peyer's patches in the small intestine, where they stimulate DCs, and subsequently activate T and B lymphocytes. Mature lymphocytes then migrate to the mucous membrane of the respiratory tract and initially stimulate the innate immune system and promoting IgA secretion [76]. Indeed, the safety of BLs use has been confirmed during many clinical studies on various diseases, including recurrent upper respiratory tract infections in children [77].

A causal relationship between a decrease in the incidence of infections in highly developed countries and an increase in allergic diseases has been proposed, potentially due to the so-called hygiene hypothesis. Therefore, using BLs, which mimic the presence of bacteria, to stimulate the immune system, is an attractive option in the case of insufficient exposure to microorganisms. Indeed, a 2018 meta-analysis including over 4800 children showed a significantly lower incidence of respiratory infections in those receiving a commercially available BL preparation compared to the control group [78].

Metabolites produced by gut microbiota

The gut microbiota produces an array of molecules, including vitamins, phenolic-derived metabolites, and aromatic amino acids. Due to high bioavailability, antioxidative features, and signaling properties, these substances are considered to be important contributors to host-microbiome crosstalk. It has been demonstrated that in situ-produced bacterial foliate can be absorbed in the colon and incorporated into the host's tissues. Folate plays an important role in DNA synthesis, reparation, and methylation, and is also considered an antioxidative agent. Therefore, intestinal-produced folate may exert systemic function. Citizens of countries with mandatory folate food fortification were reported to have a lower risk of stroke compared to the controls [79].

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 an ingredient for foods and beverages or as nutritional supplements) that are greatly sought out [80, 81]. In addition, research performed by Shenderov [9] 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 [2].

Methods used to obtain and identify postbiotics

In general, postbiotics have been obtained by using cell disruption techniques, which include heat [17, 82], and enzymatic treatments [83], solvent extraction [84], as well as sonication [52, 61, 67, 85-90]. Besides, additional extraction and clean-up steps such as centrifugation, dialysis, freeze-dried and column purification have been used to assist in obtaining procedures [60, 86, 91]. (MALDI-TOF) mass spectrometry has been employed to identify LTA produced by *L. plantarum* K8 (KCTC10887BP) [84], and HPLC and proton nuclear magnetic resonance spectroscopy (1H-NMR) was used to identify and characterize polysaccharide-glycopeptide complexes of *Lactobacillus casei* YIT9018 [60].

Additionally, chromatography coupled with tandem mass spectrometry and Fourier transform ion cyclotron resonance mass spectrometry with direct infusion has been used to identify and characterize metabolites (e.g. fatty acids, glycerolipids, purines, sphingolipids, oligosaccharides) in biological samples [92].

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 the discovery and characterization of novel postbiotics, but also to understand the mechanisms of action and the signaling pathway modulation schemes.

The concept of postbiotics conceals either metabolites or fragments of microorganisms that confer a beneficial effect to the host. The structural heterogeneity of postbiotics implies the abundance of possible techniques used for postbiotics aquastion. Lysis of bacteria cells may be achieved by chemical and mechanical techniques. These methods include enzyme extraction, solvent extraction, sonication, and heat. Extraction, cinematography, and dialysis are used to isolate and identify desired molecules.

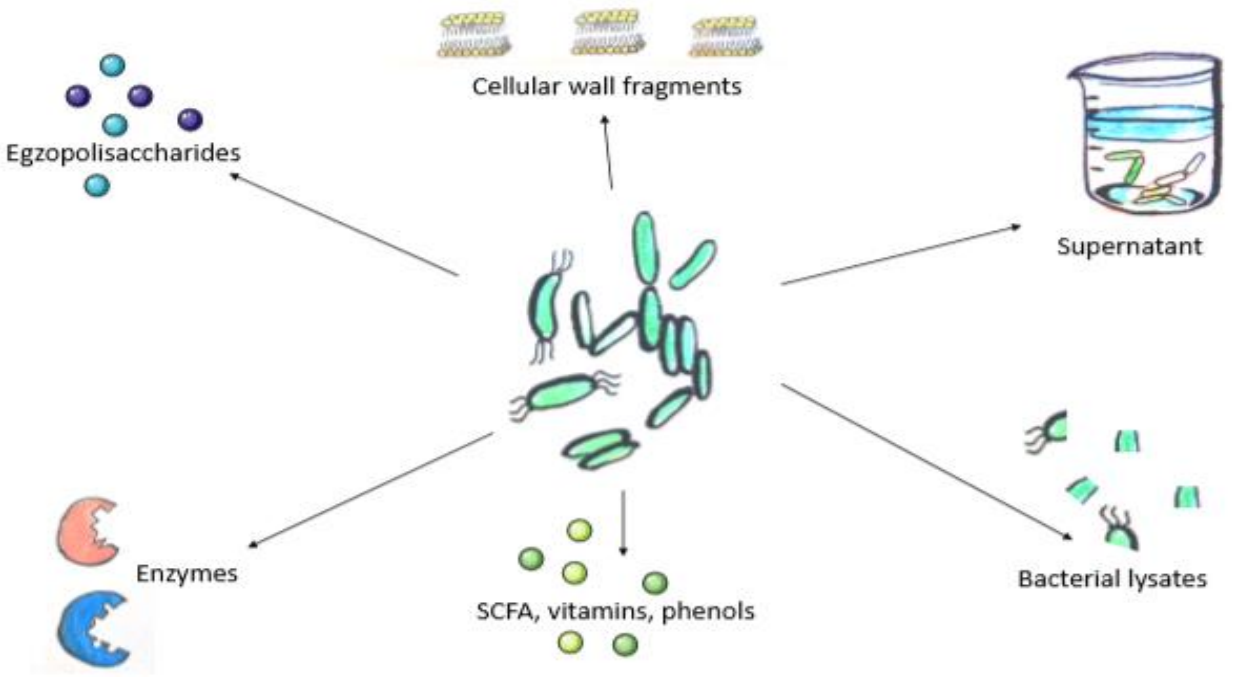

Figure 2. Methods of acquisition of postbiotics. SCFA (short-chain fatty acids) [43].

Postbiotics and gut health: an emerging field of research

All parts of the human body such as the skin, oral cavity gastrointestinal cavity, and vaginal cavity are inhabited by trillions of microbes [93, 94]. At birth, the human gut is sterile but colonized immediately after birth [95]. The pioneer microbe that" infest" the gut makes permanent adaptations and determines the physiological, immune, metabolic, and behavioral development and also influences future disease susceptibility [96].

Prenatal maternal exposure influences postnatal microbial colonization [93] and this plays a pivotal role in gut-associated lymphoid tissue (GALT) development [97], specific aspects of immune system development [98, 99], and the integrity of the mucosal barrier [98]. Therefore, the development of the gut microbiota in the early stages of life may be linked to future disease protection and/or susceptibility.

Increased understanding of the role of the gut microbiota in health has highlighted the benefits of pre-and probiotics, and now, postbiotics are emerging as a further source of support for the development of a strong and stable immune system. Produced by a natural fermentation process, postbiotics have been shown to benefit the adaptive and innate immune systems and improve gut barrier function. A healthy gut microbiota composition is essential for optimal immune system development and function in infants and has the potential to lower the risk of disease in infancy and beyond [1, 11].

Diet plays an important role in shaping the composition of the gut microbiota thereby influencing the host's health status. Various diet forms are found to influence the specific compositional patterns of the gut microbiota like the different composition of the microbiota with animal fat and protein-based diet serves us vegetable-based diets has been reported [100].

Gut microbes are capable of producing a vast range of products, the generation of which can be dependent on many factors, including nutrient availability and the luminal environment, particularly pH [101]. A more in-depth review of gut microbial products can be found elsewhere [102]. Microbial products can be taken up by GI tissues, potentially reach circulation and other tissues, and be excreted in urine or breath. Fermentation of fiber and protein by large bowel bacteria results in some of the most [103].

Postbiotics have been shown to support healthy gut microbiota. Regarding immune function, postbiotics have also been shown to improve the ability to fight infection by increasing the antibody response to pathogens, as well as directly influencing gut barrier function and intestinal immunity [15, 104].

Postbiotics Applications as Infectious Disease Control Agent

Some postbiotics can have direct antimicrobial effects by sealing the intestinal barrier, competitively binding to receptors required by some pathogenic bacteria, changing the expression of host genes, or modulating the local environment [105]. Indeed, combining postbiotics and probiotics effectively prevented rotavirus-associated diarrhea in a preclinical model [106].

Different postbiotics in aquaculture play a vital and prominent role in disease control agents. Peptides and exopolysaccharides have antimicrobial properties against bacterial pathogens. Then, short-chain fatty acids have both antimicrobial activities against bacterial pathogens and immunostimulating effects on the aquatic organism. Vitamins, peptidoglycan, and lipopolysaccharide are reported as immunostimulants. Finally, cell surface proteins and teichoic acid can act as a vaccine. Infectious disease is a serious issue in aquaculture development [107].

Postbiotics such as SCFAs, peptides, exopolysaccharides, vitamins, peptidoglycan, lipopolysaccharides, cell surface proteins, and teichoic acids are potential alternative disease control agents in aquaculture. The action mechanism of postbiotics and their role in improving host health and fighting against pathogens are not yet clearly defined. However, two mechanisms might explain how postbiotics can stimulate and modulate the host's immunological response, involving both elicit immune and acquired host response. The initial response is related to the innate immune system, and it consists of a series of pattern recognition receptors able to associate with microorganisms. Two of these pattern recognition receptors involved in the host response to postbiotics are the nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) and the toll-like receptors (TLRs) [104].

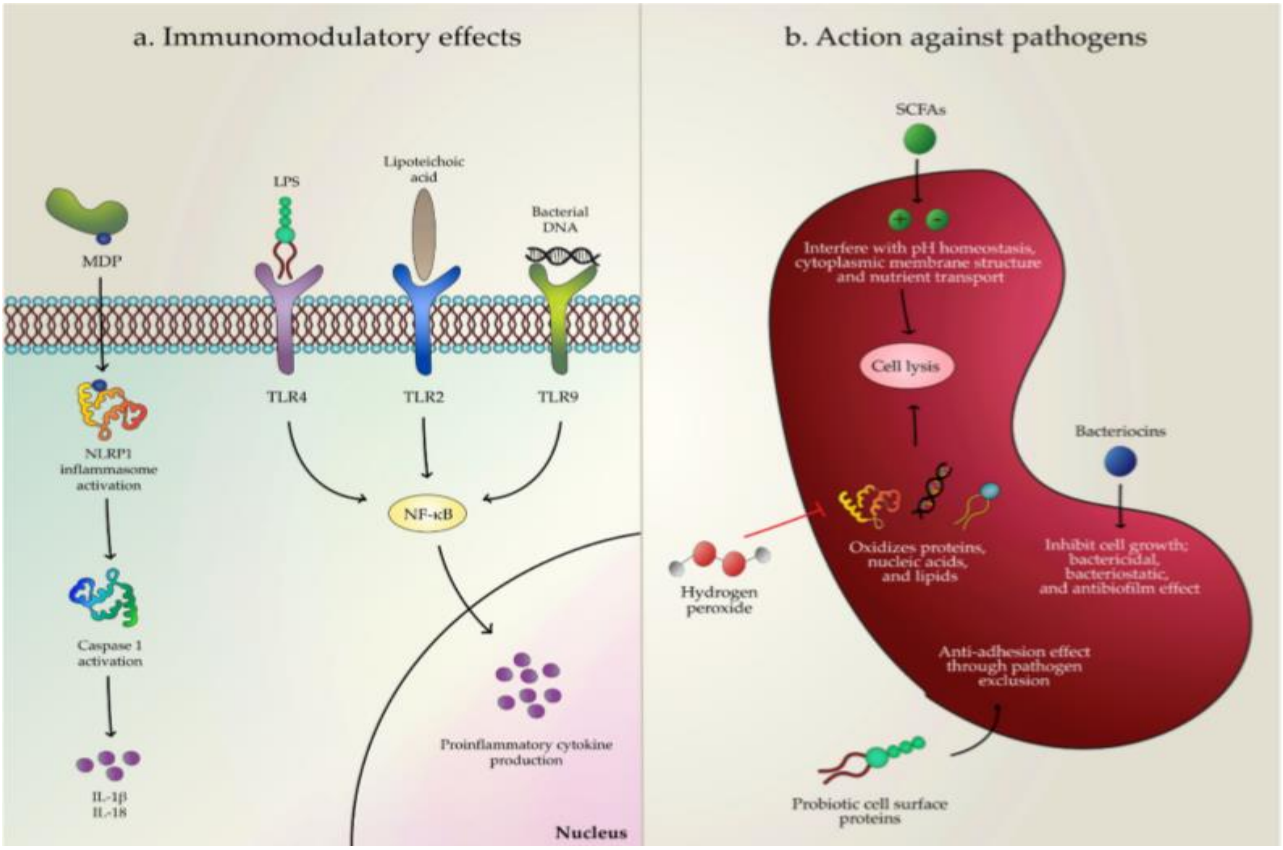

Figure 3. Potential mechanisms of action of postbiotics. (a) Modulation of the host's immune response. (b) Acting on the pathogen. TLRs= the toll-like receptors; NOD= the nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) [104].

CONCLUSION

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, hypo-cholesterolemic, 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 the 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 ensure stability during the manufacturing processes of postbiotic products and their efficacy. Special attention should be paid to the development of uniform and stringently defined culture procedures to eliminate possible variability of postbiotics production since uncontrolled environmental factors can well change metabolism and undergo unexpected transient variability. Besides, well-designed randomized placebo-controlled human/clinical intervention trials along with metabolomics studies must be conducted looking to support health claims of postbiotics supplementation.

The use of metabolites or fragments derived from microorganisms (i.e., "postbiotics") is an attractive therapeutic and preventive strategy in modern medicine. According to current data, such post biotics have pleiotropic effects, including immune-modulatory, anti-inflammatory, antioxidant, and anti-cancer properties. Some of these properties are even in clinical use. The boundary between probiotics and postbiotics is blurred in some trials, as their impact on the results is often not evaluated separately. We expect further research into the biological activities of these metabolites will unveil novel uses for postbiotics in medicine and beyond.

DECLARATIONS

Consent for publication

Not applicable.

Data availability statement

The data will be provided upon the request of the corresponding author.

Funding statement

All data used for this review are available in the manuscript.

Authors' contributions

HF, TY, MM, contribute to study design and data gathering and manuscript write-up, and editing of the manuscript. All authors have approved the submission of the manuscript.

Competing interests

All authors declared no competing conflict of interest.

REFERENCES

1. Wegh CA, Geerlings SY, Knol J, Roeselers G and Belzer C. Postbiotics and their potential applications in early life nutrition and beyond. International journal of molecular sciences. 2019; 20 (19): 4673. https://doi.org/10.3390/ijms20194673
2. Aguilar-Toalá J, Garcia-Varela R, Garcia H, Mata-Haro V, González-Córdova A, et al. Postbiotics: An evolving term within the functional foods field. Trends in Food Science & Technology. 2018; 75: 105-114. https://doi.org/10.1016/j.tifs.2018.03.009
3. Bermudez-Brito M, Plaza-Díaz J, Muñoz-Quezada S, Gómez-Llorente C and Gil A. Probiotic mechanisms of action. Annals of Nutrition and Metabolism. 2012; 61 (2): 160-174. https://doi.org/10.1159/000342079.
4. Vyas U and Ranganathan N. Probiotics, prebiotics, and synbiotics: Gut and beyond. Gastroenterology research and practice. 2012; 2012. https://doi.org/10.1155/2012/872716
5. Sanders ME. How do we know when something called "probiotic" is really a probiotic? A guideline for consumers and health care professionals. Functional Food Reviews. 2009; 1 (1): 3-12. https://doi.org/10.2310/6180.2009.00002.
6. Taverniti V and Guglielmetti S. The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: Proposal of paraprobiotic concept). Genes & nutrition. 2011; 6 (3): 261-274. https://doi.org/10.1007/s12263-011-0218-x.
7. Tsilingiri K and Rescigno M. Postbiotics: What else? Beneficial microbes. 2013; 4 (1): 101-107. https://doi.org/10.3920/BM2012.0046.

Citation: Fesseha, H Yilma, T, E Mekonnen. Postbiotics and their role in healthy life. *J Life Sci Biomed,* 2022; 12(4): 64-76. DOI: https://dx.doi.org/10.54203/jlsb.2022.8

8. Sharma M and Shukla G. Metabiotics: One step ahead of probiotics; an insight into mechanisms involved in anticancerous effect in colorectal cancer. Frontiers in microbiology. 2016; 7: 1940. https://doi.org/10.3389/fmicb.2016.01940.

9. Shenderov BA. Metabiotics: Novel idea or natural development of probiotic conception. Microbial ecology in Health and Disease. 2013; 24 (1): 20399. https://doi.org/10.3402/mehd.v24i0.20399.

10. Huang S, Vignolles M-L, Chen XD, Le Loir Y, Jan G, et al. Spray drying of probiotics and other food-grade bacteria: A review. Trends in Food Science & Technology. 2017; 63: 1-17. https://doi.org/10.1016/j.tifs.2017.02.007.

11. Reid G. Probiotics: Definition, scope and mechanisms of action. Best practice & research Clinical gastroenterology. 2016; 30 (1): 17-25. https://doi.org/10.1016/j.bpg.2015.12.001.

12. Sánchez B, Ruiz L, Gueimonde M, Ruas-Madiedo P and Margolles A. Toward improving technological and functional properties of probiotics in foods. Trends in Food Science & Technology. 2012; 26 (1): 56-63. https://doi.org/10.1016/j.tifs.2012.02.002.

13. Chua KJ, Kwok WC, Aggarwal N, Sun T and Chang MW. Designer probiotics for the prevention and treatment of human diseases. Current opinion in chemical biology. 2017; 40: 8-16. https://doi.org/10.1016/j.cbpa.2017.04.011

14. Compare D, Rocco A, Coccoli P, Angrisani D, Sgamato C, et al. Lactobacillus casei dg and its postbiotic reduce the inflammatory mucosal response: An ex-vivo organ culture model of post-infectious irritable bowel syndrome. BMC gastroenterology. 2017; 17 (1): 1-8. https://doi.org/10.1186/s12876-017-0605-x

15. Haileselassie Y, Navis M, Vu N, Qazi KR, Rethi B, et al. Postbiotic modulation of retinoic acid imprinted mucosal-like dendritic cells by probiotic lactobacillus reuteri 17938 in vitro. Frontiers in immunology. 2016; 7: 96. https://doi.org/10.3389/fimmu.2016.00096

16. Kareem KY, Ling FH, Chwen LT, Foong OM and Asmara SA. Inhibitory activity of postbiotic produced by strains of lactobacillus plantarum using reconstituted media supplemented with inulin. Gut pathogens. 2014; 6 (1): 1-7. https://doi.org/10.1186/1757-4749-6-23

17. Lee JW, Shin JG, Kim EH, Kang HE, Yim IB, et al. Immunomodulatory and antitumor effects in vivo by the cytoplasmic fraction of lactobacillus casei and bifidobacterium longum. Journal of veterinary science. 2004; 5 (1): 41-48. https://doi.org/10.4142/jvs.2004.5.1.41

18. Nakamura F, Ishida Y, Sawada D, Ashida N, Sugawara T, et al. Fragmented lactic acid bacterial cells activate peroxisome proliferator-activated receptors and ameliorate dyslipidemia in obese mice. Journal of agricultural and food chemistry. 2016; 64 (12): 2549-2559. https://doi.org/10.1021/acs.jafc.5b05827

19. Cicenia A, Scirocco A, Carabotti M, Pallotta L, Marignani M, et al. Postbiotic activities of lactobacilli-derived factors. Journal of clinical gastroenterology. 2014; 48: S18-S22. https://doi.org/10.1097/MCG.0000000000000231

20. Konstantinov SR, Kuipers EJ and Peppelenbosch MP. Functional genomic analyses of the gut microbiota for crc screening. Nature reviews Gastroenterology & hepatology. 2013; 10 (12): 741-745. https://doi.org/10.1038/nrgastro.2013.178

21. Patel RM and Denning PW. Therapeutic use of prebiotics, probiotics, and postbiotics to prevent necrotizing enterocolitis: What is the current evidence? Clinics in perinatology. 2013; 40 (1): 11-25. https://doi.org/10.1016/j.clp.2012.12.002

22. Martín R and Langella P. Emerging health concepts in the probiotics field: Streamlining the definitions. Frontiers in microbiology. 2019; 10: 1047. https://doi.org/10.3389/fmicb.2019.01047

23. Moradi M, Kousheh SA, Almasi H, Alizadeh A, Guimarães JT, et al. Postbiotics produced by lactic acid bacteria: The next frontier in food safety. Comprehensive Reviews in Food Science and Food Safety. 2020; 19 (6): 3390-3415. https://doi.org/10.1111/1541-4337.12613

24. Oberg T, Steele J, Ingham S, Smeianov V, Briczinski E, et al. Intrinsic and inducible resistance to hydrogen peroxide in bifidobacterium species. Journal of Industrial Microbiology and Biotechnology. 2011; 38 (12): 1947-1953. https://doi.org/10.1007/s10295-011-0983-y

25. Nataraj BH, Ali SA, Behare PV and Yadav H. Postbiotics-parabiotics: The new horizons in microbial biotherapy and functional foods. Microbial cell factories. 2020; 19 (1): 1-22. https://doi.org/10.1186/s12934-020-01426-w

26. Hsieh F-C, Lan C-CE, Huang T-Y, Chen K-W, Chai C-Y, et al. Heat-killed and live lactobacillus reuteri gmnl-263 exhibit similar effects on improving metabolic functions in high-fat diet-induced obese rats. Food & function. 2016; 7 (5): 2374-2388. https://doi.org/10.1039/C5FO01396H

27. Jang HJ, Song MW, Lee N-K and Paik H-D. Antioxidant effects of live and heat-killed probiotic lactobacillus plantarum ln1 isolated from kimchi. Journal of food science and technology. 2018; 55 (8): 3174-3180. https://doi.org/10.1007/s13197-018-3245-4

28. Thakur BK, Saha P, Banik G, Saha DR, Grover S, et al. Live and heat-killed probiotic lactobacillus casei lbs2 protects from experimental colitis through toll-like receptor 2-dependent induction of t-regulatory response. International immunopharmacology. 2016; 36: 39-50. https://doi.org/10.1016/j.intimp.2016.03.033

29. Robles-Vera I, Toral M, Romero M, Jiménez R, Sánchez M, et al. Antihypertensive effects of probiotics. Current hypertension reports. 2017; 19 (4): 26. https://doi.org/10.1007/s11906-017-0723-4

30. Klemashevich C, Wu C, Howsmon D, Alaniz RC, Lee K, et al. Rational identification of diet-derived postbiotics for improving intestinal microbiota function. Current opinion in biotechnology. 2014; 26: 85-90. https://doi.org/10.1016/j.copbio.2013.10.006

31. Kimura I, Ozawa K, Inoue D, Imamura T, Kimura K, et al. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor gpr43. Nature communications. 2013; 4 (1): 1-12. https://doi.org/10.1038/ncomms2852

32. Imaoka A, Shima T, Kato K, Mizuno S, Uehara T, et al. Anti-inflammatory activity of probiotic bifidobacterium: Enhancement of il-10 production in peripheral blood mononuclear cells from ulcerative colitis patients and inhibition of il-8 secretion in ht-29 cells. World Journal of Gastroenterology: WJG. 2008; 14 (16): 2511. https://doi.org/10.3748/wjg.14.2511

33. Kamiya T, Wang L, Forsythe P, Goettsche G, Mao Y, et al. Inhibitory effects of lactobacillus reuteri on visceral pain induced by colorectal distension in sprague-dawley rats. Gut. 2006; 55 (2): 191-196. http://dx.doi.org/10.1136/gut.2005.070987

34. de Almada CN, Almada CN, Martinez RC and Sant'Ana AS. Paraprobiotics: Evidences on their ability to modify biological responses, inactivation methods and perspectives on their application in foods. Trends in Food Science & Technology. 2016; 58: 96-114. https://doi.org/10.1016/j.tifs.2016.09.011

35. Hoarau C, Lagaraine C, Martin L, Velge-Roussel F and Lebranchu Y. Supernatant of bifidobacterium breve induces dendritic cell maturation, activation, and survival through a toll-like receptor 2 pathway. Journal of Allergy and Clinical Immunology. 2006; 117 (3): 696-702. https://doi.org/10.1016/j.jaci.2005.10.043

36. Menard S, Laharie D, Asensio C, Vidal-Martinez T, Candalh C, et al. Bifidobacterium breve and streptococcus thermophilus secretion products enhance t helper 1 immune response and intestinal barrier in mice. Experimental Biology and Medicine. 2005; 230 (10): 749-756. https://doi.org/10.1177/153537020523001

37. Zagato E, Mileti E, Massimiliano L, Fasano F, Budelli A, et al. Lactobacillus paracasei cba l74 metabolic products and fermented milk for infant formula have anti-inflammatory activity on dendritic cells in vitro and protective effects against colitis and an enteric pathogen in vivo. PLoS One. 2014; 9 (2): e87615. https://doi.org/10.1371/journal.pone.0087615

Citation: Fesseha, H Yilma, T, E Mekonnen. Postbiotics and their role in healthy life. *J Life Sci Biomed,* 2022; 12(4): 64-76. DOI: https://dx.doi.org/10.54203/jlsb.2022.8

38. Negi S, Das DK, Pahari S, Nadeem S and Agrewala JN. Potential role of gut microbiota in induction and regulation of innate immune memory. Frontiers in immunology. 2019; 10: 2441. https://doi.org/10.3389/fimmu.2019.02441

39. Moens E and Veldhoen M. Epithelial barrier biology: Good fences make good neighbours. Immunology. 2012; 135 (1): 1-8. https://doi.org/10.1111/j.1365-2567.2011.03506.x

40. Negi S, Pahari S, Bashir H and Agrewala JN. Gut microbiota regulates mincle mediated activation of lung dendritic cells to protect against mycobacterium tuberculosis. Frontiers in immunology. 2019; 10: 1142. https://doi.org/10.3389/fimmu.2019.01142

41. Round JL and Mazmanian SK. Inducible foxp3+ regulatory t-cell development by a commensal bacterium of the intestinal microbiota. Proceedings of the National Academy of Sciences. 2010; 107 (27): 12204-12209. https://doi.org/10.1073/pnas.09091221

42. Dhar D and Mohanty A. Gut microbiota and covid-19-possible link and implications. Virus research. 2020; 285: 198018. https://doi.org/10.1016/j.virusres.2020.198018

43. Żółkiewicz J, Marzec A, Ruszczyński M and Feleszko W. Postbiotics-a step beyond pre-and probiotics. Nutrients. 2020; 12 (8): 2189. https://doi.org/10.3390/nu12082189

44. Gosálbez L and Ramón D. Probiotics in transition: Novel strategies. Trends in biotechnology. 2015; 33 (4): 195-196. https://doi.org/10.1016/j.tibtech.2015.01.006

45. Wang Y, Xie J, Wang N, Li Y, Sun X, et al. Lactobacillus casei zhang modulate cytokine and toll-like receptor expression and beneficially regulate poly i: C-induced immune responses in raw264. 7 macrophages. Microbiology and immunology. 2013; 57 (1): 54-62. https://doi.org/10.1111/j.1348-0421.516.x

46. Singh P and Saini P. Food and health potentials of exopolysaccharides derived from lactobacilli. Microbiology Research Journal International. 2017: 1-14. Google scholar

47. Khan I, Ullah N, Zha L, Bai Y, Khan A, et al. Alteration of gut microbiota in inflammatory bowel disease (ibd): Cause or consequence? Ibd treatment targeting the gut microbiome. Pathogens. 2019; 8 (3): 126. https://doi.org/10.3390/pathogens8030126

48. Gurung M, Li Z, You H, Rodrigues R, Jump DB, et al. Role of gut microbiota in type 2 diabetes pathophysiology. EBioMedicine. 2020; 51: 102590. https://doi.org/10.1016/j.ebiom.2019.11.051

49. Zalar B, Haslberger A and Peterlin B. The role of microbiota in depression-a brief review. Psychiatria Danubina. 2018; 30 (2): 136-141. https://doi.org/10.24869/psyd.2018.136

50. Tang WW, Kitai T and Hazen SL. Gut microbiota in cardiovascular health and disease. Circulation research. 2017; 120 (7): 1183-1196. https://doi.org/10.1161/CIRCRESAHA.117.309715

51. Bingula R, Filaire M, Radosevic-Robin N, Bey M, Berthon J-Y, et al. Desired turbulence? Gut-lung axis, immunity, and lung cancer. Journal of oncology. 2017; 2017. https://doi.org/10.1155/2017/5035371

52. Zhang S, Liu L, Su Y, Li H, Sun Q, et al. Antioxidative activity of lactic acid bacteria in yogurt. African Journal of Microbiology Research. 2011; 5 (29): 5194-5201. https://doi.org/10.5897/AJMR11.997

53. Keely S, Talley NJ and Hansbro PM. Pulmonary-intestinal cross-talk in mucosal inflammatory disease. Mucosal immunology. 2012; 5 (1): 7-18. https://doi.org/10.1038/mi.2011.55

54. Dumas A, Bernard L, Poquet Y, Lugo-Villarino G and Neyrolles O. The role of the lung microbiota and the gut–lung axis in respiratory infectious diseases. Cellular microbiology. 2018; 20 (12): e12966. https://doi.org/10.1111/cmi.12966

55. Gill SR, Pop M, DeBoy RT, Eckburg PB, Turnbaugh PJ, et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006; 312 (5778): 1355-1359. https://doi.org/10.1126/science.1124234

56. Villanueva-Millán M, Perez-Matute P and Oteo J. Gut microbiota: A key player in health and disease. A review focused on obesity. Journal of physiology and biochemistry. 2015; 71 (3): 509-525. https://doi.org/10.1007/s13105-015-0390-3

57. Hall AB, Tolonen AC and Xavier RJ. Human genetic variation and the gut microbiome in disease. Nature Reviews Genetics. 2017; 18 (11): 690. https://doi.org/10.1038/nrg.2017.63

58. Hibbing ME, Fuqua C, Parsek MR and Peterson SB. Bacterial competition: Surviving and thriving in the microbial jungle. Nature reviews microbiology. 2010; 8 (1): 15-25. https://doi.org/10.1038/nrmicro2259

59. Netzker T, Fischer J, Weber J, Mattern DJ, König CC, et al. Microbial communication leading to the activation of silent fungal secondary metabolite gene clusters. Frontiers in microbiology. 2015; 6: 299. https://doi.org/10.3389/fmicb.2015.00299

60. Sawada H, Furushiro M, Hirai K, Motoike M, Watanabe T, et al. Purification and characterization of an antihypertensive compound from lactohacillus casei. Agricultural and biological chemistry. 1990; 54 (12): 3211-3219. https://doi.org/10.1080/00021369.1990.10870492

61. Shin HS, Park SY, Lee DK, Kim SA, An HM, et al. Hypocholesterolemic effect of sonication-killed bifidobacterium longum isolated from healthy adult koreans in high cholesterol fed rats. Archives of pharmacal research. 2010; 33 (9): 1425-1431. https://doi.org/10.1007/s12272-010-0917-7

62. De Marco S, Sichetti M, Muradyan D, Piccioni M, Traina G, et al. Probiotic cell-free supernatants exhibited anti-inflammatory and antioxidant activity on human gut epithelial cells and macrophages stimulated with lps. Evidence-based complementary and alternative medicine. 2018; 2018. https://doi.org/10.1155/2018/1756308

63. Escamilla J, Lane MA and Maitin V. Cell-free supernatants from probiotic lactobacillus casei and lactobacillus rhamnosus gg decrease colon cancer cell invasion in vitro. Nutrition and cancer. 2012; 64 (6): 871-878. https://doi.org/10.1080/01635581.2012.700758

64. Amaretti A, Di Nunzio M, Pompei A, Raimondi S, Rossi M, et al. Antioxidant properties of potentially probiotic bacteria: In vitro and in vivo activities. Applied microbiology and biotechnology. 2013; 97 (2): 809-817. https://doi.org/10.1007/s00253-012-4241-7

65. Makino S, Sato A, Goto A, Nakamura M, Ogawa M, et al. Enhanced natural killer cell activation by exopolysaccharides derived from yogurt fermented with lactobacillus delbrueckii ssp. Bulgaricus oll1073r-1. Journal of dairy science. 2016; 99 (2): 915-923. https://doi.org/10.3168/jds.2015-10376

66. Kullisaar T, Zilmer M, Mikelsaar M, Vihalemm T, Annuk H, et al. Two antioxidative lactobacilli strains as promising probiotics. International Journal of Food Microbiology. 2002; 72 (3): 215-224. https://doi.org/10.1016/S0168-1605(01)00674-2

67. Kim H, Chae H, Jeong S, Ham J, Im S, et al. In vitro antioxidative properties of lactobacilli. Asian-australasian journal of animal sciences. 2005; 19 (2): 262-265. https://doi.org/10.5713/ajas.2006.262

68. Izuddin WI, Humam AM, Loh TC, Foo HL and Samsudin AA. Dietary postbiotic lactobacillus plantarum improves serum and ruminal antioxidant activity and upregulates hepatic antioxidant enzymes and ruminal barrier function in post-weaning lambs. Antioxidants. 2020; 9 (3): 250. https://doi.org/10.3390/antiox9030250

69. Van Langevelde P, Van Dissel J, Ravensbergen E, Appelmelk B, Schrijver I, et al. Antibiotic-induced release of lipoteichoic acid and peptidoglycan from staphylococcus aureus: Quantitative measurements and biological reactivities. Antimicrobial agents and chemotherapy. 1998; 42 (12): 3073-3078. https://doi.org/10.1128/AAC.42.12.3073

70. Kim HG, Kim N-R, Gim MG, Lee JM, Lee SY, et al. Lipoteichoic acid isolated from lactobacillus plantarum inhibits lipopolysaccharide-induced tnf-α production in thp-1 cells and endotoxin shock in mice. The Journal of Immunology. 2008; 180 (4): 2553-2561. https://doi.org/10.4049/jimmunol.180.4.2553

71. Kaji R, Kiyoshima-Shibata J, Nagaoka M, Nanno M and Shida K. Bacterial teichoic acids reverse predominant il-12 production induced by certain lactobacillus strains into predominant il-10 production via tlr2-dependent erk activation in macrophages. The Journal of Immunology. 2010; 184 (7): 3505-3513. https://doi.org/10.4049/jimmunol.0901569

72. Zadeh M, Khan MW, Goh YJ, Selle K, Owen JL, et al. Induction of intestinal pro-inflammatory immune responses by lipoteichoic acid. Journal of inflammation. 2012; 9 (1): 1-12. https://doi.org/10.1186/1476-9255-9-7

73. Schauber J and Gallo RL. Antimicrobial peptides and the skin immune defense system. Journal of Allergy and Clinical Immunology. 2008; 122 (2): 261-266. https://doi.org/10.1016/j.jaci.2008.03.027

74. Lee C, Kim BG, Kim JH, Chun J, Im JP, et al. Sodium butyrate inhibits the nf-kappa b signaling pathway and histone deacetylation, and attenuates experimental colitis in an il-10 independent manner. International immunopharmacology. 2017; 51: 47-56. https://doi.org/10.1016/j.intimp.2017.07.023

75. Feleszko W, Jaworska J, Rha RD, Steinhausen S, Avagyan A, et al. Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of t regulatory-dependent mechanisms in a murine model of asthma. Clinical & Experimental Allergy. 2007; 37 (4): 498-505. https://doi.org/10.1111/j.1365-2222.2006.02629.x

76. Kearney SC, Dziekiewicz M and Feleszko W. Immunoregulatory and immunostimulatory responses of bacterial lysates in respiratory infections and asthma. Annals of Allergy, Asthma & Immunology. 2015; 114 (5): 364-369. https://doi.org/10.1016/j.anai.2015.02.008

77. Schaad UB, Mütterlein R, Goffin H and Group B-CS. Immunostimulation with om-85 in children with recurrent infections of the upper respiratory tract: A double-blind, placebo-controlled multicenter study. Chest. 2002; 122 (6): 2042-2049. https://doi.org/10.1378/chest.122.6.2042

78. Yin J, Xu B, Zeng X and Shen K. Broncho-vaxom in pediatric recurrent respiratory tract infections: A systematic review and meta-analysis. International immunopharmacology. 2018; 54: 198-209. https://doi.org/10.1016/j.intimp.2017.10.032

79. Hsu C-Y, Chiu S-W, Hong K-S, Saver JL, Wu Y-L, et al. Folic acid in stroke prevention in countries without mandatory folic acid food fortification: A meta-analysis of randomized controlled trials. Journal of stroke. 2018; 20 (1): 99. https://doi.org/10.5853/jos.2017.01522

80. Shigwedha N. Probiotical cell fragments (pcfs) as "novel nutraceutical ingredients". Journal of Biosciences and Medicines. 2014; 2 (03): 43. https://doi.org/10.4236/jbm.2014.23007

81. Tomar SK, Anand S, Sharma P, Sangwan V and Mandal S. Role of probiotics, prebiotics, synbiotics and postbiotics in inhibition of pathogens. The Battle against Microbial Pathogens: Basic Science, Technological Advances and Educational Programs; Méndez-Vilas, A., Ed. 2015: 717-732. Google scholar

82. Tejada-Simon MV and Pestka JJ. Proinflammatory cytokine and nitric oxide induction in murine macrophages by cell wall and cytoplasmic extracts of lactic acid bacteria. Journal of food protection. 1999; 62 (12): 1435-1444. https://doi.org/10.4315/0362-028X-62.12.1435

83. Li S, Zhao Y, Zhang L, Zhang X, Huang L, et al. Antioxidant activity of lactobacillus plantarum strains isolated from traditional chinese fermented foods. Food Chemistry. 2012; 135 (3): 1914-1919. https://doi.org/10.1016/j.foodchem.2012.06.048

84. Kim HG, Lee SY, Kim NR, Lee HY, Ko MY, et al. Lactobacillus plantarum lipoteichoic acid down-regulated shigella flexneri peptidoglycan-induced inflammation. Molecular immunology. 2011; 48 (4): 382-391. https://doi.org/10.1016/j.molimm.2010.07.011

85. Choi S, Kim Y, Han K, You S, Oh S, et al. Effects of lactobacillus strains on cancer cell proliferation and oxidative stress in vitro. Letters in applied microbiology. 2006; 42 (5): 452-458. https://doi.org/10.1111/j.1472-765X.2006.01913.x

86. Matsuguchi T, Takagi A, Matsuzaki T, Nagaoka M, Ishikawa K, et al. Lipoteichoic acids from lactobacillus strains elicit strong tumor necrosis factor alpha-inducing activities in macrophages through toll-like receptor 2. Clinical and Vaccine Immunology. 2003; 10 (2): 259-266. https://doi.org/10.1128/CDLI.10.2.259-266.2003

87. Ou C, Ko J and Lin M. Antioxidative effects of intracellular extracts of yogurt bacteria on lipid peroxidation and intestine 407 cells. Journal of Food and Drug analysis. 2006; 14 (3): 304-310. https://doi.org/10.38212/2224-6614.2474

88. Sharma S, Singh R and Kakkar P. Modulation of bax/bcl-2 and caspases by probiotics during acetaminophen induced apoptosis in primary hepatocytes. Food and chemical toxicology. 2011; 49 (4): 770-779. https://doi.org/10.1016/j.fct.2010.11.041

89. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of crohn disease patients. Proceedings of the National Academy of Sciences. 2008; 105 (43): 16731-16736. https://doi.org/10.1073/pnas.0804812105

90. Tiptiri-Kourpeti A, Spyridopoulou K, Santarmaki V, Aindelis G, Tompoulidou E, et al. Lactobacillus casei exerts anti-proliferative effects accompanied by apoptotic cell death and up-regulation of trail in colon carcinoma cells. PLoS One. 2016; 11 (2): e0147960. https://doi.org/10.1371/journal.pone.0147960

91. Vidal K, Donnet-Hughes A and Granato D. Lipoteichoic acids from lactobacillus johnsonii strain la1 and lactobacillus acidophilus strain la10 antagonize the responsiveness of human intestinal epithelial ht29 cells to lipopolysaccharide and gram-negative bacteria. Infection and immunity. 2002; 70 (4): 2057-2064. https://doi.org/10.1128/IAI.70.4.2057-2064.2002

92. Antunes LCM, Han J, Ferreira RB, Lolic P, Borchers CH, et al. Effect of antibiotic treatment on the intestinal metabolome. Antimicrobial agents and chemotherapy. 2011; 55 (4): 1494-1503. https://doi.org/10.1128/AAC.01664-10

93. Douillard FP and De Vos WM. Functional genomics of lactic acid bacteria: From food to health. Microbial cell factories. 2014; 13 (1): 1-21. https://doi.org/10.1186/1475-2859-13-S1-S8

94. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, et al. The human microbiome project. Nature. 2007; 449 (7164): 804-810. https://doi.org/10.1038/nature06244

95. Scaldaferri F, Gerardi V, Lopetuso LR, Del Zompo F, Mangiola F, et al. Gut microbial flora, prebiotics, and probiotics in ibd: Their current usage and utility. BioMed research international. 2013; 2013. https://doi.org/10.1155/2013/435268

96. Versalovic J. The human microbiome and probiotics: Implications for pediatrics. Annals of Nutrition and Metabolism. 2013; 63 (Suppl. 2): 42-52. https://doi.org/10.1159/000354899

97. Cebra JJ. Influences of microbiota on intestinal immune system development. The American journal of clinical nutrition. 1999; 69 (5): 1046s-1051s. https://doi.org/10.1093/ajcn/69.5.1046s

98. Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, et al. Molecular analysis of commensal host-microbial relationships in the intestine. Science. 2001; 291 (5505): 881-884. https://doi.org/10.1126/science.291.5505.8

99. Penders J, Stobberingh EE, Brandt Pvd and Thijs C. The role of the intestinal microbiota in the development of atopic disorders. Allergy. 2007; 62 (11): 1223-1236. https://doi.org/10.1111/j.1398-9995.2007.01462.x

100. De Filippis F, Pellegrini N, Vannini L, Jeffery IB, La Storia A, et al. High-level adherence to a mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut. 2016; 65 (11): 1812-1821. http://dx.doi.org/10.1136/gutjnl-2015-309957

101. Duncan SH, Louis P, Thomson JM and Flint HJ. The role of ph in determining the species composition of the human colonic microbiota. Environmental microbiology. 2009; 11 (8): 2112-2122. https://doi.org/10.1111/j.1462-2920.2009.01931.x

102. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, et al. Host-gut microbiota metabolic interactions. Science. 2012; 336 (6086): 1262-1267. https://doi.org/10.1126/science.1223813

103. Conlon MA and Bird AR. The impact of diet and lifestyle on gut microbiota and human health. Nutrients. 2015; 7 (1): 17-44. https://doi.org/10.3390/nu7010017

104. Mantziari A, Salminen S, Szajewska H and Malagón-Rojas JN. Postbiotics against pathogens commonly involved in pediatric infectious diseases. Microorganisms. 2020; 8 (10): 1510. https://doi.org/10.3390/microorganisms8101510

105. Khodaii Z, Ghaderian SMH and Natanzi MM. Probiotic bacteria and their supernatants protect enterocyte cell lines from enteroinvasive escherichia coli (eiec) invasion. International journal of molecular and cellular medicine. 2017; 6 (3): 183. https://doi.org/10.22088/acadpub.BUMS.6.3.183

106. Rigo-Adrover MdM, Knipping K, Garssen J, van Limpt K, Knol J, et al. Prevention of rotavirus diarrhea in suckling rats by a specific fermented milk concentrate with prebiotic mixture. Nutrients. 2019; 11 (1): 189. https://doi.org/10.3390/nu11010189

107. Ang CY, Sano M, Dan S, Leelakriangsak M and Lal TM. Postbiotics applications as infectious disease control agent in aquaculture. Biocontrol science. 2020; 25 (1): 1-7. https://doi.org/10.4265/bio.25.1