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Review

# Metabolism of alimentary compounds by the intestinal microbiota and consequences for gut health

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**Abstract**:
The intestinal microbiota in the mammalian large intestine metabolizes numerous alimentary compounds that are not digested and absorbed in the small intestine. By doing so, microbiota produces metabolites that accumulate in the luminal fluid. Several bacterial metabolites have been shown to be involved in communication between microbes and to act on the colonic epithelial cell metabolism and physiology. In fact, effects of bacterial metabolites on energy metabolism in colonic epithelial cells, water and electrolyte movements across the colonic epithelium, and epithelial renewal and barrier function have been reported. In this review, the consequences of such interkingdom metabolic interactions are summarized by presenting typical examples of bacterial metabolites that are known to affect communication between intestinal microbes and/or between microbes and the intestinal epithelial cells. Current studies indicate that the bacterial metabolites derived from alimentary compounds affect the colonic epithelial cells either positively or negatively. These findings pave the way for further experimental and clinical studies aiming at establishing what can be done in terms of alimentary intervention to optimize host-microbe communication for beneficial effects on gut health.

**Keywords**: Intestinal microbiota, Bacterial metabolites, Microbial communication, Host-microbe communication, Health benefits

## Introduction

The intestinal microbiota in the luminal fluid is a complex mixture of bacteria, archeae, viruses and fungi [1]. Protozoans in the intestine, although classically not included as part of the microbiota itself, represent a heterogeneous group of eukaryotic organisms, with some of them being considered as parasites [2]. The term gut ecosystem usually refers to the biological community of microorganisms living in the environment of the gut mucosa. Among the microbes present in the intestinal lumen, bacteria have been by far the subjects of most studies. Bacteria depend on the substrates provided by the host for their growth and physiology. These substrates are from alimentary and endogenous origins [3]. The mammalian gastrointestinal tract includes the small and the large intestines. In the proximal parts of the mammalian small intestine, the transit time is relatively short with concentration of bacteria increasing

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from the proximal to the distal part, while the transit time is much longer in the large intestine with corresponding much higher concentrations of bacteria [4]. In the ileum, the situation is intermediary. The substrates from alimentary origin are partly different in the small and in the large intestine. In the small intestine, there are evidence that bacteria use a minor part of substrates originating from the alimentation for their metabolism and physiology, while in the large intestine, bacteria use mainly substrates that have not been digested (or not fully digested) in the small intestine, thus being transferred through the ileo-caecal junction [3]. Bacteria use the available substrates in anabolic and catabolic pathways, allowing synthesis of macromolecules and diverse compounds that they need for growth, signaling, and physiological functions, as well as for energy production, while producing myriad of compounds during catabolism [3]. The aim of the present review is to give illustrative examples of metabolic and intermediary products originating from alimentary compounds that are implicated in communication between microbes and in communication between microbiota and the intestine of the lodging host.

## 1. Compounds originating from alimentation are metabolized by bacteria in the small and large intestine luminal fluids

Among the compounds present in food, most of them are digested in the luminal content of the small intestine before the products of degradation can be absorbed, while some of them, like some vitamins and minerals, can be absorbed as they are. Regarding proteins, they are digested in the small intestine by the action of proteases and peptidases originating from the exocrine pancreas. These enzymes release peptides, oligopeptides, and free amino acids. Terminal digestion of nitrogenous material is then performed by oligopeptidases in absorptive enterocytes which is followed by amino acid absorption. Although most amino acids are absorbed and recovered in the portal blood, a minor part of them is used by the bacteria present in the small intestine for their own metabolism [5]. Indeed, not all bacteria are able to synthesize all the amino acids required for protein synthesis [6], and then numerous bacterial species depend on the supply of amino acids by the host for their metabolism not only for protein synthesis, but also for energy production and synthesis of bioactive compounds [7].

Although in mammals, protein digestion is an efficient process, with most of dietary proteins being digested above 90%, a small percentage of proteins in the luminal fluid of the small intestine remains undigested or not fully digested. Indeed, in humans, it has been determined that approximately 10g of proteins are transferred every day from the terminal part of small intestine to the large intestine [8] (Figure 1). In the colon, the intestinal bacteria degrade proteins and peptides through their protease and peptidase activities, thus releasing amino acids [9]. Then, since colonocytes cannot absorb amino acids to any significant extent [10], the amino acids are used by the microbiota in anabolic and catabolic pathways, producing notably numerous bacterial metabolites including ammonia, phenolic and indolic compounds, hydrogen sulfide, polyamines, short- and branched-chain fatty acids, as well as various organic acids [3] (Figure 1).

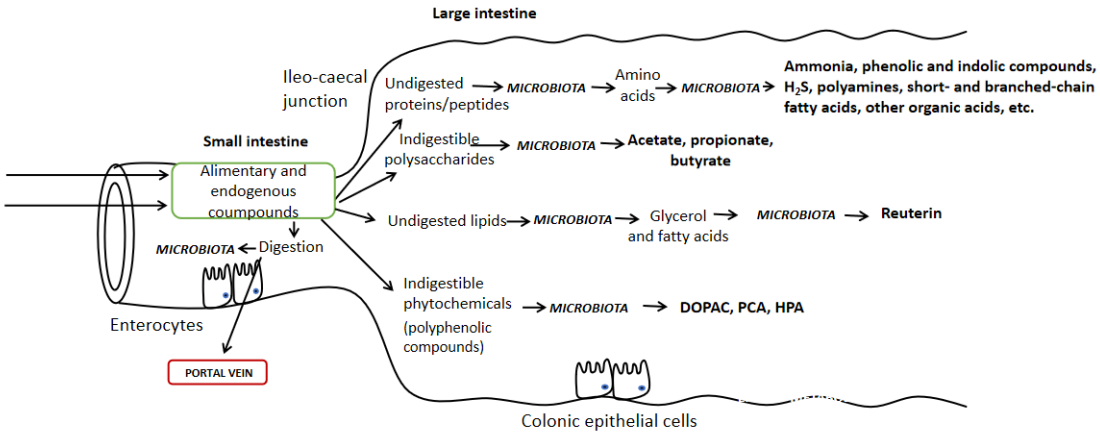


**Figure 1.** Schematic representation of the metabolism of alimentary undigested compounds by the large intestine microbiota

Regarding the indigestible carbohydrates, these alimentary compounds which include resistant starch, non-starch polysaccharides (mainly soluble and insoluble fibers), and indigestible oligosaccharides, are transferred to the large intestine where they are used as primary carbon and energy source for bacterial growth [11]. In the process of fermentation of the non-digestible carbohydrates, the gut bacteria produce large amounts of short-chain fatty acids, namely acetate, propionate, and butyrate [12] (Figure 1).

In regards with the lipid part of the food, a minor proportion of these compounds are transferred from the terminal ileum to the colon. Indeed, it has been determined that less than 5% of alimentary lipids, in condition of regular diet consumption, are usually recovered in the colonic fluid [13]. Bacteria can degrade triglycerides and phospholipids into glycerol and fatty acids. The glycerol moiety has been shown to serve as precursor in bacteria for the synthesis of reuterin, a mixture of different compounds that include 3-hydroxypropionaldehyde (3-HPA), 3-HPA hydrate, 3-HPA dimer, and acrolein [14] (Figure 1).

Among the vast family of phytochemicals contained in plants, several phenolic compounds have been shown to be transferred to the large intestine and metabolized by the intestinal microbiota. Polyphenolic compounds have been largely studied because of their beneficial effects observed both in pre-clinical and clinical studies [15]. These compounds are classified as high molecular weight tannins, that contain notably the proantocyanidins, and as the low molecular weight polyphenols. In the small intestine, low molecular weight polyphenols are partially absorbed by the enterocytes, but in contrast, the high molecular weight tannins are not absorbed in the small intestine and are thus entirely transferred to the large intestine [16]. The metabolic activity of the large intestinal microbiota towards both low molecular weight polyphenols and high molecular weight tannins releases numerous bacterial metabolites that are often organic acids and hydroxylated forms of polyphenols [3] and which include notably 3,4-dihydroxyphenylacetic acid (DOPAC), 3,4-dihydroxybenzoic acid (also called protocatechuic acid (PCA)), and 4-hydroxyphenylacetate (HPA) (Figure 1). These hydroxylated polyphenols have been studied for their action in terms of microbial communication and effects on the intestinal mucosa, as will be detailed in the subsections 2 and 3.

## 2. Production of metabolites by the intestinal microbiota from alimentary compounds and effects on bacterial growth/physiology and on microbial communication

Various metabolites produced by bacteria among the intestinal microbiota are involved in communication between members of the microbial communities. In addition, several bacterial metabolites have been shown to either stimulate or inhibit the growth of specific bacterial species. Lastly, effects of bacterial metabolites on microbial physiology have been demonstrated.

### 2.1 Several organic acids produced by the intestinal microbiota are involved in communication between members of the gut ecosystem

During the catabolism of amino acids, the bacteria present in the intestinal luminal fluid produce numerous organic acids including lactate (isomers D and L), succinate, formate, and oxaloacetate [17]. Formate secreted by the pathogenic bacteria Shigella flexneri, promotes expression of genes involved in their virulence [18]. Oxaloacetate produced by Escherichia coli helps the parasite Entamoeba histolytica to survive in the large intestine [19] (Figure 2). This latter result is of notable importance given that this parasite can trigger a strong inflammatory response upon invasion of the colonic mucosa. Lastly, succinate produced by the gut microbiota has been shown to promote infection by Clostridium difficile after antibiotic treatment [20].

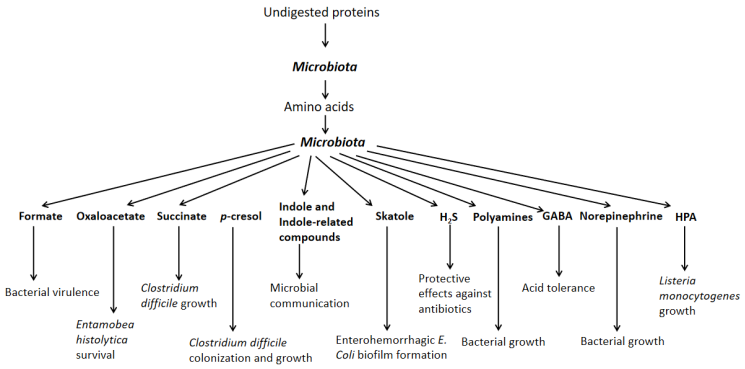


**Figure 2.** Schematic representation of the effects of amino acid-derived bacterial metabolites on microbial communication and bacterial physiology and growth in the intestine

## 2.2 P-cresol production by Clostridium difficile gives a competitive advantage to this bacterium over other gut bacteria

The phenolic compound p-cresol (4-methylphenol) is produced by the intestinal microbiota of the large intestine from the amino acid tyrosine [21]. In mammals, an increased content of proteins in the diet increases the fecal p-cresol concentration [22], while conversely, the fecal excretion of p-cresol is diminished by a diet containing undigestible polysaccharides [23]. Interestingly, the capacity of Clostridium difficile to produce p-cresol has been linked to its competitive advantage over other gut bacteria, including Escherichia coli, Klebsiella oxytoca, and Bacteroides thetaiomicron [24]. Using a model of Clostridium difficile infection in rodent, it has been shown that excessive p-cresol production affects the gut microbiota biodiversity [24]. Of note, by removing the ability of Clostridium difficile to produce p-cresol, this bacterium is less able to recolonize the intestine after an initial infection (Figure 2). This result is of major importance because Clostridium difficile is a major cause of intestinal infection and diarrhea in individuals following long-term antibiotic treatment.

## 2.3 Indole and indole-related compounds are involved in communication between bacteria of the same or different species

Intestinal bacteria convert tryptophan into indole [25]. Indole is involved in bacterial physiology and metabolism in relationship with antibiotic resistance, virulence factors, sporulation, and biofilm formation [26] (Figure 2). Indole diminishes cell motility and aggregation of L. monocytogenes [27]. Indole influences host cell invasion by non-indole-producing bacterial species such as Salmonella enterica and P. aeruginosa, as well as the fungal species Candida albicans [28]. In another study, indole was found to be bacteriostatic against lactic acid bacteria, while affecting their survival [29]. Of note, indole mitigates cytotoxicity of Klebsellia spp. by suppressing toxin production by this bacterium [30].

## 2.4 Skatole diminishes biofilm formation in the proximity of the intestinal mucosa

Skatole is a bacterial metabolite derived from tryptophan [31]. Skatole displays a strong inhibitory effect on biofilm formation by enterohemorrhagic Escherichia coli [32] (Figure 2). Biofilms are structures formed by the colon microbiota that line on the mucosal surface, and these structures have been identified as players in the modulation of colon epithelial barrier function [33].

## 2.5 Hydrogen sulfide appears protective in bacteria against the action of antibiotics

Hydrogen sulfide ($H_2S$) is produced by numerous bacterial species mainly from cysteine and sulfate in the large intestine [34, 35]. $H_2S$ appears to be a protective agent in bacteria such as Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli against the action of antibiotics and oxidative stress [36, 37] (Figure 2).

## 2.6 Polyamines are involved in the growth and physiology of intestinal bacteria

Polyamines are a family of small aliphatic amines that are present in bacterial and mammalian cells, but several polyamines synthesized by bacteria are not produced by mammalian cells [38]. Colonic bacteria represent a main source of polyamines in the intestinal luminal fluid. Polyamines produced by the intestinal microbiota include putrescine, spermidine, spermine, agmatine, and cadaverine. The precursors for putrescine, spermidine, and spermine production in bacteria are ornithine/arginine and methionine, while arginine is the precursor of agmatine, and lysine is the precursor for cadaverine synthesis [39]. Putrescine, spermidine, and spermine play a major role in bacterial growth [40] (Figure 2). Experimental evidence strongly suggests that cadaverine plays a role in the pathogenesis of Shigella infections [41].

## 2.7 Intestinal bacteria produce several metabolites known as neuroactive compounds, that are otherwise used in the microbial world as modulators of bacterial physiology and growth

Several bacterial species isolated from the gut of mammals, including humans, have the capacity to synthesize compounds that are well known to be produced by the host and which are known as neurotransmitters. These metabolites play roles in the adaptation of bacteria to changes in their environment, as well as modulators of bacterial physiology and growth, indicating a long and complex evolutionary history for the functions of these compounds in the living world. Gamma-amino butyric acid (GABA) is produced by decarboxylation of glutamate via the glutamate decarboxylase which has been shown to be implicated in bacterial acid tolerance through the maintenance of the intracellular pH homeostasis [42] (Figure 2). Regarding norepinephrine, the synthesis of this compound by bacteria can affect the growth and expression of genes related to virulence of some anaerobic bacteria such as Clostridium perfringens [43, 44] (Figure 2).

## 2.8 4-hydroxyphenylacetate can inhibit the

### growth of Listeria monocytogenes

The bacterial metabolite 4-hydroxyphenylacetate (HPA), which is produced not only from polyphenols, but also from aromatic amino acids, inhibits the growth of the food borne pathogen Listeria monocytogenes (Figure 2), an effect associated with alteration of the morphology of the bacteria, and with decreased expression of several virulence genes [45].

### 2.9 Reuterin exerts antimicrobial effects against several bacterial species

The glycerol moiety of lipids may serve in intestinal bacteria as a precursor for the synthesis of reuterin. This bacterial metabolite is known to exert broad-spectrum antimicrobial effect against several bacteria of the intestinal microbiota including Clostridium difficile and Escherichia Coli [46, 47].

Concerning the fatty acids released from triacylglycerol and phospholipids in the luminal fluid of the large intestine, there are several indications that free fatty acids display strong antimicrobial properties in vitro [48], but the impact of such property for the control of the bacterial growth in the large intestine in real life situation remained to be determined.

## 3. Production of metabolites by the intestinal microbiota from alimentary compounds and effects on the intestinal mucosa

Briefly, the absorption of nutrients and other compounds originating from food is accomplished by specialized cells of the small intestine epithelium (called enterocytes), while in the large intestine epithelium, the colonocytes, in addition to water and electrolyte absorption, display capacities for specific bacterial metabolite absorption.

The epithelium of small intestine is renewed within few days in mammals [49]. This renewal is made possible by the division of the intestinal stem cells situated at the bottom of the crypts. The cells at the boundary of the stem cell niche undergo then differentiation into progenitor cells [50]. At this step, cells undergo multiple rounds of cell division, while migrating out of the crypt towards the villus compartment. Then, the cells undergo lineage into either cells of absorptive type (enterocytes and microfold cells), or into cells of the secretory type (enteroendocrine cells, goblet cells, tuft cells, and Paneth cells). The fully mature epithelial cells are finally exfoliated in the intestinal lumen allowing maintenance of epithelium homeostasis.

The colonic epithelium is also rapidly renewed [51]. This epithelium is made of different specialized cells with some homologies with the epithelial cells found in the small intestine epithelium. The absorptive colonocytes represent the largest proportion of the colonic epithelial cells. The large intestine epithelium is characterized by a high proportion of goblet cells since these cells represent approximately 20% of all differentiated epithelial cells [52]. The different peptides that are produced and released by the epithelial entero-endocrine cells of the large intestine are much more restricted than the ones released in the small intestine. Tuft cells have also been identified in the large intestinal epithelium [53], but in the large intestine, in contrast with the small intestine, Paneth cells are not detected [54].

### 3.1 Branched-chain fatty acids are regulators of electrolyte transport through the colonic epithelium

The branched-chain fatty acids isobutyrate, 2-methylbutyrate, and isovalerate are produced from indispensable branched-amino acids that are valine, isoleucine, and leucine respectively. In a rodent model, the consumption of a diet with a high protein content markedly increases the total content of branched-chain fatty acids in the colon when compared with a diet containing a lower protein content [55]. Among branched-chain fatty acids, isobutyrate appears to exert regulatory roles on electrolyte transport through colonic epithelial cells in experimental works (Figure 3), and this capacity appears to be shared with short-chain fatty acids. Indeed, isobutyrate increases the expression of one of the apical transporters of $Na^+$ in colonic epithelial cells [56], activates the $Na^+/H^+$ exchanger in colonic crypts [57], and stimulates sodium absorption in colonic biopsies [58].

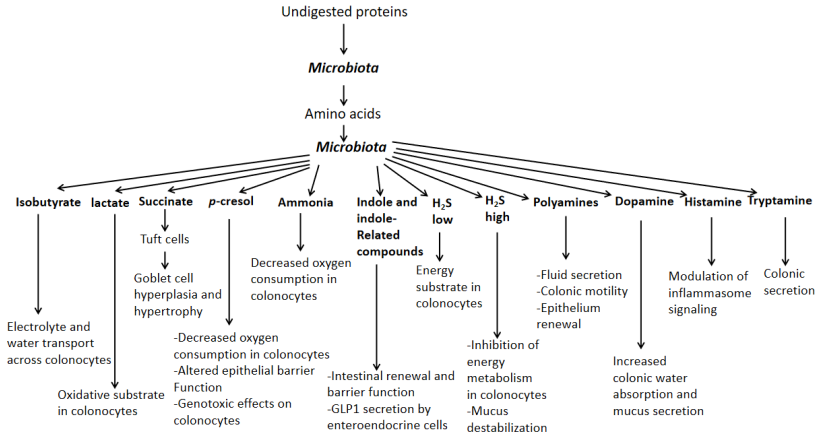


**Figure 3.** Schematic representation of the effects of amino acid-derived bacterial metabolites on the metabolism and physiology of intestinal epithelial cells

## 3.2 L-lactate is an oxidative substrate in colonocytes while succinate triggers hyperplasia and hypertrophy of goblet cells

Absorptive colonocytes are characterized by a high capacity for L-lactate oxidation [59] (Figure 3). The detection of succinate by intestinal Tuft cells triggers hyperplasia and hypertrophy of goblet cells in the distal intestine epithelium [60] (Figure 3). In addition to be detected by Tuft cells, succinate produced by the intestinal microbiota promotes the expansion of these cells, an effect that was associated with a reduction of signs of intestinal inflammation in the mice model [61].

## 3.3 Ammonia in excess impairs energy production in colonocytes

Ammonia in excess, either originating from the colonic metabolic activity, or produced in colonocytes from glutamine utilization, inhibits in a dose-dependent manner the mitochondrial oxygen consumption in colonocytes [62], thus representing a metabolic troublemaker towards cell respiration, and thus energy production in this rapidly renewed structure (Figure 3). In addition, high millimolar concentrations of ammonia inhibits short-chain fatty acid oxidation in colonic epithelial cells [63]. However, colonocytes are equipped with enzymatic activities that allow them to partly detoxify ammonia in the mitochondria of colonocytes during the transfer of this compound from the luminal content to the bloodstream. This can be done by converting ammonia into citrulline in two metabolic steps [64]. Then, above the capacity of colonocytes to detoxify ammonia, this compound can presumably affect mitochondrial ATP synthesis.

## 3.4 P-cresol in excess affects energy production in colonic epithelial cells and epithelial barrier function

In excess, the bacterial metabolite p-cresol diminishes in vitro mitochondrial oxygen consumption in human colonocytes, such inhibition being associated with an increased production of anion superoxide, thus indicating that p-cresol affects the mitochondrial function in these cells [65] (Figure 3). This effect is associated with a reduction of the capacity of colonic epithelial cells to proliferate. After pretreatment of colonocytes for three days with increasing concentrations of p-cresol, the intracellular concentration of ATP is dose-dependently decreased, thus indicating energy deficiency in these cells under such experimental conditions. Using monolayers of human colonocytes, p-cresol was found to increase the paracellular transport between colonocytes dose-dependently [66], suggesting that p-cresol at high concentrations can induce alteration of the colonic epithelial barrier function, maybe partly because of energy depletion in colonocytes.

In addition to its adverse effect on energy metabolism in colonocytes and to its deleterious effect on intestinal barrier function, p-cresol in excess may alter DNA structure in colonic epithelial cells. Indeed, by using the measurement of DNA double-strand breaks, this bacterial metabolite dose-dependently alters DNA integrity in colonocytes [65]. Interestingly, by using a fermentation system containing fecal samples from volunteers in the presence of different substrates, and by testing the supernatants on human colonocytes for their genotoxic potential, p-cresol was identified among the compounds present in the supernatants as the greatest predictor of genotoxicity against colonocytes [67] (Figure 3).

## 3.5 Indole and indole-related compounds are overall protective for the intestinal mucosa

Several indole-related compounds, including indole-3-acetate, indole-3-propionate, indole-3-aldehyde, indole-3-acetaldehyde, and indole acrylate bind to the aryl hydrocarbon receptor present in different cell types of the host including cells present in the intestinal mucosa, notably intestinal epithelial and immune cells. The binding of these compounds to AhR participates in the maintenance of the intestinal mucosa homeostasis by acting on the control of the intestinal epithelium renewal, its barrier function, and activities of several intestinal immune cell types [68]. Exposure of human enterocytes to the tryptophan-derived bacterial metabolite indole increases the expression of genes involved in the intestinal epithelial barrier function and mucin production [69] (Figure 3). Also, oral administration of indole-containing capsule to rodent resulted in an increased expression in colonocytes of genes coding for tight junction proteins between epithelial cells [70]. In accordance with these results, indole increases transepithelial resistance in in vitro experiments using colonocyte monolayers [71], thus reinforcing the view that indole participates in the basal barrier function. Thus, indole and several related compounds exert beneficial effects on the intestinal mucosa in different experimental situations.

Beneficial effects of bacterial metabolites in the context of intestinal mucosal inflammation have been reported for the indole and its related compounds [72-74]. Indole and indole-related compounds decrease mucosal inflammation and injury in experimental models of enteropathy [75, 76]. Indole-3-propionate given by the oral route exerts beneficial effects on the intestinal barrier function when this latter is experimentally altered, such as in the model of radiation injury [77], or in the context of high-fat diet consumption [78]. In a model of experimental colitis induced in mice, other indole-related compounds given by the oral route, namely indole-3-pyruvate, indole-3-aldehyde and indole-3-ethanol, the protect against increased intestinal permeability observed in this model [79]. Indole-3-acrylate diminishes intestinal inflammation in mice and upregulates Mucin 2 gene expression [80] (Figure 3).

However, indole when used at a 2.5 millimolar concentration affects the respiration of colonocytes by diminishing mitochondrial oxygen consumption [71], and thus mitochondrial ATP production. This latter effect is paralleled by a transient oxidative stress in colonocytes, which is followed by an increased expression of antioxidant enzymes, presumably as an adaptive process against the deleterious effect of indole exposure at excessive concentration [71].

Lastly, indole has been shown to affect hormone secretion by entero-endocrine cells of the large intestine epithelium. In in vitro experiments performed with immortalized and primary mouse colonic enteroendocrine L cells, indole modulates the secretion of glucagon-like peptide-1 (GLP-1) [81] (Figure 3).

## 3.6 Hydrogen sulfide is used as a mineral energy substrate by colonocytes at low concentrations while high concentrations affect mitochondrial ATP synthesis

The effects of $H_2S$ on energy production in intestinal epithelial cells have been tested. In isolated colonocytes, low micromolar $H_2S$ concentrations instantaneously increases the cell oxygen consumption [82], in association with an inner mitochondrial energization and synthesis of ATP [83]. $H_2S$ has thus been established as the first mineral energy substrate in human cells [84] (Figure 3). This discovery has challenged the previous concept that mammalian cells are exclusively dependent on carbon-based molecules, such as simple sugars, fatty acids, and amino acids, for energy production. This $H_2S$-dependent mitochondrial ATP synthesis in colonocytes is made possible through the oxidation of $H_2S$ by the mitochondrial sulfide oxidation unit which allows the conversion of hydrogen sulfide into thiosulfate [85].

In contrast, at higher concentrations, $H_2S$ severely inhibits colonocyte oxygen consumption by inhibiting the mitochondrial cytochrome C oxidase activity [82], therefore decreasing the capacity of mitochondria to synthesize ATP, and thus depriving colonocytes of their main source of energy (Figure 3). Thus, the sulfide oxidation unit in mitochondria represents a metabolic way to detoxify hydrogen sulfide, up to a certain threshold, and to recover energy from it.

Of note, hydrogen sulfide in excess induces the expression of genes involved in the production of pro-inflammatory cytokines and pro-oxidant mediators in colonocytes [82]. In addition, high concentration of $H_2S$ destabilizes the protective mucous layer that covers the intestinal epithelium through the reduction of disulfide bounds linking the mucin-2 network, a process that would increase the interactions between bacteria and the epithelium [86]. In addition, such $H_2S$-induced mucus destabilization may increase the contact between deleterious compound present in the colonic luminal fluid and the colonic epithelial cells. For instance, experimental evidence suggests that $H_2S$ is indirectly implicated in the deleterious effect of heme on the colonic epithelium. Indeed, dietary heme supplementation increases the abundance of the mucin-degrading bacteria Akkermansia muciniphila [86]. Since mucin-degrading bacteria metabolize the sulfate-containing mucin, and thus increase $H_2S$ production, and since, as detailed above, $H_2S$ in excess fragilizes the mucus barrier, it has been proposed that heme increases the accessibility of luminal compounds (including heme itself) to colonic epithelial cells by favoriting $H_2S$ production. These results are important since invalidation of the gene coding for one of the main mucins in intestine leads to the appearance of mucosal inflammation [87].

Apart from the effect of H2S on colonic absorptive cells,

this metabolite has been shown to regulate endocrine function of the gut. Indeed, $H_2S$ stimulates in vitro the secretion of GLP-1 by the enteroendocrine L-cells [88]. In this latter study, the authors, by using the prebiotic chondroitin sulfate, which increases the abundance of the sulfate-reducing bacteria D. piger and sulfate moiety in the distal intestine, measured an increased $H_2S$ production.

## 3.7 Polyamines produced by the intestinal microbiota display important beneficial effects on the intestinal mucosa metabolism and physiology, but excessive concentrations of putrescine and spermine are deleterious for the intestinal epithelium barrier function

Putrescine, spermidine and spermine are involved in fluid secretion by colonic crypts [89], and in post-prandial colonic motility [90] (Figure 3). Dietary spermidine supplementation reinforces the intestinal barrier function in mice [91]. Putrescine stimulates DNA synthesis in intestinal epithelial cells [92], and polyamines appear requiring for intestinal epithelium renewal [93]. A mixture of putrescine, spermidine and spermine has been found to be necessary for normal post-natal development of the small intestine and colon mucosa [94]. Microbial putrescine represents a stimulant for the proliferation of colonic epithelial cells [95] (Figure 3). Interestingly, putrescine and agmatine exert opposite effects, with putrescine being strictly necessary for proliferation of colonic epithelial cells [96], and agmatine displaying strong anti-mitotic effect [97]. Thus, polyamines, depending on their chemical structure may exert opposite effects on colonic epithelial cell growth. Spermine modulates inflammation in the intestinal epithelium by acting on the inflammasome signaling and IL-18 secretion [98].

However, the reported effects of the polyamines are not exclusively beneficial, and the effects observed depend on the extracellular concentrations. Indeed, supplementation in mice with exogenous putrescine in excess disrupts tight junction permeability between epithelial cells [99]. This latter effect is paralleled by a capacity of excessive putrescine to increase gut permeability and inflammatory cytokine concentrations in the colonic tissues.

Regarding spermine in excess, in a specific context of infection by enteroxigenic B. fragilis, this polyamine which is efficiently taken up by colonic epithelial cells [100], increases reactive oxygen species production and DNA damage in these cells through its increased catabolism by the spermine oxidase activity [101].

## 3.8 Several bacterial metabolites known as neuroactive compounds affect intestinal physiological functions

Administration of dopamine in the colonic lumen increased colonic water absorption in mice [102] (Figure 3). In addition, in in vitro experiments, dopamine promotes mucus secretion in rat distal colon [103].

Interestingly, histamine produced by the intestinal microbiota modulates inflammation in the intestinal epithelium by modulating the inflammasome signaling and IL-18 secretion [98] (Figure 3). Limited inflammasome activation serves critical functions in pathogen defense by intervening in the removal of damaged host cells, and by stimulating an adaptive immune response, while inappropriate inflammasome activation is linked to several inflammatory disorders [104].

Gut microbiota promotes serotonin synthesis in enteroendocrine cells of the colonic epithelium [105]. Thus, bacteria can interact with the host to induce the endogenous production of serotonin, such induction being able to affect intestinal motility [105].

In the intestinal tract, tryptamine activates the 5-HT4 receptor expressed in the colonic epithelium, and such activation is involved in the control of colonic secretion [106] (Figure 3).

## 3.9 Short-chain fatty acids are involved in energy metabolism, gene expression, barrier function, and water/electrolyte movements in the intestine

Butyrate, acetate, and propionate, after their entry inside absorptive colonocytes through the brush-border membranes, are highly oxidized in these cells [107], thus serving as luminal fuels for colonocytes (Figure 4). In colonocytes, in addition to be used as energy substrates, short-chain fatty acids act as regulators of gene expression. Indeed, it has been shown that a mixture of the three short-chain fatty acids regulates the expression of different genes in colonic cells [108] (Figure 4). The mechanisms involved in the regulation of gene expression by butyrate in colonocytes include notably the capacity of butyrate to increase the acetylation of specific nuclear histone proteins [109]. Histone hyperacetylation in colonocytes represents an epigenetic mechanism driven by the environment that regulates gene expression in these cells [110].

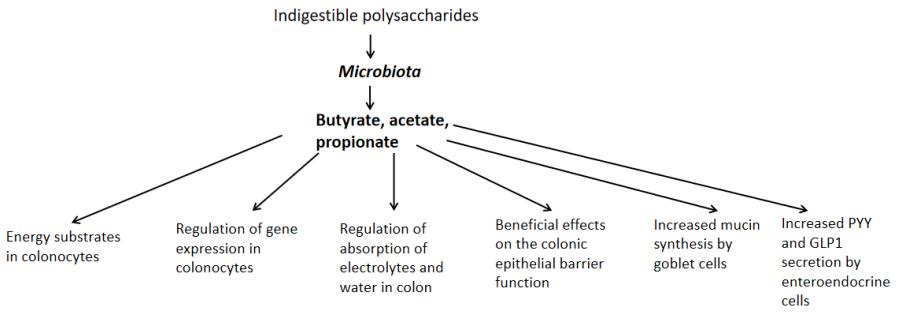


**Figure 4.** Schematic representation of the effects of indigestible polysaccharides-derived short-chain fatty acids on the metabolism and physiology of intestinal epithelial cells

The concept that butyrate oxidation regulates its intracellular concentration has been proposed [111] taking into consideration the central article of Roediger published in 1982 [107]. This paper demonstrated that, although well oxidized in the mitochondria of the colonocytes, butyrate very modestly increases oxygen consumption in these cells. This surprising result was explained by the capacity of butyrate to suppress the oxidation of endogenous substrates in colonocytes [107]. In other worlds, when butyrate is available from the microbial activity of colonocytes, these cells use butyrate as a preferential fuel for ATP synthesis, and thus use less endogenous substrates to maintain energy homeostasis. Consequently, butyrate metabolism allows the regulation of its concentration within colonocytes, and thus presumably its effect on gene expression [3].

Of note, and in the same line of thinking, it has been shown that butyrate oxidation by differentiated colonocytes in the surface epithelium and in the upper part of the colonic crypts regulates the concentration of butyrate in vicinity of proliferating epithelial stem/progenitor cells in the lower part of the crypts, thus protecting them from the deleterious effects of butyrate at excessive concentrations [112].

Butyrate, and to a minor extent acetate and propionate, has been shown to play a role in the movement of electrolytes across the colonic epithelium, thus participating in the regulation of the absorption of electrolytes and water by the colonic absorptive cells [56-58]. Short-chain fatty acids increase colonic fluid and electrolyte absorption in healthy individuals by involving $Na^+/H^+$, short-chain fatty acid/$HCO_3^-$, and $Cl^-$/short-chain fatty acid exchangers in apical membranes of colonocytes [113] (Figure 4).

The short-chain fatty acids have been shown to exert beneficial effects on the intestinal barrier function. In vitro experiments performed with monolayers of human colonocytes showed that butyrate stimulates tight junction assembly, thus enhancing the epithelial barrier function [114] (Figure 4). In another in vitro study performed with intestinal epithelial cells grown as monolayers, butyrate increased epithelial barrier function in a process involving increased expression of gene coding for claudin-1, a component of the tight junctions involved in intestinal barrier function [115].

Attention has also been paid to the potentially protective effects of the short-chain fatty acid butyrate on intestinal mucosal inflammation, given its regulatory effects on the intestinal immune system in experimental studies. Regarding the process of intestinal mucosa inflammation, treatment of lipopolysaccharide-treated macrophages with butyrate reduced the production of pro-inflammatory mediators including nitric oxide, interleukin-6, and interleukin-12 [116]. In addition, butyrate promotes the differentiation of colonic regulatory T cells (Tregs), which act as anti-inflammatory effector [117].

Some data are available regarding the effects of short-chain fatty acids on non-absorptive intestinal epithelial cells. Regarding the mucous-secreting goblets cells, butyrate and propionate increase the expression of the gene coding for MUC2 in human goblet cells [118], and acetate and butyrate induce mucin secretion in the colon after intraluminal administration [119] (Figure 4). In biopsies recovered from colonic resection samples, butyrate can increase the synthesis of mucin, and this stimulating effect is dependent on the oxidation of butyrate [120], thus suggesting that energy provision through butyrate metabolism in biopsies likely participates in this latter process.

Lastly, the role of short-chain fatty acids on hormone secretion by the enteroendocrine cells has been also investigated. Although butyrate receptors have been identified in endocrine cells present in the colonic crypts [121], the physiological significance of the presence of such receptors in the large intestine remains still unclear [3]. Propionate and butyrate have been shown to stimulate in vitro the production and secretion of PYY in human enteroendocrine cells partly through binding to free fatty acid receptors (FFAR) [122]. When delivery of propionate to the colon in volunteers was performed by oral ingestion of inulin-propionate, increased PYY and GLP-1 plasma concentrations were measured [123]. An infusion of acetate

in the distal colon of human subjects resulted in an increased circulating concentration of PYY [124] (Figure 4).

### 3.10 Acrolein affects intestinal barrier function while fecapentaenes are mutagenic in colonic epithelial cells

Among the bacterial metabolites present in reuterin, acrolein in excess has been shown to exert deleterious effect towards intestinal epithelial cells, affecting tight junction proteins, and damaging intestinal barrier function, resulting in increased intestinal permeability [125]. In regards with other bacterial metabolites derived from lipids, fecapentaenes present in the human feces, are produced by the intestinal microbiota from polyunsaturated ether phospholipids and represent potent mutagens towards colon epithelial cell DNA [126].

### 3.11 Several polyphenol-derived bacterial metabolites exert beneficial effects on the intestinal mucosa

Some data are available regarding the effects of the polyphenol-derived-bacterial metabolites on the host intestinal mucosa. The metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) has been shown to possess capacity for free radical scavenging [127]. In addition, DOPAC reduces the secretion of pro-inflammatory cytokines in mononuclear cells [128]. Thus, this bacterial metabolite displays interesting and beneficial potential considering its capacity to reduce events associated with the inflammatory processes. Regarding the other bacterial metabolite 3,4-dihydroxylbenzoic acid (also called protocatechuic acid (PCA), this compound has been shown in several preclinical experiments with animal models to reduce the severity of chemically induced colitis. Indeed, PCA given intraperitoneally reduces the severity of colitis in mice as attested by reduced damages to colonic mucosa, lower neutrophil infiltration, attenuated oxidative stress, and lower expression of genes coding for the pro-inflammatory cytokines IL-6, TNF-alpha, and IL-1beta in colonic tissues [129]. However, in this latter study, the administration of the bacterial metabolite PCA was done by peritoneal injection and not by the intestinal luminal way. Nevertheless, other studies have confirmed the potentially beneficial effect of PCA towards intestine. In the pig model, dietary PCA supplementation increased the expression of several tight junction proteins in the ileal epithelium [130], while dietary supplementation with this bacterial metabolite in rodents with colitis ameliorates the incidence of diarrhea and bleeding, as well as the histological aspect of the colon mucosa. Interestingly, this compound lowers the infiltration of neutrophils in the colonic mucosa, while it decreases the expression of the inducible form of nitric oxide synthase (iNOS) [131]. Overexpression of iNOS has been found in colonic samples obtained from patients with inflammatory bowel diseases [132]. Such iNOS overexpression in the colonic mucosa results in excessive production of nitric oxide which reacts with reactive oxygen species, forming strong oxidant like peroxynitrite [133].

Beneficial effects of polyphenols have been related to their capacity to decrease the concentration of deleterious metabolites by the large intestine microbiota. For instance, proanthocyanidin-containing polyphenol plant extracts reduce the production of $H_2S$ and ammonia by human fecal samples [134]. Furthermore, in rats, proanthocyanidin-containing polyphenol extract attenuates the increase of $H_2S$ concentration that is provoked in the large intestine by consumption of a high-protein diet [135]. These results are overall of interest as $H_2S$ and ammonia in excess, as presented above, inhibit the respiration of colonocytes [136]. Lastly, proanthocyanidin-containing polyphenol extracts from plant origin, as well as the bacterial metabolites derived from proanthocyanidins, namely 3-phenylpropionic acid, 3,4-dihydrophenylpropionic acid, and 4-hydroxyphenylacetic acid are all able to prevent the alteration of barrier function provoked by excessive concentrations of the tyrosine-derived bacterial metabolite p-cresol [66].

## 4. Conclusion and perspectives

As presented in this review, the results of pre-clinical studies clearly indicate that numerous metabolites produced from alimentary compounds by the intestinal microbiota are biologically active on the intestinal mucosa cells, notably on the intestinal epithelial cells. These effects are related notably to the metabolism of colonic absorptive colonocytes and on the physiological functions of the different cellular phenotypes present within the intestinal epithelium.

However, the experimental works performed are generally characterized by several limitations that need to be taken into consideration for future research. Firstly, the concentrations of the bacterial metabolites tested are not necessarily within the range of concentrations that are present in proximity of the intestinal epithelial cells [137]. Indeed, the bacterial metabolite concentrations used in experiments often refer to the concentration measured in feces which can be different when compared with the concentrations in the different segments of the intestine. This is an important aspect to be considered, as the effects of several bacterial metabolites on the intestinal mucosa, either beneficial or deleterious, depend on the concentrations tested. Secondly, the intestinal luminal fluid contains a complex mixture of bacterial metabolites that can exert additive, synergistic, or opposite effects on metabolism and functions of the intestinal mucosa cells. In fact, in most experimental works, the bacterial metabolites

are tested individually, thus making extrapolation from experimental works to "real life situation" difficult. In other words, experimental works are required regarding the test of mixture of bacterial metabolites mimicking the mixtures that are present within the intestinal luminal fluid for their effects on the different cell phenotypes that are present within the colonic crypts. Regarding this latter point, utilization of cultured mammalian colonic organoids represents a timely opportunity for performing such research work [138].

With these latter limitations in mind, schematically, it is feasible to classify the different bacterial metabolites as beneficial or deleterious, keeping in mind that some bacterial metabolites have been shown to be beneficial at one given concentration, and deleterious at higher concentrations. Bacterial metabolites can be considered as beneficial towards the intestinal mucosa if they contribute to the maintenance of the epithelial homeostasis, selective barrier function, normal endocrine activity, and appropriate immune response. Inversely, bacterial metabolites can be considered as deleterious when they are at excessive concentrations with adverse effects on the coordinated renewal of the epithelium, on the barrier function, on the normal physiological functions of the intestine, and if they participate in an inappropriate activation of the immune system.

However, at this step of discussion, it appears important to also consider the available data from a strictly “microbial point of view”. This point is related to the fact that, as presented in this review, several bacterial metabolites are implicated in the first place for communication between microbes of the same or from different species, either commensal (with no known pathogenicity) or conversely pathogenic. In addition, many bacterial metabolites exert bioactive effects on bacterial physiology. It is thus plausible that depending on substrate availability and on bacterial metabolic capacities, the profile of bacterial metabolites in the colonic fluid will participate in the microbiota composition.

Then, it can be considered that along the very long story of evolution, ways for intestinal microbes to communicate between each other have emerged, while it is also necessary to consider the interkingdom metabolic and physiological relationships between the microbes present in intestine and the intestinal mucosa. The role of the availability of alimentary compounds supplied by the host as a central player in these intra-and inter-kingdom communication has been reinforced by recent experimental works, as presented in this review. There is no doubt that progresses on that topic will depend on a constant research effort to further study the mechanisms that underpin such communication, and finally to document the ways to allow equilibrium between the intestinal microbiota and the intestinal mucosa of the lodging host.

Unfortunately, a limited number of dietary interventions has been made in volunteers to test the potential efficacy of modulation of the bacterial metabolic activity in different situations. In healthy situation, the results of such dietary intervention could help in defining, in a preventive strategy perspective, optimal personalized nutrition allowing to increase the beneficial over deleterious bacterial metabolite ratio. Such a strategy must consider the individual metabolic capacities and relative risk of different pathological processes. The same reasoning can be made regarding patients affected by diseases such as the chronic inflammatory bowel diseases for which a component related to an inappropriate metabolic activity of the intestinal microbiota has been suggested to be involved in disease development.

## Disclosure

The authors declare no conflict of interest.

## Authors' contributions

Both authors participated in the writing of the review. FB wrote the first draft that was annotated by XK.

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