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Postbiotics: Metabolites and mechanisms involved in microbiota-host interactions

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ABSTRACT

Background: The knowledge on the mechanisms through which the metabolites produced by the gut microbiota (postbiotics) prevent diseases, induce therapeutic responses, and behave differently in response to dietary and environmental changes, is one of the major challenges in nutrition research and paves the route for the development of new therapeutic strategies against non-communicable diseases.

Scope and approach: In this review, the main mechanisms by which postbiotics provide a link between nutrition, microbiota, and human health are discussed. Postbiotics are the repertoire of metabolites produced in the fermentation process of dietary components (mainly fibers and polyphenols, but also complex carbohydrates, proteins, and lipids), as well as the endogenous components generated by bacteria-host interactions that influence human health.

Key findings and conclusions: Short-chain fatty acids denote a primary energy source for colonocytes, also acting on the gut-brain axis to reduce appetite and performing epigenetic roles. Polyamines promote homeostasis and affect epigenetic processes, apoptosis, and cell proliferation through interaction with proteins and nucleic acids. Bile acids are involved in glucose metabolism and modulation of the host immune response. p-Cresol features antimicrobial and antioxidant properties, but has been related to enteric pathogens, autism, and kidney diseases. The role of trimethylamine N-oxide (TMAO) in cardiovascular diseases is still under debate. Bacteriocins have antibiotic action against pathogens. The beneficial effects of polyphenols are demonstrated by their essentiality in the production of metabolites. Summarizing, metagenomic sequencing, intervention studies, and metabolomics are enabling to understand the modulation and effects of microbiota metabolic activity. However, in order to clearly elucidate the food-microbiota axis, the interplay among the host microbiota and the metabolites secreted by intestinal cells, and the intestine-liver-brain axis, the studies must be directed to the subject habitat.

Abbreviations: AAs, amino acids; AAD-antibiotic, associated diarrhea; ABC, ATP- binding cassette; ADC, arginine decarboxylase; AHR, aryl hydrocarbon receptor; AID, acid-induced diarrhea; AMPK, adenosine monophosphate activated protein kinase; ASD, Autism Spectrum Disorder; BCAAs, Branched-chain amino acids; cAMP, cyclic adenosine monophosphate; CD, chronic disease; CDCA, chenodeoxycholic acid; CVD, cardiovascular disease; CRC, colorectal cancer; DHR, dihydro-resveratrol; DMB, 3,3-dimethyl-1-butanol; ERK1/2, extracellular signal-regulated kinases; FMO3, flavine monooxygenase 3; FXR, farnesoid X nuclear receptor; GI, gastrointestinal; GOS, galactooligosaccharide; HDACi, histone deacetylase enzyme inhibitor; IBS, Irritable bowel; IBD, Inflammatory Bowel Disease; IAA, indole-3- acetic acid; IS, indoxil sulfite; LAB, lactic acid bacteria; LGG, *Lactobacillus rhamnosus* GG; LTA, lipoteichoic acid; MAMP, microorganism associated molecular patterns; NAFLD, non-alcoholic fatty liver disease; NCDs, noncommunicable diseases; ODC, ornithine decarboxylase; PCS, p-cresyl sulfate; PPA, propionic acid; PPAR-γ, peroxisome proliferator-activated receptor gamma; PRR, pattern recognition receptor; PSA, polysaccharide A; QS, quorum sensing; SCFAs, short-chain fatty acids; SAM, S-adenosyl-l-methionine; TA, Teichoic acids; TDO, tryptophan 2,3 dioxygenase; Th2, T helper cells; THC, tetrahydrocurcumin; TLR, toll-like receptor; TMA, trimethylamine; TMAO, trimethylamine N-oxide; TNBS-N-oxide, trinitrobenzene sulfonic acid; UT, uremic toxicity.

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1. Introduction

The human gastrointestinal (GI) tract houses a unique, complex microbial ecosystem comprising trillions of bacteria, archaea, fungi, and viruses (Rajakovich & Balskus, 2019). This microbial community inhabits the human gut since birth and plays a critical role in the development and maintenance of healthy human physiology. Recent advances have emphasized the key role that involves the microbiome, the host, the metabolites released in the process, and the activated metabolic pathways. The type of cell-cell communication known as quorum sensing (QS) remains unexplored as far as understanding the intestinal microbiota and its influence on human physiology and nutrition (Choudhary & Schmidt-Dannert, 2010).

Despite the scientific advances in biotechnology, the true function of some bacteria, the synthesis of metabolites by the host-microbiota contact, and their mechanisms of action still require efforts to be better elucidated. The mechanisms of action of the microbiota in the host are known to vary according to the diversity of the microbiota, the health status of the host, and the dietary intake. Furthermore, non-viable microbial cells (paraprobiotics) and the molecules named parabiotics, arising from cell walls, microbial fractions, or cell lysates, might also offer physiological benefits to the host (Aguilar-Toalá et al., 2018). The soluble factors produced by probiotics (known as postbiotics), for example, are recognized as promising for providing therapeutic benefits as they interfere with pathogen development, preserve the barrier integrity of intestinal mucosa, and improve host-microbiome balance, thus contributing to eubiosis maintenance (Cicenia et al., 2016; Gilbert, Ijssennagger, Kies, & van Mil, 2018). The postbiotics act by cellular and molecular mechanisms such as the control of immune and nervous system, and their functions depend on the clinical setting in which they are administered (e.g., caution needs then to be exerted when administering probiotics in patients with acute inflammation). Also, the postbiotics are able to boost innate immunity, reduce pathogen-induced inflammation, and promote the survival of intestinal epithelial cells (Cicenia et al., 2014). According to Gilbert et al. (2018), the fermentation of undigested protein in the large intestine results in the formation of branched-chain amino acids, biogenic amines, short-chain fatty acids, ammonia, phenolic and indolic compounds, hydrogen sulfide, and nitric oxide. Although the knowledge about this machinery is still to be established, each individual is known to have its own microbiome, and there is increasing evidence that gut dysbiosis may cause changes in the bidirectional communication between brain and gut, triggering neurological, behavioral, and physiological dysfunctions. Examples include Parkinson's and Alzheimer's diseases, Autism Spectrum Disorder (ASD), multiple sclerosis, Inflammatory Bowel Disease (IBD), and non-communicable chronic diseases such as obesity, type 2 diabetes, and cancer (Furtado, Silva, & Walfall, 2018; Hongyu Zhang, 2014; Konstantinov, Kuipers, & Peppelenbosch, 2013; Hoyles & Wallace, 2010). Evidences that the composition of the intestinal microbiota can influence human physiology are increasingly emerging (Miquel et al., 2013). Therapeutic strategies capable of modulating gut microbiota may represent a new approach for the treatment of disorders involving the central nervous system.

In this context, "postbiotics" are herein considered the metabolites produced in the anaerobic fermentation of non-digestible dietary components, or even digestible ones (e.g., complex carbohydrates, proteins, and lipids), and those released by bacterial metabolism in the GI tract. The endogenous components generated by bacteria-host interactions involved in both desirable and undesirable activities to the organism are also considered "postbiotics" (Fig. 1).

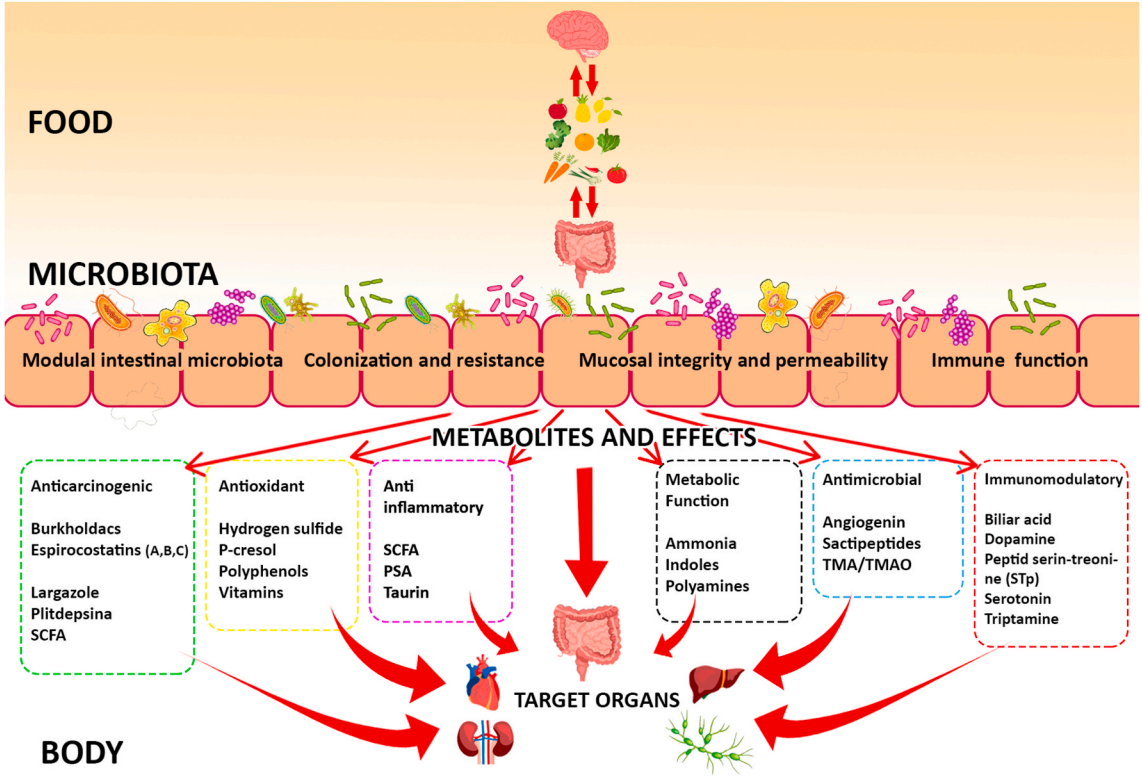

Fig. 1. Overview of the metabolites synthesized by bacteria colonizing the human gut and their physiological effects. In the center, the big arrow represents the great link between the brain-intestine axis and the interrelationship with the different body organs. Each colored rectangle represents the main functions of the metabolites. Green = anticancer activity, yellow = antioxidant activity, pink = inflammatory activity, black = action on human metabolism, blue = antimicrobial activity, red = immunomodulatory activity. The arrows indicate the interrelations of the intestinal metabolites with different organs and the human system. SCFA = small-chain fatty acid; PSA = polysaccharides A; TMA = trimethylamine; TMAO = trimethylamine N-oxide. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

This review provides and discusses the main mechanisms by which the postbiotic metabolites resulting from host-microbiota cross-talk affect the onset and development of non-communicable diseases.

2. Interaction between the main bacteria, metabolites, and host involved in the health-disease process

More than 45 years have passed since probiotics were first used for disease management. Their use was initially based on three basic principles, namely:

1) The need for alternative drugs to those displaying suboptimal efficacy or serious adverse effects;
2) The growing interest in natural products and microorganisms, particularly driven by studies showing the interrelationships among microorganisms within the human body and the external environment as a whole (interaction with the environment);
3) Evidences on the genetic and metabolic properties of probiotic strains, and clinical studies showing their effectiveness (Puebla-Barragan & Reid, 2019).

However, one of the most carefully examined areas for the use of probiotics and their metabolites in the treatment of illnesses currently refers to diseases related to the gastro-digestive tract, having as flagship the prevention of antibiotic-associated diarrhea (AAD). A recent systematic review compared the efficacy and tolerability of different probiotics in AAD, and *Lactobacillus rhamnosus* GG (LGG) was elected as significantly superior to any other probiotic strain when used to prevent this condition. Thus, the probiotic of choice should always depend upon the patient's situation, as well as on the pursued outcome (Cai et al., 2018). The abundance of *Bifidobacterium* genus, *Bifidobacterium longum*, *Clostridium coccoides*, *Clostridium leptum*, *Akkermansia muciniphila*, *and Lactobacillus plantarum* was found in one of the studies of our group, when obese women were evaluated in relation to lean. The physiological importance of these differences seems to be more related to the *Bifidobacterium* genus and to *Clostridium coccoides*, which might play a role in insulin sensitivity (Teixeira et al., 2013).

Table 1 lists the main probiotic bacteria strains involved in the treatment of noncommunicable diseases (NCDs).

According to the Virtual Metabolic Human database, 5607 metabolites involved in intestinal microbiota metabolism in humans have already been identified. However, it should not be forgotten that, despite the choice of metabolite as a biomarker related with the host, other factors such as age, gender, and diet may be important when selecting the biomarker. Further research on clinical and mechanistic data of microbiota biomarkers and their usefulness for diagnostic and therapeutic purposes is therefore needed (Noronha et al., 2019; Qin et al., 2010).

Even in face of differences in species composition in each microbiota, distinct profiles may converge towards common functions. The intestinal ecosystem appears to be highly dependent on the presence of nutrients from the external environment, such as the degradation of complex carbohydrates, thereby orchestrating the functioning of the host's environment (Castellarin et al., 2012; Felizardo, Castoldi, Andrade-Oliveira, & Câmara, 2016; Kostic et al., 2013; Tsilingiri et al., 2012; Wong & Levy, 2019).

3. Postbiotics: metabolites and mechanisms of action in human health

Regarding the metabolite spectrum involved in beneficial events upon probiotic bacteria-induced fermentation, in addition to short-chain fatty acids (SCFAs), trimethylamine (TMA), and polyamines, other direct products of the microbiome-host interaction process may be pointed out, namely: reuterin, taurine, histamine and spermine organic metabolites, lactocepin, bioactive peptides, tryptophan degradation

Table 1
Main strains of probiotic bacteria used in the treatment of noncommunicable diseases (NCDs).

Bacterial strains	Diseases	References
Bifidobacterium infantis 3562 Bifidobacterium animalis DN-173 010, E. coli Faecalibacterium prausnitzii Lactobacillus rhamnosus GG	Irritable bowel syndrome (IBS).	Puebla-Barragan & Reid, 2019; Sanders, Merenstein, Merrifield, & Hutkins, 2018; Zolnikova, Komkova, Potskherashvili, Trukhmanov, & Ivashkin, 2018.
Faecalibacterium prausnitzii	Crohn disease.	Zolnikova et al. (2018).
Bifidobacterium lactis DN-173010 Lactobacillus reuteri DSM 17938	Constipation.	Puebla-Barragan and Reid (2019)
Combination of Lactobacillus acidophilus CL 1285 Lactobacillus casei LBC80R + Lac-tobacillus rhamnosus CLR2, Lactobacillus reuteri DSM 17938, Lactobacillus rhamnosus GG Saccharomyces boulardii, Lactobacillus plantarum	Antibiotic-associated diarrhea (AAD).	Kostic et al., 2013; Puebla-Barragan & Reid, 2019; Cai et al., 2018; Zolnikova et al., 2018.
Lactobacillus reuteri DSM 17938 Lactobacillus rhamnosus GG	Treatment of *Helicobacter pylori.*	Kostic et al., 2013, Puebla-Barragan & Reid, 2019.
Lachnospira, Clostridium, Enterobacterium, Catenibacterium, Prevotella stercorea, P. copri, Lactobacillus plantaram, rhamnosus, gasseri, Bifidobacterium lactis, Bifidobacterium breve Akkermansia muciniphila,	Obesity.	Sanders et al., 2018; Reynés et al., 2019.
Lactobacillus rhamnosus GR-1 + Lactobacillus reuteri RC-14 Lactobacillus rhamnosus Lcr35 Lactobacillus rhamnosus PBO1 and Lactobacillus gasseri EN-15347 (EB01)	Bacterial vaginosis (VB).	Puebla-Barragan and Reid (2019).
Lactobacillus rhamnosus GG	Atopic dermatitis (AD).	Puebla-Barragan and Reid (2019).
Lactobacillus acidophilus + Bifidobacterium lactis Lactobacillus plantarum	Hypercholesterolemia.	Puebla-Barragan and Reid (2019).
Lactobacillus strains (Lactobacillus fermentum, L. coryniformis, L. gasseri), Oxalobacter formigenes	Chronic renal disease (CRD).	Rooks and Garrett (2016).
Faecalibacterium, Bifidobacterium, Lactobacillus, Coprococcus, Methanobrevibacter, Streptococcus spp., *Enterobactericeae, Clostridium leptum, Lactobacillus* spp., *Anaerococcus hydrogenalis, Clostridium asparagiforme, Clostridium hathewayi, Clostridium sporagenes, Escherichia fergusonii, Proteus penneri, Providencia rettgeri, Edwardsiella tarda*	Cardiovascular disease.	Sanders et al. (2018).
Lactobacillus rhamnosus GG, L. casei rhamnosus, L.	Respiratory diseases.	

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Table 1 (*continued*)

Bacterial strains	Diseases	References
paracasei CBA L74, B. Lactis, L. acidophilus CUL21 e CUL60; B. bifidum CUL20; B. animalis subsp. lactis, B. longum SP07/3, L. casei D114001, L. gasseri PA16/8, B. longum SP07/3, B. bifidum MF 20/5, L. casei, Shirota, L. plantarum		Felizardo, de Almeida, et al., 2019; Zolnikova et al., 2018.
Lactobacillus lactis, Streptomices higroscopicus, Bifidobacterium lactis.	Colon cancer.	Hoyles and Wallace (2010).
Lactobacillus plantarum, Bifidobacterium brevis (B. brevis), and B. lactis	Ulcerative colitis.	Martin et al. (2019).
Clostridium difficile, Bacterioidetes, Desulfovibrio, Bifidobacterium infantis	Autism Spectrum Disorder (AED).	Gosálbez & Ramón, 2015; Pedersen et al., 2016.
Lactobacillus reuteri DSM 17938	Baby colic.	Cai et al. (2018).
Bifidobacterium lactis, B. longum, Lactobacillus casei, Lactobacillus rhamnosus GG	Celiac disease.	Pedersen et al., 2016; Orlando et al., 2014.

metabolites, bile acids, and other nutrients important to the body like B and fat-soluble vitamins (B_1, B_3, B_9, B_{12}, K, and A). There may be a pattern recognition receptor (PRR) in the gut itself, where the host is able to detect and respond to specific microbial elements produced after bacterial-host interactions (Noronha et al., 2019; Qin et al., 2010). The main metabolites produced by probiotics, some of the conditions at which they originate, and their mechanisms of action are listed in Table 2.

The main confirmed metabolites and their mechanisms of action or performance in different clinical conditions, aiming at their use in the prevention and/or treatment of NCDs, are listed in Table 3.

4. Vitamins

Bacteria from the GI tract contribute to the indispensable vitamin *pool* as a whole, though the release pathway is not always well established, i.e., there are speculations on whether bacteria export vitamins for the host to capture and/or vitamins are released to the host as a result of bacterial death (Rajakovich & Balskus, 2019).

The biosynthesis pathway of vitamins and cofactors in the microbiome involves a variety of chemical transformations, many of which are catalyzed by members of the enzyme superfamilies that feature the radical SAM (S-adenosyl-l-methionine) system. This is the case of the syntheses of the B_1 (thiamine) and K_2 (menaquinone) vitamins, which require SAM as catalyst. Thiamine, in turn, acts as a cofactor in essential pathways such as those involved in the metabolisms of amino acids and carbohydrates (Rajakovich & Balskus, 2019).

Vitamin D affects T-cell activation and some studies have related retinoid deficiency to IBD, colitis, and colon cancer, condition in which receptor expression for this vitamin is found to be reduced (Levy, Thaiss & Elinav, 2016).

Biotin, also known as vitamin B_7, was discovered between 1920 and 1930 as a factor that prevented dermatitis, hair loss, and neurological abnormalities caused when rats were fed with high doses of raw eggs. Biotin also plays an essential role as a cofactor for carboxylase enzymes, especially in the biosynthesis of fatty acid, catabolism of branched-chain amino acid, and gluconeogenesis pathways. A study published by Hayashi et al. (2017) showed that antibiotic-induced gut dysbiosis led to the development of alopecia in biotin-deficient mice. Animals fed a

Table 2
Metabolites produced and/or originated from the metabolism of other molecules and main bacteria involved.

Metabolites	Origin	References
Metabolites in general		
Vitamins B, A, and K	Synthesized by specific bacteria such as *Acetobacter pomorum* and *Bifidobacterium*.	Rajakovich & Balskus, 2019; Levy, Thaiss & Elinav, 2016; Hayashi et al., 2017; Levy et al., 2017; Shapiro et al., 2014.
Polysaccharide A	Produced by the commensal bacteria *Bacteroides fragilis* and colinization by *Helicobacter hepaticus.*	Levy, Thaiss & Elinav, 2016; Levy et al., 2017; Shapiro et al., 2014; Wang et al., 2006; Wheeler & Liss., 2019; Wong et al., 2014.
Bile acids	Commensal bacteria (*Bacteroides, Eubacterium and Clostridium*) can metabolize bile acids and share metabolites in the process of synthesis of inflammasomes and cytokines.	Levy et al., 2017; Reynés et al., 2019; Shapiro et al., 2014.
Taurine	Produced by the host and general bacterial metabolism. The deconjugation of bile salts releases free glycine and taurine, which can be sources of carbon, nitrogen, and sulfur, as well as substrates for energy production.	Rajakovich & Balskus, 2019; Levy et al., 2017; Li et al., 2016.
Tryptophan metabolites: indol-3-aldehyde, indol-3-acetic acid, indolelactic acid, indolpropyl acid, and indolacrylic acid	Tryptophan metabolism may occur by bacteria like *Escherichia coli,* producer of indoles, and *Lactobacilli*, which utilize tryptophan as an energy source.	Rajakovich & Balskus, 2019, Jie et al., 2017; Hashimoto et al., 2012; Shapiro et al., 2014.
Trimethylamine (TMA) and trimethylamine N-oxide (TMAO)	Proteobacteria (*Escherichia* and *Klebsiella* spp.) strongly contribute to the production of TMA from TMAO in the human gut via the TMAO reductase pathway and the genus *Actinobacteria*.	Rajakovich & Balskus, 2019; Hoyles et al., 2018; Rosenberg et al., 2009; Janeiro et al., 2018.
Triptamine	Produced by two Firmicutes phylum bacteria: *Clostridium sporogenesis* and *Ruminococcus gnavus.*	Dalmasso et al., 2008; Levy, Thaiss & Elinav, 2016.
p-Cresol	Metabolite formed from tyrosine oxidation. It is proposed as a marker of invasion by *C. difficile* enteric pathogen.	Rajakovich & Balskus, 2019, Cosola et al., 2018; Frye et al., 2017.
Ammonia	Ammonia from amino acid catabolism is used by bacteria as a source of nitrogen. Ammonia causes an increase in pH, which helps to offset the acidity arising from gut microbiota-produced SCFAs.	Rajakovich & Balskus, 2019; Cosola et al., 2018.
Hydrogen sulfide	Metabolite derived from the fermentative process of the diet by bacteria, which may have a beneficial effect on the processes of apoptosis and oxidative stress.	Rajakovich & Balskus, 2019; Cosola et al., 2018; Dalmasso et al., 2008.
	Products of fermentation of undigested	Shapiro et al., 2014; Hoyles et al., 2018.

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Table 2 (*continued*)

Metabolites	Origin	References
SCFAs (acetate, butyrate, and propionate)	carbohydrates by commensal anaerobic bacteria.	
Angiogenin 4 (Ang4)	Its expression is induced in the mucosa in response to contact with commensal bacteria.	Levy, Thaiss & Elinav, 2016.
Polyamines	They can act as secondary messengers, mediating the effects of hormones and growth factors, and support high proliferation of intestinal epithelial cells. The activation of the NLRP6 inflammasome is influenced by the microbiota-modulated metabolites taurine, histamine, and spermine.	Levy et al., 2017; Russo et al., 2014; Thomas, Manghi, et al., 2019; Timmons et al., 2013.
Polyphenol metabolites	Polyphenols are transformed into bioavailable metabolites by resident bacteria, and may be more bioactive than their precursors.	Etxeberria, U., 2013; Herath et al., 2007; Kassaa et al., 2019.
Serotonin	Over 90% of the body's serotonin is produced in the intestines.	Dalmasso et al., 2008; De Simone et al., 2013.
Dopamine	More than 50% of dopamine is generated in the gut by the following bacteria: *Escherichia coli, Bacillus cereus, Bacillus mycoides, Bacillus subtilis, Proteus vulgaris, Serratia marcescen*, and *Staphylococcus aureus.*	Belizário, Faintuch, & Garay-Malpartida, 2018; Noronha et al., 2019.
Branched-chain amino acids (BCAAs)	BCAAs are directly produced in the gastrointestinal tract due to strong proteolytic activity by the genera *Bacteroidetes*, *Clostridium*, *Propionibacterium*, *Fusobacterium*, *Streptococcus*, and *Lactobacillus.* BCAAs can regulate defensin expression and decrease oxidative stress.	Egan et al., 2016; Zheng, Gänzle, Lin, Ruan, & Sun, 2015; Dalmasso et al., 2008.
Uremic toxins	Metabolites generated in the intestine, whose excess alters the composition of the gut microbiome and may be a biomarker of perturbed renal function.	Devlin et al., 2016; Brito et al., 2017; Glorieux & Tattersall, 2015.
Peptides		
Serine-Threonine peptide (STp)	Released by bacteria and resistant to intestinal proteolysis.	Egan et al. (2016).
Sactipeptides	Produced by intestinal tract bacteria and inhibit the growth of pathogenic bacteria.	Vijaya Saradhi et al., 2010; Egan et al., 2016.

biotin-deficient diet showed higher levels of branched-chain amino acids (isoleucine, leucine, and valine) than those fed a normal diet. This suggests that normal amino acid metabolism was perturbed by the biotin-deficient diet, and that such a metabolic alteration may be exacerbated by *Lactobacillus murinus* overgrowth. Biotin supplementation reversed the symptoms of alopecia, suggesting that *Lactobacillus murinus* plays a central role in inducing biotin-dependent hair loss. Collectively, these results indicate that luminal metabolic changes associated with intestinal dysbiosis and dietary changes may

Table 3
Possible mechanisms of action and beneficial effects of bacterial metabolites on human health.

Metabolites	Mechanisms of action	References
Metabolites in general		
Vitamins B, A, and K	These vitamins influence T cell biology. *Bifidobacterium* and *Lactobacillus* are important for the synthesis of B_9, A, C vitamins, which are survival factors for Treg cells. They modulate the activity of some cell types, such as B cells, which neutralize toxins derived from luminal bacteria, leading to an anti-inflammatory microenvironment. Among its multiple functions, vitamin A regulates the balance between the anti-inflammatory and pro-inflammatory immune responses.	Rajakovich & Balskus, 2019; Shapiro et al., 2014; Li et al., 2016.
Polyphenol metabolites	They could have anti-inflammatory, antioxidant, and delipidating properties. They are produced when the gut microbiota acts on resveratrol, genistein, quercetin, catechins, proanthocyanidins, and other phenolic compounds.	Etxeberria et al., 2013; Herath et al., 2007; Kassaa et al., 2019.
Polysaccharide A	It has an anti-inflammatory effect by inhibiting IL-17 and promoting IL-10 expression in TCD4+ cells by binding to TLR2.	Shapiro et al., 2014; Wang et al., 2013.
Bile acids	Gut microbiota controls bile acid signaling and biotransformation through the Farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (GPBAR1) or G protein-coupled Takeda 5 receptor (TGR5). Actions attributed to the secondary bile acid are modulation of the host immune response by inhibiting pro-inflammatory gene induction via NF-κB may affect adaptive immune cell response in IBD.	Frye et al., 2017; Wang et al., 2013.
Taurine	The deconjugation of bile salts by the gut microorganisms releases glycine and taurine. Taurine can activate the inflammasome, contributing to intestinal homeostasis. It has inhibitory effects on neurotransmitter release and stimulates bile acid production.	Rajakovich & Balskus, 2019; Frye et al., 2017.
Serotonin	Serotonin is involved in anxiolysis and fear. *Lactobacillus brevis* apparently affects the number and function of chromaffin cells by promoting serotonin release.	Belizário et al., 2018; Noronha et al., 2019.
Dopamine	Dopamine has a central role in the reward behavior. Bacteria produce hormone-like neurochemicals involved in mood and behavior (e.g.,	Belizário et al., 2018; Noronha et al., 2019.

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Table 3 (*continued*)

Metabolites	Mechanisms of action	References
	E. coli, *B. cereus*, *B. mycoides*, *Proteus vulgaris*, and *Serratia marcescens)*.	
Tryptophan metabolites: indol-3-aldehyde, indol-3-acetic acid, indolelactic acid, indolpropyl acid, and indolacrylic acid	They strengthen the intestinal epithelial barrier, influence the differentiation and function of immune cells, stimulate IL-10 production, and inhibit IL-6 production, thus preventing diseases. When produced by the *Lactobacillus* genus, they decrease colitis.	Levy et al., 2017; Shapiro et al., 2014.
Trimethylamine (TMA) and trimethylamine N-oxide (TMAO)	TMA is perhaps one of the most substantial molecules of intestinal bacterial origin, playing a role in cardiometabolic diseases. The causal role of TMAO in cardiovascular disease is still under debate and may be dependent on the concentration of TMA in the plasma.	Rosenberg et al., 2009; Shapiro et al., 2014; Wang et al., 2013.
p-Cresol	p-Cresol has antioxidant and antimicrobial properties and is considered a biomarker of the presence of pathogenic bacteria and correlated with some neurological disorders. Beyond the bactericidal effects of p-cresol, it can also be sulfated or glucuronidated by human enzymes, generating products known as uremic toxins. p-Cresol has been described to potentially interact with xenobiotics for sulfate deconjugation, which can impair the capacity of the host in detoxifying them.	Rajakovich & Balskus, 2019; Frye et al., 2017.
Ammonia	Ammonia if found among the variety of uremic compounds with beneficial or toxic effects identified in the colon of patients with CKD. It is metabolized by urease-positive bacteria in the GIT, where it acts or recirculates to the liver, offering a good opportunity for disease diagnosis and prevention.	Rajakovich and Balskus (2019).
Hydrogen sulfide	This metabolite can be used as an electron acceptor for anaerobic bacterial respiration.	Rajakovich & Balskus, 2019; Cosola et al., 2018.
Short-chain fatty acids - SCFAs (acetate, butyrate, and propionate)	SCFAs participate in the modulation of immune signaling by activating inflammasomes and increasing the synthesis of mucins (butyrate); regulate intestinal epithelial cell energy metabolism and preserve mucosal immunity; increase the number of Tregs cells and their regulatory function in the large intestine through epigenetic regulation; inhibit stem cell proliferation by acting as a histone deacetylase inhibitor (HDAC); improve protection against infections; and activate GPR43 and GPR109a in the intestinal cell	Shapiro et al., 2014; Wang et al., 2013; Marcon et al., 2019

Table 3 (*continued*)

Metabolites	Mechanisms of action	References
	epithelium, resulting in the activation of the NLRP3 (NOD-like receptor) inflammasome and leading to IL-18 production.	
Angiogenin 4 (Ang4)	Ang4 has strong antibacterial activity. *Bacteroides thetaiotaomicron* can increase Ang4 expression.	Noronha et al. (2019).
Branched-chain amino acids (BCAAs)	BCAAs can regulate the expression of defensins in enterocytes. Decreases in BCAAs have been associated with improved insulin resistance rather than weight loss itself when obese individuals improved mucosal integrity and increased *Bacteroides*.	Wang et al., 2013; De Simone et al., 2013.
Uremic toxins	Uremic toxins can be used as biomarkers for disease diagnosis and prevention, as well as assessment and repositioning for dietary changes as a result of microbiota modification.	Devlin et al., 2016; Brito et al., 2017; Glorieux & Tattersall, 2015; Fernandes et al., 2012.
Polyamines	These small polycationic bacterial molecules are involved in the production of specific bacterial enzymes, reactive oxygen species, and effects on the host metabolome, being also involved in cell proliferation and apoptosis. The anticarcinogenic properties studied at the molecular level may involve the knowledge about proliferation biomarkers such as polyamines (putrescine, spermidine, spermine, and histamine).	Reynés et al., 2019; Russo et al., 2014; Thomas, Manghi, et al., 2019.
Peptides		
Serine-threonine peptide (STp)	STp is found in the healthy human colon and induces regulatory properties in gut dendritic cells. It is also found in Crohn's Disease (CD) and Ulcerative Colitis (UC).	Felizardo, de Almeida, et al., 2019; Vijaya Saradhi et al., 2010.
Sactipeptides	Sactipeptides are bacteriocins that have a thioether bond to metalloproteinases, with antibiotic action to pathogens by creating pores in the bacteria's membrane.	Rajakovich & Balskus, 2019; Khavinson et al., 2016.

compromise skin physiology (Hayashi et al., 2017).

Lactobacilli and *Bifidobacterium* can synthesize vitamins such as B_9 (folate), A, C, and some members of the B complex, influencing host mechanisms. Retinoic acid, a vitamin A metabolite, is a major example, as its deficiency increases the susceptibility to infections and mortality, leading to impairments in both humoral and cellular immunity in the mucosa. Vitamin A also plays an important role in the integrity of mucus-secreting goblet cells (Rajakovich & Balskus, 2019; Levy, Thaiss & Elinav, 2016). In a review on the benefits of vitamins and SCFAs produced by commensal and probiotic bacteria, Le Blanc et al. (2017) highlighted the pathways of neogluconeogenesis and glycogenolysis as important means of providing adequate glucose synthesis and, consequently, maintaining energy for the cells. Thus, the B-complex vitamins (B_1 thiamine, B_2 riboflavin, B_3 niacin, B_5 pantothenic acid, B_7 biotin, and B_{12} cobalamin) mainly act as important catalysts for enzymes in energy

metabolism. The authors also propose that SCFAs and B vitamins can increase ATP production and thus modulate the development and progression of fatigue in individuals with chronic fatigue syndrome. The pathogenesis of the disease is directly associated with the altered intestinal microbiota, but the maintenance of energy production balance using bacterial species from food-grade and probiotic bacteria or fermenting metabolites from the fibers in the GI tract are still to be understood.

5. Minerals

In relation to micronutrients, especially minerals and their interaction with the intestinal microbiota, studies are increasingly more elucidative. It is worth mentioning, for example, the binding of iron to probiotic bacteria, minimizing the formation of free radicals and, consequently, reducing oxidative processes and/or changes that trigger the formation of Chronic diseases (CD). In addition, increases bacteria availability to the host, minimizing changes in the intestinal wall itself (Skrypnik, Bogdański, Schmidt, & Suliburska, 2019). Vazquez-Gutierrez et al. (2015) demonstrated that *Bifidobacterium* in infant stools, even under conditions of iron deficiency, can limit intestinal iron content for its high sequestration properties in order to preserve the development of pathogenic bacteria. In this case, an attempt was made to tailor the inflammatory activity by controlling the amount of bacteria, recovering the homeostasis of the medium. In general, some minerals such as iron, calcium, phosphorus, and zinc depend upon bacteria for the processes of absorption and/or maintenance of homeostasis in the body. In a pioneering review by Skrypnik and Suliburska (2017), the main evidence between the interaction of the intestinal microbiota and minerals was highlighted, namely modification of mineral-binding particles by microbiota; alterations of the gut environment, modifying the absorption of minerals; promotion of pathogenic or, on the contrary, minerals involved in the development of commensal strain; competition for minerals by different bacterial strains; modification of bacterial biochemical processes by minerals; modification of host's biochemical pathways by both microorganisms and minerals; and alterations of host's synthesis and modifications of disease intensity by microorganisms (Skrypnik & Suliburska, 2017).

In this way, Dostal et al. (2015) demonstrated that the dietary availability of iron can change the metabolic properties of the microbiota such as decreased butyrate and propionate syntheses. Then, different iron availabilities were mimicked in an *in vitro* colonic fermentation model, inoculated with immobilized gut microbiota from a child and in batch cultures of the butyrate producer *Roseburia intestinalis*. The data reveal that the different levels of dietary iron reaching the colon affect the microbiome and its essential function of providing the host with beneficial butyrate (Dostal et al., 2015).

In addition, the effects of dietary supplementation with selenium/zinc-enriched probiotics (SeZnP) on growth performance, serum enzyme activity, antioxidant capability, inflammatory factors, and gene expression were investigated in Wistar rats inflated under high thermal-stress ambient. SeZnP supplementation significantly enhanced glutathione content, superoxide-dismutase activity, and glutathione-peroxidase, while decreased malondialdehyde content (Malyar et al., 2020).

6. Short-chain fatty acids (SCFAs)

It is increasingly accepted that the host and its microbiota, instead of existing separately, make up a complex metaorganism called "holobiont". Together, both regulate multiple aspects of mammalian physiology, including the development of the immune system as well as metabolic and nervous system functions (Levy, Thaiss & Elinav, 2016).

The fermentation of prebiotics, such as fructooligosaccharides (FOS) and inulin, results in SCFAs, markedly acetate, propionate, and butyrate. These acids decrease the intestinal pH, inhibiting the growth and/or activity of pathogenic bacteria, thus representing a hurdle against colonization by these microorganisms. In addition, in the acidic environment, the absorptions of ammonia and potentially toxic amines, recognized as promoters of carcinogenesis, are reduced (De Preter, Hamer, Windey, & Verbeke, 2011; Fotiadis, Stoidis, Spyropoulos, & Zografos, 2008). *Bifidobacterium* spp. are responsible for the fermentation of galactooligosaccharide (GOS), one of the major components of breast milk, to produce SCFAs (Marcobal et al., 2010).

Thus, among the most abundant molecules produced by bacteria and recognized by G-coupled-receptors (GPR41, GPR43 and GPR109a), SCFAs have diverse regulatory functions, and their effects on host physiology and immunity continue to be revealed (Rooks & Garrett, 2016). The effects of SCFAs on gut integrity, metabolic control, and appetite regulation have been demonstrated. SCFAs are capable of influencing satiety because they interfere with the production of leptin, a hormone released by white adipose tissue and whose signaling pathway defects are associated with severe obesity, hyperphagia, infertility, and immune system disorders. Controlling multiple aspects of human metabolism and immunity, SCFA concentrations in the gut can range from 20 to 140 mM, depending on host microbiota composition, intestinal transit time, metabolic flow, and fiber content (Levy, Blacher, & Elinav, 2017, Levy, Thaiss & Elinav, 2016). They can be detected by peroxisome proliferator-activated receptor gamma (PPAR-γ) and G-protein-coupled receptor (GPCR), such as GPR41, GPR43, and GRP109. They modulate intracellular receptor binding to cyclic adenosine monophosphate (cAMP), as well as calcium levels, and activate extracellular signal-regulated kinases (ERK1/2). SCFAs also lead to hematopoietic alterations, resulting in increased myeloid cell production, promoting the clearance of systemic infection and the improvement of allergic processes (Gosálbez & Ramón, 2015; Lamas et al., 2016; Rooks & Garrett, 2016).

Among SCFAs, butyrate is of particular interest, as it is the most used by intestinal mucosa. This fatty acid can act as a local anti-inflammatory and even intracellularly inhibit histone deacetylase enzyme (HDACi), contributing to control gene expression, being considered to belong to a class of antitumor agents that regulate tumor proliferation, differentiation, apoptosis, and angiogenesis. Studies have shown that the imbalance between histone acetylation and deacetylation in promoter regions contributes to the deregulation of gene expression, which may lead to carcinogenesis (Castellarin et al., 2012; Marcon et al., 2019). The ability of butyrate and other HDACi to promote apoptosis and suppress cell growth is related to the attenuation of the Wnt/β-catenin pathway activation by mechanisms not yet fully understood. The intestinal microbiota is also directly related to this process, as the amount of butyrate produced varies according to it. Moreover, intestinal colonization by pathogenic microorganisms could negatively influence body role pathway activation, triggering the process of malignancy, hence the importance of proper colonization of intestinal microbiota (Cruz et al., 2020).

Both propionate and butyrate have a local effect as primary energy sources for intestinal mucosa cells, also by activating intestinal gluconeogenesis (specifically propionate) through diverse mechanisms. In the liver, propionate also activates gluconeogenesis, but also de novo lipid and protein syntheses. Acetate, in turn, is a precursor of cholesterol synthesis. As probiotics, acetic acid bacteria are known to produce a wide variety of antibacterial substances as well as primary inhibitory metabolites, such as acetic, lactic, and propionic acids, ethanol, diacetyl, hydrogen peroxide, bacteriocins, and antibiotic-like substances with activity against Gram-negative bacteria (Foo et al., 2003).

In a recent study, our research group demonstrated the effective role of SCFAs in preventing colorectal carcinogenesis by detecting the increase of these acids in the intestinal mucosa of experimental animals after the use of prebiotics (Cruz et al., 2020). *Lactobacillus* and *Bifidobacterium* proliferation can be stimulated upon the increase of SCFAs, consequently increasing intestinal homeostasis, stimulating the host immune response modifying the metabolism of tumor cells, and

regulating cell apoptosis. Having these acids as final products of fermentation, these bacteria can modulate transcriptional factors responsible for the adaptive immune response in the colon, decreasing RORγt expression and thus reducing stimulation for Th17 cell differentiation. It induces a significant increase in the percentage of Treg cells in the colon of animals and higher Treg cells conduce to reduced activation of pro-inflammatory cells, and subsequent appearance of an anti-inflammatory microenvironment (Cruz et al., 2020; Foo et al., 2003; Marcon et al., 2019). Furthermore, there is evidence that SCFAs can influence satiety, leading to increased leptin production, whose signaling pathway defects are associated with severe obesity, hyperphagia, infertility, and immune system disorders (Rooks & Garrett, 2016).

7. Bile acids

The intestine is equipped with elaborate bile acid-sensing mechanisms that allow elegant coordination of different intestinal functions and control the crosstalk between the gut and other organs in the body (Levy et al., 2017; Rooks & Garrett, 2016). Microbiota, in addition to being an important regulator of the primary bile acid metabolism, is essential for the synthesis of secondary bile acids, releasing enzymes such as bile acid hydrolases mainly by *Clostridium* and *Lactobacillus*. These enzymes promote bile acid dehydrogenation, dihydroxylation, and deconjugation, and the interaction between the gut microbiota and bile acids modulates signaling via farnesoid X nuclear receptor (FXR) and G protein-coupled receptor 5 (TGR5 or GPR1), which in turn regulate lipid and lipoprotein metabolism (Ticho, Malhotra, Dudeja, Gill, & Alrefai, 2019).

Already in 1992, Calmus et al. demonstrated the effects of bile acids on immune cells by showing that the incubation of monocytes with chenodeoxycholic acid (CDCA) inhibited lipopolysaccharide (LPS)-stimulated secretion of cytokines, including the tumor necrosis factor (TNF)-α (Calmus et al., 1992).

The use of germ-free and FXR receptor knockout mice has made possible to prove that microbiota is involved in diet-induced obesity and associated phenotypes. These events can be mediated by changes in the bile acid profile (such as reduced diversity of secondary bile acids) and altered FXR receptor signaling (Lamas et al., 2016; Ticho et al., 2019). The opposite effect can also be speculated since secondary bile acids such as lithocholic and deoxycholic are signaling molecules that bind to cell receptors (GPCR5 or TGR5), which are involved in glucose metabolism, and are TGR5 receptor agonists expressed by Kupffer cells, gallbladder, brown adipose tissue, immune, and enteroendocrine cells. TGR5 activation can occur through multiple pathways and consequently trigger the role of secondary bile acids as a specific receptor activator for modulating biological processes (Ticho et al., 2019; Parséus et al., 2017). A range of five to ten percent intestinal bile acid biotransformation occurs mainly by colon-resident anaerobic intestinal microbiota, such as the genera *Bacteroides*, *Eubacterium*, and *Clostridium*, while the remainder is excreted in the feces. Mice lacking FXR show overgrowth of bacteria and disruption of the epithelial barrier, suggesting that FXR may have a protective effect on bacterial proliferation. Other actions of the secondary bile acid are attributed to the host, namely: modulation of the host immune response by inhibiting pro-inflammatory gene induction via NF-κB may affect adaptive immune cell response in IBD. Also, fibroblast growth factor-15 (FGF15), which is a FXR target gene in ileum, leads to CYP7a1 suppression, and is a limiting enzyme for bile acid synthesis in the liver (Round et al., 2011; Shapiro, Thaiss, Levy, & Elinav, 2014).

As for bile acid action in diseases, microbiota is known to regulate bile acid homeostasis and the passage through the enterohepatic circulation, affecting a variety of metabolic diseases (Sanmiguel, Gupta, & Mayer, 2015). Microbiota can promote intestinal cell proliferation, stimulating cell differentiation and preventing colonization by bacteria such as *Clostridium difficile* by regulating bile acid metabolism. Bile acid axis and FXR can regulate lipid and glucose metabolism, improving insulin sensitivity, steatosis, and fat-induced obesity; for instance, high levels of TGR5 lead to increased GLP-1 levels, which are known to increase glucose tolerance in obese mice. Moreover, TGR5 also activates the process of energy expenditure and thus protects against risks related to diet and obesity. Bile acids can also activate signaling by binding to nuclear receptors and GPCRs on the cell surface. FXR nuclear receptor activation stimulates the transcription of genes that regulate various metabolic pathways, including bile acid synthesis, cholesterol production, and glucose metabolism, which have been linked to improvements in glucose and lipid profiles Sanmiguel et al., 2015). Dietary fat content may increase bile acid production with subsequent effect on microbiota composition. For example, it was observed that mice fed a high-fat diet, after only 12 h, increased bile acid levels (specifically cholic acid), which were positively associated with the presence of Firmicutes, Proteobacteria, and Actinobacteria. In addition, cholic acid-fed mice restored changes in gut microbiota, just as an obesity phenotype, while inhibition of bile acid synthesis using an FXR receptor agonist significantly slowed down these changes (Jia, Liu, Pan, Lu, & Ge, 2019).

8. Teichoic and lipoteichoic acids

Teichoic acids (TA), in particular lipoteichoic acid (LTA), are important immunomodulatory structures found in Gram-positive bacteria. Bacterial LTA activates the immune system through toll-like receptor (TLR) interactions. The interaction between mononuclear cells and LTA was found to be of great importance to the host. The *Lactobacillus plantarum* probiotic strain that was deficient for LTA was much more efficient in triggering IL-10 production compared to its wild duplicate. In a similar study, compared with wild type NCK56, LTA-deleted *Lactobacillus acidophilus* (NCK2025) revealed down-regulation of IL-12, TNFα, and IL-10, and increases in dendritic cells, which were also associated with increased IL-10 induction in Treg cells (Kelly, Delday, & Mulder, 2012; Orlando, Linsalata, Notarnicola, Tutino, & Russo, 2014).

9. Polyamines

The main and best-known polyamines are spermidine, spermine, and putrescine. They are also called “natural amines”, because they are formed *in situ*, or even “growth amines”, because of their involvement in cell proliferation and differentiation. Polyamine synthesis is a complex process. Like other bioactive amines, polyamines originate from a decarboxylation reaction, in this case of ornithine or arginine by their respective enzymes, ornithine decarboxylase (ODC) or arginine decarboxylase (ADC) (Reynés, Palou, Rodríguez, & Palou, 2019).

According to Russo, Linsalata, and Orlando (2014), the main route of putrescine formation in animals is through ODC enzyme, promoting decarboxylation of ornithine and, consequently, putrescine formation. In plants and microorganisms, ADC is the main enzyme responsible for this process by promoting arginine decarboxylation and the resulting formation of agmatine. The latter, in microorganisms and animals, is converted to N-carbamoylputrescine and subsequently to putrescine by agmatine urea hydrolase (agmatinase) enzyme. ODC is closely involved in normal cell proliferation, but it also relates to colon carcinogenesis, as increased ODC activity and polyamine synthesis are a phenomenon that occurs in rapidly proliferating cells, including colon cancer (Thomas, Manghi, et al., 2019).

The anticarcinogenic properties studied at the molecular level may involve knowledge on proliferation biomarkers such as polyamines (putrescine, spermidine, spermine, and histamine). These small, low-molecular weight molecules are constantly required at pre-neoplastic and neoplastic events to support cell proliferation. Timmons, Chang, Wang, and Rao (2013) reported that deep mucosal defects, such as ulcers, result in tissue necrosis and mucosal muscle layer penetration. Chronic injury requires different repair processes that need more than

one cell-replication pathway, protein synthesis, and DNA and mRNA syntheses. In this situation, polyamines are required for eukaryotic cell growth.

In addition to the role of polyamines in cell proliferation, the administration of mice with microbiota-associated metabolites like taurine, histamine, and spermine induced changes in the host-microbiome interface by co-modulating NLRP6 inflammasome signaling, IL-18 epithelial secretion, and antimicrobial peptide (AMP) profile regulation (Levy, Thaiss, Zeevi, & Elinav, 2015). There was no specific change in microbiota composition, but it was clear that metabolites do not act directly on commensal bacteria and require signaling through host to alter microbial ecology. Distortion of AMP adjustment and inflammasome function deficiency can lead to dysbiosis. In this way, using an integrated metabolomic-metagenomic access, taurine was identified as an inflammasome activator, while histamine and spermine metabolites were inflammasome inhibitors (Hoyles & Wallace, 2010). The increase in the polyamine content appears to arise from the loss in polyamine homeostasis occurring during the dysregulation of cell proliferation. On the other hand, by using *Lactobacillus* GG administration, a significant reduction of polyamine biosynthesis was observed using two human GI tract cell lines, one originating from undifferentiated gastric carcinoma (HGC-27) and one originating from colon adenocarcinoma (DLD-1). Interestingly, when the cytoplasmic extract derived from *Lactobacillus* GG homogenate was tested, the cytoplasmic extract, unlike the cell wall extract, was suppressive. Moreover, in an *in vivo* mice study, the same group demonstrated that VSL#3 probiotic ingestion reduced polyamine levels and ODC enzyme activity in colorectal mucosa (Reynés et al., 2019). These findings support the idea that probiotics can directly modulate epithelial cell function. Since polyamines and their enzymes are strongly related to neoplastic proliferation in the GI tract, actions to prevent them deserve attention. There has been a growing body of evidence that different microbes may contribute to gastric tumorigenesis, and exogenous administration of probiotic bacteria might be of some help in preventing/contrasting neoplastic transformation of the gastric mucosa (Russo et al., 2014).

Conversely, the cationic nature of polyamines allows them to interact with nucleic acids and proteins (basic structural elements), promoting homeostasis. Their dysregulation affects cancer-related processes like epigenetics, cell proliferation, and apoptosis (Perry et al., 2016; Rooks & Garrett, 2016; Russo et al., 2014).

10. Trimethylamine and trimethylamine N-oxide

Trimethylamine (TMA) is a methylamine synthesized from dietary components, such as L-carnitine, lecithin, choline, and betaine, by microbial enzymes under anaerobic conditions. TMA is oxidized to trimethylamine N-oxide (TMAO) in the liver, predominantly by the enzyme flavin-containing monooxygenase 3 (FMO3) (Hoyles et al., 2018). The *in vivo* retroconversion of TMA into TMAO may increase the circulating TMA pool, which in turn may be oxidized back to TMAO by FMO3 in the liver (Hoyles et al., 2018; Rosenberg, Giardina, & Tanaka, 2009). Although there is no consensus so far, it is hypothesized that microorganisms could also metabolize dietary phosphatidylcholine to choline and consequently generate TMA (Wang et al., 2015). TMA is one of the most substantial molecules of intestinal bacterial origin, playing a role in cardiometabolic diseases (Rooks & Garrett, 2016). High TMAO plasma levels have been associated with increased risk of type 2 diabetes mellitus, cardiovascular disease, kidney disease, colorectal cancer, non-alcoholic fatty liver, incident thrombosis risk, and increased carotid intima-media thickness in population and intervention studies. The relationship between TMA and cardiovascular diseases was experimentally confirmed in mice, wherein high TMAO levels in circulation resulted in increased aortic atherosclerotic plaque (Jaworska, Bielinska, Gawrys-Kopczynska, & Ufnal, 2019). A study by Hoyles et al. (2018), who administered deuterated TMAO to C57BL6/J mice, examined the ability of transforming TMA into TMAO with uptake in the bloodstream and subsequent conversion to TMAO. Metabolization of TMAO to TMA by gut bacteria (predominantly Enterobacteriaceae) was confirmed. Correlation of metabolomic and abundance data from fermentative processes did not show a true picture of the members of the intestinal microbiota responsible for converting TMAO to TMA. Studies on pure cultures, added or not by these metabolites to the medium, expanded the understanding of TMAO bioconversions by human gut microbiota (Hoyles et al., 2018).

Evidences suggest that Proteobacteria (especially *Escherichia* and *Klebsiella* spp.) strongly contribute to the production of TMA from TMAO in the human gut via the TMAO reductase pathway and the *Actinobacteria* (Eggerthellaceae) genus, which becomes more important under stress. The use of antibiotics in mice dramatically reduces the conversion of TMAO to TMA, indicating microbiota dependence. There is evidence that some bacteria participating in this process are resistant to antibiotics. TMA produced by the microbiota is absorbed and re-oxidized to TMAO by the liver. In an *in vitro* system, the growth of Enterobacteriaceae, a major TMA producer, was rapidly affected by the presence of TMAO (Hoyles et al., 2018).

Consequently, TMAO provided by diet is believed to interact in metabolic retroconversion in mammals, increasing the amount of TMA produced as a product of bacterial fermentation in the host intestine and conversion back to TMAO by FMO3 in hepatocytes. Lactic acid-producing bacteria clearly grow best in the presence of TMAO. According to the literature, TMAO is a biomarker for non-alcoholic fatty liver disease (NAFLD), insulin resistance, and cardiovascular disease (CVD) when present in urine and plasma. TMAO increases in plasma after a TMAO-rich diet, for example, with the consumption of saltwater fish and seafood, a diet considered healthy. TMAO stabilizes the protein's tertiary and quaternary structures and its protective role has been recognized in marine animals that are exposed to osmotic and hydrostatic stress. Nonetheless, the causal role of TMAO in cardiovascular diseases is still under debate and may be dependent on the concentration of TMA in plasma (Rosenberg et al., 2009).

Furthermore, Wang et al. (2015) investigated the impact of first-step inhibition of the TMAO generation pathway by bacterial TMA and the associated impact on atherosclerosis induction. A choline-like molecule, 3,3-dimethyl-1-butanol (DMB), showed non-lethal inhibition of TMA in bacterial cultures, reducing TMA level in mice with a high choline or carnitine diet. DMB showed inhibitory action of microbiota-dependent TMA and TMAO formation by the host from multiple dietary precursors containing TMA *in vitro* and *in vivo*. The authors demonstrated that TMA, specifically, and non-lethal microbial inhibitors in general, may serve as potential therapeutic agents for the treatment of cardiometabolic diseases (Wang et al., 2015).

11. p-Cresol

As a result of the strong proteolytic activity, bacteria of the genera *Bacteroides*, *Clostridium*, *Propionibacterium*, *Fusobacterium*, *Streptococcus*, and *Lactobacillus* degrade amino acids such as tyrosine and phenylalanine by deamination, transamination, and decarboxylation processes, releasing metabolites such as p-cresol. This metabolite in the liver and enterocytes can undergo a sulfation process by releasing p-cresyl sulfate (PCS) as an end product that will be excreted in the urine, outlining strategies for controlling organism-toxic metabolites. p-Cresyl sulfate may be considered as a substrate for the intestinal protein-bound uremic toxins (UTs) and their identification may contribute to the prevention of the risk of diseases such as cardiovascular and chronic kidney diseases (Cosola, Rocchetti, Cupisti, & Gesualdo, 2018).

p-Cresol is a metabolite featuring both antioxidant and antimicrobial properties. Virulent strains of the enteric pathogen *Clostridium difficile* metabolize the tyrosine-derived oxidation product p-hydroxyphenylacetate to p-cresol. The production of p-cresol in the gut by *Clostridium difficile* has been considered as a mechanism to eliminate microbial competitors during invasion (Cosola et al., 2018; Rajakovich

& Balskus, 2019).

Beyond the bactericidal effects of p-cresol, it can also be sulfated or glucuronidated by human enzymes generating products known as UTs, which are involved in the genesis of chronic kidney disease. p-Cresol has been demonstrated to potentially interact with xenobiotics for sulfate deconjugation, which can impair the capacity of the host to detoxify them (Cosola et al., 2018; Frye et al., 2017).

Furthermore, regarding the changes caused by metabolites and their consequences for the host, p-cresol is considered as a metabolomic biomarker in humans, since increased levels of this molecule and derived sulfates or similar molecules, such as 4-ethylphenylsulfate, in urine have been detected in young children with Autism Spectrum Disorders (ASD), being correlated with disorder severity. High abundance of *Clostridium difficile* has also been found in the GI tract of these children. GI symptoms and altered intestinal barrier are more common in autistic patients, with elevated irritability, anxiety, and social withdrawal. The possibility of modulating the composition of intestinal bacteria in the restoration of intestinal homeostasis could offer improvements in autistic behavior. In fact, future probiotic and prebiotic drugs could improve gut health with beneficial bacteria against anomalous colonizing bacteria. Among the beneficial bacteria proposed as a potential treatment for ASD, several probiotic strains might offer therapeutic applications. *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Lactobacillus acidophilus* increase macrophage activity and enhance phagocytosis, decrease gut permeability, exert antimicrobial activities, secrete antimicrobial proteins, increase T helper cells (Th2), decrease Th1, and allergic response, increase anti-inflammatory IL-10, TGF beta. *Lactobacillus reuteri* decreases pro-inflammatory cytokines. *Bifidobacterium* and *Lactobacilli* also help against constipation and diarrhea. These strains, as well as others, could ameliorate ASD-associated dysbiosis. Indeed, ASD is associated with altered composition and function of gut microbiota, which can affect the levels of several low-molecular weight bioproducts, such as propionic acid (PPA), polyamines, polyphenols, glycan peptides, and lipopolysaccharides (LPS). In autism, PPA is able to modulate mitochondria leading to atypical immune dysfunction and activation, thus highlighting ubiquitous effect as a product of bacterial metabolism (Cosola et al., 2018; Frye et al., 2017; Janeiro, Ramírez, Milagro, Martínez, & Solas, 2018). In particular, PPA has a close relationship with ASD due to the link between dietary variations that can influence the production of SCFAs, which in turn would influence PPA production and ASD etiology. Consequently, the disease is strongly influenced by both genetic and environmental factors, being microbiome an important environmental factor that may contribute to the etiology of the disease, since microbiome disruption is directly associated with the development of ASD. PPA can also evoke atypical immune activation in abnormal metabolic lymphoblast cell lines detected in ASD (Cosola et al., 2018).

12. Tryptophan metabolism products: indole-3-aldehyde, indole-3-acetic acid, indolelactic acid, indolepropionic acid, indoleacrylic acid, and acrylates

Fermentation products derived from tryptophan, like indole-3-aldehyde, indole-3-acetic acid, indole-lactic acid, indolepropionic acid and indoleacrylic acid, may enhance the function of the intestinal epithelial barrier and affect the function and differentiation of immune cells (Cosola et al., 2018). They act as binders (more specifically indole-3-aldehyde) for pregnane X receptor (PXR) and aryl hydrocarbon receptor (AHR), a mechanism by which they could protect against chemically induced colitis, as observed in mice. Some metabolites derived from aromatic amino acid fermentation undergo metabolization by gut bacteria to associate with essential molecules in the human organism. For example, *Escherichia coli* is a classic indole producer that can serve as a signal detector by regulating virulence and formation of biofilms of *E. coli* and other bacteria (Hashimoto et al., 2012; Jie et al., 2017; Rajakovich & Balskus, 2019). *Lactobacilli* use tryptophan as energy source to produce ligands of the aryl hydrocarbon receptor (AhR), such as the metabolite indole-3-aldehyde (Zelante et al., 2013).

Other tryptophan-derived metabolites are acrylate and propionate derivatives. In fact, aromatic amino acid metabolism can be carried out by a wide variety of bacteria belonging to the phylum Firmicutes, which is very important for human health (Jie et al., 2017; Rajakovich & Balskus, 2019). Thus, Hashimoto et al. (2012) demonstrated the relationship between intestinal amino acid homeostasis and epithelial immunity using mice deficient in angiotensin-converting enzyme 2 (ACE2), showing increased susceptibility to intestinal inflammation caused by damage to the epithelium. The effect was transferable by microbiota transplantation in germ-free (GF) mice and, when fed with a tryptophan-rich diet, composition was reversed. The importance of tryptophan is also demonstrated in mice deficient in indoleamine 2, 3-dioxygenase (IDO), a tryptophan catalyst enzyme. Also, IDO −/− showed *Lactobacillus* growth, similar to mice with a tryptophan-rich diet, leading to the production of aryl hydrocarbon receptor (AhR) ligand-indol-3-aldehyde (Hashimoto et al., 2012; Kummen et al., 2017; Lamas et al., 2016; Li, Lin, Vanhoutte, Woo, & Xu, 2016).

13. Taurine-derived compounds

Taurine, a nonessential amino acid synthesized from cysteine and methionine that resembles gamma aminobutyric acid (GABA), has inhibitory effects on neurotransmitter release and stimulates the production of bile acids, the latter participating in fat emulsification during the digestive process (Gilbert et al., 2018).

Taurine can be metabolized by the Deltaproteobacterium *Biophila wadsworthia*, almost undetectable in the human intestine. The end product of taurine metabolism and sulfur respiration is hydrogen sulfide, detected at high concentrations in human with ulcerative colitis. Hydrogen sulfide can also act as a beta-oxidation inhibitor of bacterial SCFAs produced in colonocytes, thereby compromising energy acquisition and the epithelial tissue barrier (Rajakovich & Balskus, 2019).

The hepatic bile acid output determines the gut microbiota composition once the bile acid composition to increased amounts of taurocholic acid with the abundance of *Biophila wadsworthia* (Gilbert et al., 2018).

Conversely, this metabolite may contribute to intestinal homeostasis by modulating inflammation signaling in epithelial cells (Rajakovich & Balskus, 2019). This is the case of the NLRP6 receptor (inflammasome that contributes to intestinal homeostasis), whose activation is influenced by taurine, histamine, and spermine metabolites, regulating interleukin-8 (IL-8) level, microbial peptide secretion, and intestinal community composition. Consequently, microbiome activity is detected by the immune system, and this detection results in antimicrobial activity directed to stable colonization of microbiota. In the absence of recognition by the immune system, pathway disruption will lead to the development of dysbiosis and manifestations of inflammatory diseases (Li et al., 2016).

14. Branched-chain amino acids (BCAAs)

Some bacteria are involved in the metabolism of amino acids (AAs) in the intestine, helping to recycle nitrogen compounds. Thus, it can synthesize essential AAs that participate in the regulation of energy metabolism, and other active molecules involved in the regulation of signal transduction and nutrient metabolism in humans (Kho & Lal, 2018).

AAs and their metabolites are directly released in the GI tract by bacteria of strong proteolytic activity of the genera *Bacteroides*, *Clostridium*, *Propionibacterium*, *Fusobacterium*, *Streptococcus*, and *Lactobacillus* (Dalmasso et al., 2008).

High circulating levels of BCAAs and aromatic AAs have been found in obese individuals with insulin resistance or type 2 diabetes. More specifically, a BCAAs decrease has been associated with improved

insulin resistance rather than weight loss itself when obese individuals improved mucosal integrity and increased *Bacterioides* spp proportion, which was attributed to higher BCAAs degradation efficiency (Vallianou, Stratigou, Christodoulatos, & Dalamaga, 2019). In this context, Pedersen et al. (2016) evaluated quantitative intestinal metagenomic data from 277 non-diabetic and 75 Danish patients with type 2 diabetes. The authors concluded that the serum metabolome of insulin-resistant individuals was characterized by increased levels of BCAAs, which correlated with an intestinal microbiome that had few genes encoding bacterial transporters for these AAs but had an enriched biosynthetic potential for BCAAs. *Prevotella copri* and *Bacteroides vulgatus* were identified as the main species responsible for the association between BCAAs biosynthesis and insulin resistance. In rats, they observed that *Prevotella copri* aggravate glucose intolerance, can induce insulin resistance, and increase BCAAs circulation.

In vitro and *in vivo* studies demonstrated that BCAAs can regulate defensin expression in enterocytes (De Simone et al., 2013). In this context, interleukins may promote β-defensin expression in different epithelial cells. A concentration of 100–250 mg/mL of BCAAs resulted in β-defensin overexpression in two colon carcinoma cell lines (HCT-116 and CACO-2). Similar results were observed for leucine and valine (Wang et al., 2013).

15. Peptidoglycans and microorganism-associated molecular pattern (MAMP)

Peptidoglycans are polymers that serve as key structures to support the bacterial cell wall shape and also provide internal resistance to pressure. However, peptidoglycan fragments, also called muropeptides, are released in intestinal lumen as a result of cell wall remodeling during cell division. . Therefore, muropeptides are a signal between bacteria and the host's organism during symbiotic and pathogenic interactions (Ma & Ma, 2019).

The innate immune system faces antigens and finds various self or non-self antigens. It is equipped with pattern recognition receptors (PRR) of these molecules to monitor, coordinate, and respond to changes. Peptidoglycan recognition proteins (PGRP) may occur through reduced receptor binding, as was observed with the wall teichoic acids, which reduced peptidoglycan binding to *Staphylococcus aureus*. PRR also detect microorganism-associated molecular patterns (MAMP) from bacterial, fungal, and viral origin, including lipopolysaccharides (LPS), flagellins, peptidoglycans, formyl peptides, and unique nucleic acid structures. Cytoplasmic and transmembrane PRR initiate the signaling cascade by directing and regulating effector responses crucial for host defense (Dworkin, 2014; Levy et al., 2017; Rooks & Garrett, 2016).

16. Bacteriocins

Bacteriocins are peptides or proteins synthesized ribosomally by gut microbiota that have antimicrobial activity and contribute to the stability of the human bacterial community homeostasis. They are usually associated with human immunity proteins and are produced by all major bacterial strains and some Archaea. Gram-negative bacteria produce bacteriocins that include some higher-molecular weight proteins (e.g., 449 to 629 amino acid colicins), whereas Gram-positive bacteriocins are peptides of less than 70 AAs. Bacteriocins also have synergistic/additive effects when used in combination with other treatments such as heating, high pressure, organic compounds, and part of a food packaging (Egan et al., 2016).

They are categorized into four classes according to peptide structure, namely: Class I: contain polycyclic AAs, thioether lanthionine or methyllanthionine. There are different types: glycocines, lantibiotics, sactipeptides, and lasso peptides. According to its structure and function, this class is subdivided into types A and B. Class II: formed by small pH-resistant and heat-stable peptides. They are subdivided into four subtypes:

a) Class IIa: pediocin-like bacteriocins. They contain the conserved N-terminal-AAs YGNGVXCXXXCXV sequence and form a disulfide bridge with two cysteines;
b) Class IIb: requires two different peptides for antimicrobial activity;
c) Class IIc: are circular bacteriocins;
d) Class IId: bacteriocins that do not match the other three categories above. Class III: large bacteriocins (>10 kDa), heat-labile proteins that exert antimicrobial activity by cell-wall hydrolysis (e.g., bacteriolysins). Class IV: bacteriocins formed by a complex of proteins conjugated with lipids or carbohydrates (Egan et al., 2016).

Today, more than ever, the balance of the intestinal microbioma is being sought in order to prevent colonization by increasingly resistant pathogens, preventing infections and reducing the abuse of antibiotics. The class of lactic acid bacteria (LAB) is suitable for acting as probiotics due to their ability to modify the environment in which they are producing different metabolites. They can also inhibit the growth of enteropathogenic bacteria (including antibiotic resistant strains) by competitive exclusion, and are widely used as a natural alternative to food preservation and/or as an adjunct to antibiotic use (Hols, Ledesma-García, Gabant, & Mignolet, 2019).

Due to the range of bacteriocins produced by LAB and the large database already scattered in the literature, a database specializing in LAB bacteriocins (LABiocin) was built (Vijaya Saradhi et al., 2010). In 2019, this interactive database gathered up to 517 LAB bacteriocins. Bacteriocins are presumed to have low or no cytotoxicity, mainly because the tested bacteriocins originate from LAB, which have long been used in fermentation and biopreservatives in dairy products, in addition to healthy human digestive tracts being hypercolonized by commensal strains of these bacteria. Also, postbiotics are being investigated as a safer alternative to antibiotics in animal husbandry, particularly in birds and pigs (Vieco-Saiz et al., 2019).

Nisin, produced by Gram-positive bacteria such as *Lactococcus lactis* and some *Streptococcus* spp, is the most studied lantibiotic. It is being used as a food preservative and has been recognized as safe by the US Food and Drug Administration (Administration Food and Drug, 2017). Also, nisin and other lanthipeptides have been proven to be cytoneural to various eukaryotic cell lines, even at doses 100 times greater than the lethal concentration, exerting its antimicrobial activity by binding to lipid II of the bacterial cell wall. The complex created induces pore formation and permeability alteration, inhibiting the synthesis of glycan peptides. It has wide application in clinical treatments, especially local and external applications (Kassaa et al., 2019; Vieco-Saiz et al., 2019). For example, *Streptococcus salivarius* secreting a cocktail of bacteriocins as highly potent lantibiotic, salivaricin D (slvD), is resistant to proteases such as trypsin and has a broad spectrum of sensitive strains, including *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Clostridium* spp., and *Micrococcus luteus*. Beside sensory, modification, and transport proteins, the slvD locus encodes four immunity proteins and a second nisin-like precursor (SlvN) that is potentially active and large repertoire of antimicrobial compounds scattered in different organisms (pan-predatiome) may ensure a defense of antibacterial in hostile environments (Bajagai, Klieve, Dart, & Bryden, 2016).

Other LAB less used from an industrial perspective (i.e., *Lactococcus*, *Streptococcus*, *Lactobacillus*, *Pediococcus*, and *Enterococcus)* are also of interest to the food industry. Among the desirable properties of their bacteriocins, a few may be highlighted, as follows: i) being *Generally Regarded As Safe* (GRAS), considered safe and viewed by the consumer public as promoting health benefits; ii) being responsive to digestive proteases such as pancreatin, trypsin, and chymotrypsin, not impacting negatively the intestinal microbiota; iii) not being toxic; iv) being active even at pH variations and sometimes not temperature-sensitive; v) having coded genes favorable to genetic manipulation where desirable; vi) not all bacteriocins produced by LABs having the same modes of action; and vii) being active against foodborne pathogenic and spoilage bacteria (Bajagai et al., 2016).

17. Uremic compounds

Interest in uremic toxicity (UT) has grown exponentially in the last years due to the adversities regarding the evolution and therapy of CKD. With the development of the European Uremic Toxin Working Group (EUTox; www.uremic-toxins.org), an encyclopedic list of uremic retention solutes and their concentrations in the uremia process has become available. Toxins are classified according to the physicochemical characteristics affecting dialysis, which is the main therapy for its removal (Wheeler & Liss, 2019). Among the various uremic compounds with beneficial or toxic effects identified in the colon of patients with CKD, some can be pointed out: trimethylamine N-oxide (TMAO), trimethylamine (TMA), indole-3-acetic acid (IAA), organic anion transporter (OAT), flavin-containing monooxygenase (FMO), organic cation transporter 2 (OCT2), ATP-binding cassette (ABC-ATP), tryptophan 2,3 dioxygenase (TDO), indolamine 2,3-dioxygenase (IDO), indoxyl sulfate (IS), urea, ammonia, p-cresyl sulfate (pCS), indoxyl glucuronide, p-cresyl glucuronide, phenyl glucuronide, phenylacetylglutamine, hippuric acid, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid, and indoleacetic acid. The high affinity of some of these molecules for whey proteins, such as albumin, makes their identification difficult (Jaworska et al., 2019). Wong et al. (2014) evaluated individuals with end-stage renal disease and verified the abundance of bacteria that have urease, uricase, p-cresol, and indole producing enzymes, showing an increase of these enzymes and a decrease of SCFA-converting enzymes that act on dietary fiber (Khavinson, Lin'kova, & Tarnovskaya, 2016; Wong et al., 2014). IS and p-cresyl sulfate pCS derive from UT produced during the onset of advanced CKD, when the kidney is no longer able to compete with the bacteria that produce these metabolites. In this situation, UT initiate a cascade of oxidative and inflammatory reactions inducing a pro-fibrotic effect (Khavinson et al., 2016).

Urea, the main product of nitrogen metabolism in humans, is also metabolized by urease-containing bacteria and hydrolyzed to generate ammonia. In turn, urease activity inhibitors have been studied for over 50 years with important application in combating *Helicobacter pylori* gastric and *Proteus* urinary infections. Circulating molecules derived from UT, despite being associated with the progression of CKD risk, may offer a good opportunity for disease diagnosis and prevention, in addition to assessment and repositioning dietary changes according to microbiota modification (Castillo-Rodriguez et al., 2018).

In this sense, Devlin et al. (2016), who identified the presence of *Bacteroides* tryptophanase that converts tryptophan to indole distributed throughout the intestine, found that the deletion of this gene eliminates *in vitro* IS production. The alteration of the status or abundance of *Bacteroides* tryptophanase has exhibit to be able to modulate IS levels in gnotobiotic mice and the community background in the conventional murine intestine. These results demonstrate that it is possible to control host IS levels by targeting the microbiota, suggesting a possible strategy for managing kidney disease (Brito et al., 2017; Devlin et al., 2016; Glorieux & Tattersall, 2015).

18. Polysaccharide A

Molecules such as polysaccharide A (PSA) produced by *Bacterioides fragilis*, a Gram-negative symbiotic found in the outer mucus layer of the colon, participate in preserving tolerance and immunity on the surface of the intestinal mucosa by promoting Treg-mediated responses, having an effect on the inflammation progression. PSA suppresses IL-17 production and promotes IL-10 expression by CD4+T cells by binding to TLR2, thereby inhibiting inflammation (Levy et al., 2017).

In a trinitrobenzene sulfonic acid (TNBS)-induced colitis model, PSA-treated mice had a higher number of Treg cells when compared to controls. In addition, GF mice monoclonalization with *Bacteroides fragilis* modulated CD4+T cell homeostasis and cytokine production (IL-10) in a PSA-dependent manner, and thereby improved intestinal inflammation. Recognition of *Bacteroides fragilis* PSA by TRL2 on Treg cells mediates immune regulation and bacterial niche colonization (Shapiro et al., 2014).

Studies with human peripheral blood mononuclear cells suggested that PSA can enhance the expansion and suppressive function of IL-10-producing $CD4^{+}CD39+FOXP3+$ Treg cells. Deficiency of CD39 in Treg cells was linked to an inability to suppress experimental colitis, and increased CD39 expression in patients with inflammatory bowel disease was associated with disease remission. Studies with preclinical models and *in vitro* experiments with human cells indicate that PSA may be a useful immunomodulatory detect microorganism associated molecular patterns (MAMP) for the treatment of human autoimmune diseases (Rooks & Garrett, 2016). In addition to PSA being essential for the growth and efficiency of *B. fragilis* colonization, this structure also mediates the interaction with other microorganisms present in the host mucosa. It has a full modulatory effect on the innate and adaptive immune system cells (Rooks & Garrett, 2016). On the other hand, Toll-like receptors (TLR) play a critical role in early innate immunity, sensing the presence of pathogens and initiating immune response. Eleven TLRs that can signal via their distinct adapter proteins (MyD88) have been identified, although sometimes this signaling is independent of MyD88. Bacterial products such as peptidoglycan, atypical LPS (as found in *Porphyromonas*), lipoproteins, and lipoarabinomannan can also activate TLR. This signaling ultimately results in NF-κB-mediated gene transcription. In fact, bacterial-induced TLR signaling induces transcription of many immunologically important genes, such as those encoding the molecular histocompatibility complex (MHC), costimulatory molecules, cytokines, chemokines, and adhesion molecules (Wang et al., 2006).

19. Metabolites derived from polyphenols

The role of dietary polyphenols in human health depends mainly on their bioavailability, absorption, and metabolism (Cueva et al., 2017). Only a small percentage of the polyphenols that are ingested (5–10%) is absorbed by the small intestine and 90–95% will be able to reach the colon, where polyphenols can be transformed by residing bacteria into bioavailable metabolites, which in turn may be more bioactive than their precursors (Etxeberria et al., 2013). Thus, Fernandes, Nave, Gonçalves, De Freitas, and Mateus (2012) conducted a study to verify the transepithelial transport of a flavanol-anthocyanin dimer using Caco-2 cells, also verifying the influence of structural characteristics on the transport efficiency of these compounds. They concluded that not only polyphenols, but also the dimeric structure can cross the cell barrier. Though not analyzed, it infers the possibility that polyphenol metabolites crossed the barrier and reached the plasma, yet at low concentrations.

In fact, polyphenol bioavailability is very low; for example, after the consumption of wine, which is typically rich in flavan-3-ols and anthocyanins, the concentration of phenolic compounds in the plasma ranges from micromolar to nanomolar low quantity. Resveratrol has the poorest bioavailability: human consumption reaches 1 g, maximum plasma concentration is around 0.6 μM (Luca et al., 2019).

In vivo, polyphenols usually undergo glucuronidation, sulfation, and/or methylation in the intestine and later in the liver, producing conjugated metabolites. These, in turn, are more readily eliminated back to the intestinal lumen or via an enterohepatic cycle where conjugated metabolites may be metabolized by colonic microbiota to smaller molecules, such as phenolic acids, before being reabsorbed or eliminated through feces (Cueva et al., 2017).

In general, the main phenolic metabolites derived from gut microbiota found in urine and plasma after ingestion of wine polyphenols are: epicatechins, 3-hydroxybenzoic acid, syringic acid, phenolic acids, gallic and methyl gallic acid, vanillic acid, protocatechuic acid, phloroglucinol, glucuronides, sulfates, and methylated flavan-3-ol derivatives, such as anthocyanins, aglycones, flavanols (quercetin), and resveratrol, as well as bacterial catabolism derivatives that may also be found in the conjugate form (Devlin et al., 2016).

The beneficial effects of polyphenols on human health have always aroused attention. Together with the gut microbiota, polyphenols have demonstrated their essentiality in metabolite production; for example, isoflavones with estrogen-like activity or anti-inflammatory properties may affect the abundance of *Prevotella* and *Bacteroides* genera (Etxeberria et al., 2013).

Resveratrol is a stilbene synthesized by plants in adverse situations such as mechanical damage, presence of bacteria and/or fungi, and excessive exposure to ultraviolet light. This compound has a high degree of lipophilicity. Because it is not able to circulate alone in the plasma, it binds to proteins such as albumin and low-density lipoprotein (LDL). Intestinal bacteria contribute to resveratrol metabolism by converting it into 3,4-dihydroxy-trans-stilbene, 3,4-dihydroxy-bibenzyl (lunularin), and dihydro-resveratrol (DHR), which is partially absorbed and converted to conjugated forms of resveratrol monosulfate and monglucoronide, easily eliminated in the urine. The best-known resveratrol-metabolizing bacteria are *Slackia equolifaciens* and *Adlercreutzia equolifaciens*. Resveratrol metabolites were tested and revealed *in vitro* cytotoxicity, inhibiting the growth of CRC cells such as Caco-2, HCT116 and CCL-228, inducing arrest of the G1 phase of the cell cycle through cyclin D1 depletion, phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and adenosine receptor activation. Moreover, evidence points to anti-inflammatory, antioxidant, and delipidating properties of resveratrol (Etxeberria et al., 2013; Luca et al., 2019). These activities are shared by other metabolites such as curcuminoids, isoflavones, tannins, and proanthocyanidins.

Curcuminoids, such as curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (Bis-DMC), occur in curries and mustards and are associated with various health benefits (Herath, Ferreira, & Khan, 2007). Tan et al. (2015) used an *in vitro* model containing human fecal starters to investigate the colonic metabolism of curcuminoids. The three curcuminoids (curcumin, DMC, and Bis-DMC) were degraded after 24 h of fermentation with human fecal microbiota. When analyzing the ability of different gut microorganisms to metabolize curcumin via NADPH-dependent curcumin/duhydrocurcumin reductase, *Escherichia* coli exhibited the highest activity (Herath et al., 2007; Kassaa et al., 2019).

A study evaluating the microbial metabolism of curcumin with *Pichia anomala* resulted in the identification of four major metabolites, namely: 5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1- (4-hydroxyphenyl) heptan-3-one, 5-hydroxy-1,7-bis (4-hydroxy-3-methoxyphenyl) heptan-3-one, 5-hydroxy-1,7-bis (4-hydroxyphenyl) heptane-3-one, 1,7-bis (4-hydroxy-3-methoxyphenyl) heptan-3,5-diol, and two minor products (Dou, Chen, & Fu, 2019). Tetrahydrocurcumin (THC), the main metabolite of curcumin and converted by intestinal bacteria such as *E. coli*, showed greater availability and stability at physiological pH than curcumin itself in mouse plasma when given intraperitoneally (half-life from 111 to 232 min) (Cueva et al., 2017). Consequently, THC has been thoroughly studied for its spectrum of curcumin-like biological properties (Vijaya Saradhi et al., 2010).

Bioaccessibility and bioavailability of carotenoids and polyphenols, which are known to be improved by intestinal microbiota, may determine the extent of their benefits to human health. In this sense, a study was carried out to evaluate the leaves of *Moringa oleifera*, also known as white acacia, for bioaccessibility, bioactivity, and modulatory effect on microbiota after *in vitro* gastrointestinal digestion. The results showed that, in addition to releasing a major oral phenolic compound, 6,8-di-C-glucosylapigenin, catechin was released during gastric digestion, and quercetin-3-O-beta-d-glucoside during small intestine digestion. The antioxidant activity was in accordance with the release of flavonoids and phenolics. Leaf fermentation induced the production of SCFAs as well as the growth of beneficial colonic bacteria (Dou et al., 2019).

New phenolic compounds are emerging. For example, Kershaw and Kim (2017) revised the beneficial effects of piceatannol, a stilbene similar to resveratrol, on metabolic syndrome. They evidenced that piceatannol inhibited adipogenesis in 3T3-L1 adipocytes. The effect of piceatannol on the differentiation process was further confirmed by lower protein and gene expression of key adipogenic markers, such as peroxisome proliferator-activated receptor γ (PPAR γ) and CCAAT/enhancer-binding protein β (C/EBPβ). Furthermore, piceatannol inhibited adipogenesis by targeting mitotic clonal expansion during the early phase of adipocyte differentiation. It is also important to futher probe the need for studies revealing piceatannol effects on multiple signaling pathways, diaphony between metabolic organs, intestine and microbiome, and insulin resistance, which will provide further information, filling some of the hypotheses raised regarding human microbiome (Kershaw & Kim, 2017).

20. Conclusion

In conclusion, some of the most interesting metabolites derived from the gut microbiota are SCFAs, peptides, bile acids, and polyamines. SCFAs have been shown to interfere with the carcinogenic process, as an energy source for colonocytes, regulators of host metabolism and immunity, and promoters of a trophic action in the mucosa. Polyamines are responsible for enhancing the maintenance of the intestinal epithelial cell barrier; observations suggest that host–microbial polyamine synthesis is an important function of the gut microbiome that is acquired early in life and is necessary for postnatal development of the gastrointestinal tract. In similar veins, some beneficial bacteria can produce peptides with epigenetic regulatory action or anti-hypertensive properties (i.e., the tripeptides produced by *Lactobacillus helveticus*). The beneficial effect of commensal bacteria on bile acid signaling via FXR and TGR5 comprise attenuation of pro-inflammatory innate immune response, regulating bile acid diversity and biological function. Polyphenols are secondary metabolites of plants that have promising beneficial effects on human health through multiple mechanisms including interference with inflammatory transduction pathways and antimicrobial activity. However, due to their poor bioavailability, they reach the large intestine and the gut microbiota is essential in the production of polyphenol-derived metabolites, such as isoflavone-derived molecules with estrogen-like activity.

In summary, it is necessary to consider the gut microbiota as a diverse microbial community that acts cooperatively for providing nutrients and food-derived metabolites that have beneficial effects on human health. The idea of the virtual organ within an organ and the microbiota and the brain communicated with each other via various routes is gaining ever more traction in fields investigating the biological and physiological basis of psychiatric, neurodevelopmental, and neurodegenerative disorders.

20.1. Final considerations

This review seeks to understand the interaction between microbiota metabolites and the host at different conditions, in the microenvironment of the human organism, in addition to the different methods used to unravel the vast universe of activity of gut microorganisms. Few studies detailed the information on the main mechanisms through which the metabolites produced by the gut microbiota (postbiotics) interact with the host, maintaining human health and preventing diseases. Therefore, the mechanisms involved in the regulation of the immune, neurological or even physiological systems are complex and it is necessary to know that each human being has a specific microbiota. There is a great need to intensify pre-clinical and clinical studies using human data, and future studies should not only investigate the composition of the intestinal microbiota, but also the intestinal metabolome.

Declaration of interest

The authors have no relevant interests to declare.

Maria do Carmo Gouveia Peluzio designed the study, conducted the literature search, and drafted the manuscript. J. Alfredo Martinéz and

Fermin I. Milagro had primary responsibility for the final content and provided other contributions (including revising the paper critically for important intellectual content). All authors read and approved the final manuscript.

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