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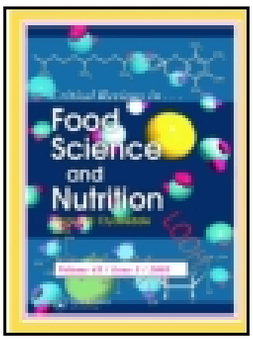

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Influence of functional food components on gut health

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Abstract

Intestinal epithelial cells (IECs) lining the gastrointestinal tract establish a barrier between external environments and the internal milieu. An intact intestinal barrier maintains gut health and overall good health of the body by preventing from tissue injury, pathogen infection and disease development. When the intestinal barrier function is compromised, bacterial translocation can occur. Our gut microbiota also plays a fundamentally important role in health, for example, by maintaining intestinal barrier integrity, metabolism and modulating the immune system, etc. Any disruption of gut microbiota composition (also termed dysbiosis) can lead to various pathological conditions. In short, intestinal barrier and gut microbiota are two crucial factors affecting gut health. The gastrointestinal tract is a complex

environment exposed to many dietary components and commensal bacteria. Dietary components are increasingly recognized to play various beneficial roles beyond basic nutrition, resulting in the development of the functional food concepts. Various dietary modifiers, including the consumption of live bacteria (probiotics) and ingestible food constituents such as prebiotics, as well as polyphenols or synbiotics (combinations of probiotics and prebiotics) are the most well characterized dietary bioactive compounds and have been demonstrated to beneficially impact the gut health and the overall well-being of the host. In this review we depict the roles of intestinal epithelium and gut microbiota in mucosal defence responses and the influence of certain functional food components on the modulation of gut health, with a particular focus on probiotics, prebiotics and polyphenols.

Keywords

bacterial translocation; functional food; gut health; gut microbiota; intestinal integrity

Introduction

The term “gut health” has been frequently used in the literature to generalize about a largely symptom-free bowel status. However, the concept of “gut health” is not well-defined in the literature and varies with different cultures- gut is considered as the location of soul in Asian medicine, on the other hand, as an organ merely for digestion and absorption in the West. Recent advances in the medicine discover that gut has much far-reaching impact, more than food processing and nutrient uptake, on the overall good health of the body: immune tolerance, defence against infections and signalling to the brain. With accumulating evidence from animal experiments and epidemiological studies, “gut health” is now regarded as a new objective in medicine, not only a target of treatment to widespread gastrointestinal disorders but also an approach to maintain status of well-being and resist illness. Bischoff (2011) defined “gut health”, based on World Health Organization (WHO) definition of health, as “a state of physical and mental well-being in the absence of gastrointestinal complaints that require the consultation of a doctor, in the absence of indications or risks of bowel disease, and in the absence of confirmed bowel disease”. Apparently, “gut health” is coined as a positive gut feeling and symptom-free status. However, from a scientific point of view, the definition is largely subjective and “gut health” defined in this way is hard to be measured with objective parameters. Over the years, gastrointestinal researches gathered enough evidence to suggest that two major criteria contribute to a healthy gut, namely intact gut barrier and balanced gut microecology. Structurally, gut (lower gastrointestinal tract) includes most of the small intestine and all of the large intestine, it consists of a stratified monolayer of differentiated epithelial cells of which columnar enterocytes are the most abundant cell type, laying down the basic architecture of the gut. This continuous layer of intestinal epithelial cells (IECs) is an important site of defence barrier, physically and biochemically, against foreign substances, such as bacteria, toxins and allergens. The intestinal barrier is more than a mechanical barricade; it also takes part in intestinal immune responses via secretion of cytokines, chemokines, antimicrobial peptides (AMPs) and mucins. The physical and

immunological integrity of this intestinal barrier, therefore, plays a key role in regulating gut health. The gut, mainly the large intestine, is infested with a complex community of around 100 trillions (10^{14}) commensal bacteria. This large reservoir of intestinal bacteria, variously known as microbiota, microbiome, microflora or microecology, is another key factor regulating gut health. Sufficient evidence vindicates that microbial imbalance (dybiosis) undermines intestinal defence system (Dethlefsen et al. 2008, Jeong et al. 2009). Interrelationship between intestinal barrier and gut microbiota exists: in one way, a functional intestinal barrier can regulate the diversity of bacterial species, counteracting harmful bacteria and cooperating with beneficial ones; and in reverse, the microbiota can alter the intestinal barrier integrity by modulating the innate immune system (Sharma et al. 2010). In short, intestinal barrier and gut microbiota are two crucial factors affecting gut health: any intervention to barrier integrity or microbiota composition risks gastrointestinal disorders.

Role of intestinal epithelium in mucosal host defence responses

The intestinal mucosa has the largest body surface of around 300 m^2 in the greatest contact with the external environment in human adults, which protects the body against potential harmful substances, viruses, microorganisms or antigens. Furthermore, the human intestine is considered as one of the most densely populated microbial ecosystems on Earth, with up to about 10^{14} bacteria in colons per person (10 times more bacteria than the total number of human cells in the body) and consists of 500 to 1000 species including both pathogenic and health-promoting microorganisms. It is the metabolism in the intestinal epithelia together with the complex and diverse microbial ecosystem, which influence variably the overall bioavailability and also the pharmacological activity of various drugs and xenobiotics.

Intestinal epithelium is covered by a highly organized single layer of IECs, which forms an interface between the lamina propria (internal environment) and the gut lumen (external environment). In the past, the intestinal epithelium was considered as a structure simply for digestion and absorption, and

as a physical barrier against environmental insults. In recent years, studies showed that intestinal epithelium is also a regulator to innate and adaptive immune responses, likely through interaction with the underlying immune cells and the microbiota (Madsen 2012, Peterson and Artis 2014). Gut needs to harbour beneficial microbes but keep pathogens at bay. To accomplish this apparently contradicted task (nurture versus kill; segregation versus coexistence) in such a dynamic environment, IECs should be able to sense, distinguish and react differentially to microbial stimuli; initiate proper immune responses against only the pathogens but not beneficial bacteria; and meanwhile, maintain barrier function at all time. In short, the IEC-mediated defence system needs to coordinate three functionalities adequately, including barrier, sensor and mediator, in order to maintain gut health (Figure 1).

Functional entities of intestinal barrier

As mentioned above, IECs are the primary cell types that form a biochemical and physical barrier, which maintain segregation between luminal and external environments by preventing infiltration of microorganisms, toxins and antigens. Breach of barrier integrity and normality leads to intestinal hyper-permeability which is more commonly known as “leaky gut”, indicating a loss of selective permeability of the intestinal epithelium. It is tempting to assume that the non-specific mechanical/ physical barriers, such as tight junctions (TJ) and mucins, are equivalent to the whole intestinal barrier. However, the entire intestinal barrier is far more than a passive physical barricade. Various biological and structural components work together as a proactive barrier, which is capable of launching attack against harmful intruders suitably (Peterson and Artis 2014). In a broad sense, an effective and functional intestinal barrier encompasses three components, namely mechanical barrier, immunological barrier and ecological barrier. Functional entities of different barrier components orchestrate, solely or interactively, to achieve gut health (Figure 2).

Intestinal barrier dysfunction & bacterial translocation

A functional intestinal barrier is the key to gut health, barricading the body from microbes, toxins and allergenic proteins. Any impairment of the intestinal barrier risks infectious, inflammatory and functional intestinal diseases. Normally, the intestinal barrier is very effective- the luminal side is heavily infested with more than 10^{12} microbes per millilitre of faecal materials, but the basolateral side (portal blood and mesenteric lymph nodes) is virtually sterile. Insults from the external environment, such as food toxins, drugs and pathogens, can undermine intestinal integrity (Figure 3). Consequently, bacteria could easily translocate across the intestinal epithelium, leading to gastrointestinal diseases, such as Crohn's disease, Celiac disease, duodenal ulcer disease, acute pancreatitis, infectious diarrhoea or inflammatory bowel disease; or much far-reaching extra-intestinal disorders, for instance, systemic inflammatory response syndrome, sepsis, arthritis, steatohepatitis or multiple organ dysfunction syndrome (Balzan et al. 2007, Bischoff 2011).

The passage of indigenous intestinal bacteria, as well as endotoxins or antigens, through the intestinal epithelia into sterile tissues is defined as "bacterial translocation". The term was first coined in 1979 for detecting *E. coli* in the mesenteric lymph nodes in mice (Berg and Garlington 1979). The gut is literally a reservoir of microbes and endotoxins; it is incumbent upon a functional intestinal barrier to confine these harmful substances from infiltration across the intestinal epithelia. A balanced microbiota maintains gut health; nevertheless, these microbes could potentially be a source of infection if they translocate (Farhadi et al. 2003). Under normal physiological condition, bacteria are mostly prevented from translocation. In case of bacterial penetration, patrolling phagocytes can easily get rid of the intruders (Farhadi et al. 2003). However, insults from drugs, toxins, stress or pathogens can undermine the intestinal barrier function, facilitating bacterial translocation. For example, *Campylobacter jejuni*, a pathogenic bacterium capable of disrupting TJ (Chen et al. 2006), induces translocation of commensal bacteria *in vitro* and *in vivo* (Kalischuk et al. 2009). Plenty of evidence showed that bacterial translocation predisposes one to gastrointestinal diseases as well as other infectious complications that may cause

multiple organ dysfunction syndrome or even death (Farhadi et al. 2003, MacFie 2004). Intestinal hyperpermeability is the only clinical predictor to the syndrome, with death rate positively correlated to the level of hyperpermeability. Bacterial translocation, depending on bacterial species and physiological conditions, can be paracellular (between cells) and/or transcellular (through cells) (Figure 4) (Kalischuk et al. 2009). Paracellular translocation (aka TJ translocation) is normally restricted by the TJ. Intestinal hyperpermeability promotes paracellular translocation: bacteria were observed within the paracellular space of undermined enterocyte monolayer (Nazil et al. 2004). Transcellular migration, on the other hand, involves endocytosis and intracellular trafficking, and it is regulated by specific membrane pumps and channels (MacFie 2004, Balzan et al. 2007). In general, drugs (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs)), pathogens (e.g. *Vibrio cholera*) and food toxins (e.g. mycotoxins) are two key risk factors leading to intestinal hyperpermeability. However, these have been described in another review by (Groschwitz and Hogan 2009) and thus would not be discussed further in this review.

Role of gut microbiota for maintaining health

The mammalian intestine is home to a complex and dynamic community of trillions of microorganisms comprising hundreds of species. These microorganisms are usually referred to as commensal microflora (normal microflora, indigenous microbiota), which are separated from the internal milieu by a single layer of epithelial cells. Commensal bacteria colonize its host immediately after birth and are essential to host development and health. Its composition is species-specific, and varies among individuals and within the same individual throughout life. There are many factors that can influence the gut microbiota composition, including diet, age, medications, illnesses, stress and lifestyle. Microbes in our gut outnumber the total body cells by more than ten times. They are essential components to a healthy body-assisting digestion, modulating immune system and even treating diseases, such as cancer (Tremaroli and Backhed 2012, Pennisi 2013). This microbial community is dominated by bacteria (others

include archaea and fungi), with *Firmicutes* and *Bacteroidetes* being the most abundant species (Tremaroli and Backhed 2012).

Maintenance of a balanced microbial ecosystem is crucial for gut health as an ecological barrier to the external insults. A disruption to this micro-ecology, technically coined as intestinal dysbiosis (disequilibrium in microbiota), impairs intestinal homeostasis and results in excessive growth of some harmful bacteria known to promote colon carcinogenesis via chronic inflammation or local immune-suppression (Wu et al. 2011). Studies from germ free (born and raised in the absence of all microbes) rodents have also demonstrated that absence of gut microbiota resulted in defects in tissue formation, compromised cellular and molecular profiles of intestinal immune system, which rendered the animals usually susceptible to infections (Salzman et al. 2007, Lee and Mazmanian 2010). These animals have reduced mucosal turnover, vascularity, lamina propria cellularity, digestive enzyme activity, muscle wall thickness, cytokine production and serum immunoglobulin levels, smaller Peyer's patches and fewer intraepithelial lymphocytes, but increased enterochromaffin cell area and calorie intake to maintain body weight. However, re-colonization of germ-free mice with intestinal microflora is sufficient to restore the mucosal immune system.

Although diversity of the microbiota varies with people, studies indicated that a core set of gut colonizers is shared among healthy people. A man is virtually a human-microbial "super-organism", in need of microbiota to subsist and thrive. All these findings underscore a functional commensal microbiota as an "ecological" barrier to gut health.

Dietary intervention for maintaining health

Instead of taking drugs, in which some cases like NSAIDs that could possibly do more harm than good, to treat gastrointestinal diseases, dietary intervention with functional foods has wide opened a window of opportunity for gut health. It is not without a good reason that functional foods are justified

alternatives to drugs- probiotics, prebiotics and polyphenols are three well-known cases in point. Probiotics and prebiotics can modulate gut microbiota to enhance the intestinal immune system; and polyphenols, on the other hand, are renowned for their anti-inflammatory activities (Shimizu 2010, Magrone et al. 2014). Other dietary components (e.g. vitamins and minerals) and food-derived chemicals by microbiota (e.g. short-chain fatty acids and bioactive peptides) are attention-getting, but their function remains largely unclear.

Probiotics

Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit for the host" by United Nations and WHO (FAO/WHO 2002). In this sense, a bacterium (or any microbe) needs to be isolated, purified, characterized, and proved to be beneficial to health when administered before it can be designated as a probiotic. Strains deemed successful — in terms of the ability to survive passage through the upper gastrointestinal tract, proliferate, colonize and function in the gut- are mostly of human origin (Saarela et al. 2000, Reuter 2001). In a recent review, some 31 most commonly used strains are listed: *Lactobacillus* (13 species) and *Bifidobacterium* (8 species) are among the most prevalent, and the rest of them are species from *Enterococcus*, *Lactococcus*, *Leuconstoc*, *Pediococcus*, *Streptococcus*, *Escherichia* and *Saccharomyces* (Saad et al. 2013). *Lactobacillus* and *Bifidobacterium* have a very long research history: the first record was as early as 1800s (by Dr. Metchnikoff) and 1900s (by Dr. Tissier), respectively (Gordon 2008). *Lactobacilli*, belonging to a heterogeneous group of lactic acid bacteria, are Gram-positive, catalase-negative and non-spore-forming. They are in either rod or coccobacilli shape and produce lactic acid as the main end-product of carbohydrate fermentation (Felis and Dellaglio 2007). *Bifidobacteria*, mistakenly known as *Lactobacillus bifidus* before 1960s and incorrectly listed among lactic acid bacteria, are Gram-positive, catalase-negative, non-spore-forming, non-motile, non-filamentous and anaerobic. They are polymorphic

branched rods occurring singly, in chains or clusters, and produce predominantly lactic acid and acetic acid as the main end-products of carbohydrate fermentation (Felis and Dellaglio 2007).

A body of evidence supports multi-functional health effects of probiotic intervention, yet a barrage of criticisms or doubts over probiotic supplementation is accompanied (Boyle et al. 2006). There is an array of claims (or assertion) upon probiotic consumption: from the sensible ones, such as mitigating diarrhoea or alleviating irritable bowel syndrome, to the rather extraordinary ones, such as abating symptoms of common colds or reducing absence from work (Lenoir-Wijnkoop et al. 2007). It is believed that probiotics mediate their beneficial effects either by the whole microbes (viable or dead) or through various bioactive components, including bacterial cell wall structures (e.g. proteins, polysaccharides or lipoteichoic acids), microbial nucleic acids, secretions (e.g. antimicrobial proteins or other soluble proteins), metabolites (e.g. organic acids or short-chain fatty acids) and other less soluble factors (Johnson-Henry et al. 2007, Lewis et al. 2010, Stetinova et al. 2010, Saad et al. 2013). It explains why studies using spent culture supernatant from probiotics, instead of probiotics themselves, showed positive immuno-modulatory properties (Ewaschuk et al. 2008, Paszti-Gere et al. 2012). Probiotics can improve gut health and prevent pathogen- or chemical-induced intestinal barrier dysfunction by stimulating the secretion of mucins, AMPs or secretory immunoglobulin A (sIgA), enhancing the TJ, or modulating the microbiota (Ohland and MacNaughton 2009, Wan et al. 2016).

Probiotics are mostly reassuring (generally recognized as safe) and overall have a very good safety record as reviewed (Ishibashi and Yamazaki 2001). However, there are still heated debates over their safety — worrying about the potential feasibility of bacterial translocation and virulence, especially the risk of sepsis in immune-compromised patients (Boyle et al. 2006). Physicians remain skeptical as cases of probiotic sepsis in humans or in experimental animals were occasionally reported (Wagner et al. 1997, Boyle et al. 2006). While some food technologists strive for safer probiotic strains, others switch their attention to other functional foods- prebiotics or polyphenols for example.

Prebiotics

Prebiotics were first defined in 1995 as "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria already resident in the colon" (Gibson and Roberfroid 1995). In order to classify a food ingredient as a prebiotic, it has to fulfil (1) resistance to gastric acidity, and mammalian enzymes, and absorption in the upper gastrointestinal tract; (2) susceptibility to be fermented by gut microbiota; and (3) ability to stimulate the growth and/ or activity of beneficial intestinal bacteria (Gibson and Roberfroid 1995). It is documented that there are numerous health benefits for prebiotics which include reducing the prevalence and duration of infectious and antibiotic-associated diarrhoea; reducing risks of cardiovascular disease and colon cancer; alleviating the inflammation and symptoms associated with inflammatory bowel diseases; and promoting satiety and weight loss and preventing obesity (Slavin 2013). The beneficial effects of prebiotics primarily depend on their impact on the gut microbiota composition and derived metabolites, although their own structure and direct action (e.g. inhibition of pathogen adhesion due to their homology structure with bacterial receptors) may also play certain roles. The usual target bacterial genera for prebiotics are lactobacilli and bifidobacteria. Fructooligosaccharides (FOS) and inulin, lactulose and galactooligosaccharides (GOS) are all popular prebiotics and are commercially available. These oligosaccharides can alter gut microbiota towards a more beneficial composition, with increased numbers of bifidobacteria in particular (Laparra and Sanz 2010). For example, GOS, non-digestible oligosaccharides derived from lactose naturally found in human milk, can stimulate the growth of bifidobacteria (Laparra and Sanz 2010). Moreover, GOS may inhibit enteric pathogen adhesion and infection by structurally mimicking the pathogen binding sites on the surface of gastrointestinal epithelial cells (Shoaf et al. 2006). Inulin and its hydrolytic product (oligofructose), on the other hand, can modulate gut microbiota composition, prevent pathogens adhesion and colonization, trigger anti-inflammatory effects, decrease food intake, modulate bowel habits, and regulate lipid and glucose metabolism (Laparra

and Sanz 2010). Most of these effects are mainly due to their structural resistance to mammalian digestive enzymes and their ability to trigger the growth of beneficial bacteria in the colon and increase the production of short chain fatty acids (SCFAs) (Meyer and Stasse-Wolthuis 2009). SCFAs are important energy sources for the colonocytes and they play a role in regulating intestinal permeability. In particular, butyrate (2 mM) significantly enhanced the intestinal integrity by augmenting TEER of a Caco-2 cell monolayer (Peng et al. 2007). It was later suggested that butyrate facilitated TJ assembly via modulation of AMP-activated protein kinases (Peng et al. 2009). In addition, butyrate (2 mM), as well as acetate (8 mM) and propionate (4 mM), could partially restore ethanol-induced barrier dysfunction via AMPK signaling pathway (Elamin et al. 2013).

Furthermore, there are certain other non-starch polysaccharides such as cellulose, dextrins, chitins, pectins, beta-glucans, and waxes and lignin that can exert similar beneficial effects as those of inulin-type fructans by regulating the transit time through the gut. Other than altering the gut microbiota compositions, these dietary soluble fibres have also been found to improve gut barrier function and regulate gut microbiota composition in a number of *in vivo* studies (Durmic et al. 1998, Gómez-Conde et al. 2007, Gómez-Conde et al. 2009, Chen et al. 2013).

Polyphenols

Polyphenols are widely present in plant-based foods and beverages, for example, fruits, vegetables, red wine, coffee and tea, with daily consumption estimated at up to several hundred milligrams. Studies showed that polyphenols can prevent diseases associated with oxidative stress, such as cardiovascular diseases, cancers, inflammation, neurodegenerative diseases and diabetes (Nijveldt et al. 2001, Scalbert et al. 2005). It is suggested that the beneficial effects of polyphenols rely on their anti-oxidative, anti-microbial, anti-carcinogenic, cardio- and neuro-protective activities (Middleton et al. 2000). Recent studies revealed that polyphenols can interfere with xenobiotic-metabolizing enzymes

(Sergent et al. 2009) or interact with drugs (Yang and Pan 2012), food toxins (Sergent et al. 2005), and other nutraceuticals (e.g. probiotics) (Bustos et al. 2012) to yield deleterious or beneficial outcomes. For example, naringenin (a predominant flavanone in grapefruit) could increase drug (e.g. felodipine and verapamil) toxicity by inhibiting intestinal cytochrome P450 3A4, a detoxifying enzyme; quercetin (a flavonol rich in onion) induced cellular accumulation of ochratoxin A (a food-borne mycotoxin) in the Caco-2 cells by competitively inhibiting multidrug resistance-associated proteins efflux pumps. All these findings stressed a need to further characterize the interaction between polyphenols and other ingested substances, such as drugs, nutrients, xenobiotics, food contaminants, etc.

Humans lack polyphenol-specific digestive enzyme, intestinal catabolism of polyphenols is attributed to fermentation by the digestive microflora. Over 90% of dietary polyphenols pass through the upper gastrointestinal tract without absorption. Unabsorbed polyphenols accumulate in the colon, where most of them are extensively metabolized by the intestinal microbiota. The metabolic pathway varies with different polyphenols and microbiota composition, but in general, it starts firstly with deconjugation or hydrolysis (the cleavage of glycosyl or other moieties from the phenolic backbone) to yield aglycones or monomers. The products then undergo further transformation, such as fission (ring or lactone), reduction, dehydroxylation, demethylation, decarboxylation and/ or isomerization, to produce wide ranges of microbial polyphenol metabolites, mainly aromatic acids (Aura 2008, Selma et al. 2009). As a result, the microbiota metabolites of polyphenols are more readily absorbed in the intestine, and their enterohepatic circulation ensures the extension of the residence time in the plasma compared to that of their parent compounds and is ultimately excreted in urine (Laparra and Sanz 2010).

Most human cells are exposed to dietary polyphenols, if any, at a very low level of conjugated forms, except for the cells lining the gastrointestinal tract. Gut cells are constantly and directly exposed to a high dose of dietary polyphenols in both native and modified forms. Also, polyphenols represent the only antioxidants of dietary source in the hindgut, particularly in the colon, since vitamins and most

carotenoids are absorbed in the foregut. Therefore, dietary polyphenols can exert immense effects, locally and systemically, on gut health.

Polyphenols represent an enormous pool of chemicals. Some estimate the total number of polyphenols at around 8000, others consider more. Polyphenol-mediated modulation to the intestinal inflammatory responses is well-studied *in vitro* and *in vivo* (for review, see (Romier et al. 2009)), it is suggested that polyphenols can suppress inflammation of enterocytes via multiple ways: modulation of the mitogen-activated protein kinase (MAPK), protein kinase B (Akt) or nuclear factor kappa B (NF-κB) signalling pathways; inhibition to the inflammatory cytokines and chemokines production; suppression against the cyclooxygenases (COX) or inducible nitric oxide synthase (iNOS) activities; as well as reduction in the production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) (Veres 2012). For example, resveratrol ameliorates colonic inflammation in mice by reducing tumour necrosis factor (TNF)-α and interleukin (IL)-1β gene expression and secretion (Sanchez-Fidalgo et al. 2010). Moreover, it was proven that isoflavone metabolites produced by gut microbiota exhibit different anti-inflammatory properties (Park et al. 2007). Previous *in vitro* and *in vivo* experiments have shown that quercetin exerts a bigger anti-inflammatory effect than quercitrin, which is mediated through the inhibition of the NF-κB pathway (Comalada et al. 2005). On the contrary, studies of polyphenol-mediated effects on intestinal TJ remain limited, only a few polyphenols (less than 20) were tested (Table 1), representing less than 1% of all known polyphenols. With the exception of cytokines, polyphenol-mediated effects on the intestinal secretion of mucins (D'Agostino et al. 2012), AMPs (Wan et al. 2016) or sIgA are scarcely reported, let alone protective effects of polyphenols against bacterial translocation. Apparently, the role of polyphenols in intestinal integrity is a largely unexplored terrain.

Furthermore, it is increasingly recognized that health benefits attributed to polyphenols may be associated with modification of gut microbiota composition. Polyphenols may promote growth, proliferation, or survival for beneficial bacteria- mainly lactobacilli-and thus, exerting prebiotic-like

effects. Polyphenols may also inhibit the growth of certain pathogenic bacteria such as *Salmonella* and *Helicobacter pylori* species (for review, see (Hervert-Hernández and Goñi 2011)). Therefore, polyphenols may potentially confer health benefits to the host via modulation the gut micro-ecology. However, the effects of interaction between polyphenols and particular gut microbiota functions remain largely unexplored.

Other dietary components & food-derived chemicals

Apart from probiotics and polyphenols, other dietary components and food-derived chemicals by microbiota are suggested to pose positive effects on intestinal barrier function. Vitamins are potent antioxidants: it was shown that dietary supplementation with vitamin E ameliorated hypoxia-induced intestinal damage in rats (Xu et al. 2014). Also, in a double-blind trial conducted in Brazil, children prescribed with vitamin A, zinc and glutamine showed improved intestinal barrier function, possibly via interaction with leptin (Lima et al. 2014). Dietary polysaccharides from wild jujube were shown to alleviate 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced intestinal barrier dysfunction in rats via modulation of TNF-α, IL-1β, IL-6 and myeloperoxidase (MPO) activities; and in the same study, the polysaccharides facilitated assembly of TJ proteins in Caco-2 cells stimulated with TNF-α (Yue et al. 2015). Moreover, dietary polyunsaturated fatty acids, particularly n-3, were shown to reduce intestinal permeability during colitis, likely through anti-inflammatory action or modulation of TJ protein expression (Knoch et al. 2010).

Proteolysis of dietary proteins *in vivo* (by digestive enzymes or microbiota) or *in vitro* (via food processing) leads to the generation of bioactive peptides (Martinez-Augustin et al. 2014). In a recent review, effects of some bioactive peptides (e.g. casein enzymatic hydrolysate) on intestinal barrier function are summarized (Martinez-Augustin et al. 2014). It was documented that bioactive peptides can enhance intestinal barrier in multiple ways: increasing mucus secretion, stimulating sIgA secretion,

stabilizing TJ or modulating cytokine production. Nevertheless, as concluded in the same review paper, many factors remain unsolved. Further studies are required to characterize the responsible peptides and elucidate mode of action (Martinez-Augustin et al. 2014).

Effect of other phytochemicals apart from polyphenols on intestinal barrier function remains mostly unexplored. Berberine, a plant alkaloid, exhibited no effect on the permeability of HT-29/B6 cell monolayer. However, berberine ameliorated TNF-α-induced barrier dysfunction *in vitro* and in rat colon by preventing claudin-1 disassembly, apparently via tyrosine kinase, pAKt and NF-κB signaling pathways (Amasheh et al. 2010). However, not all phytochemicals are gut-friendly. Capsianoside, a diterpene glycoside found in sweet pepper, undesirably increased TJ permeability in the Caco-2 cell monolayer (Hashimoto et al. 1997). Phytochemicals and their derived products, on the other hand, can also affect the intestinal micro-ecology due to the fact that a majority of them are not fully absorbed and metabolised in the liver, excreted through the bile as glucuronides and thus are accumulated in the ileal and colorectal lumen (Laparra and Sanz 2010).

Conclusion

The intestinal barrier is one of the most important interfaces connecting a person to his or her external environment. An intact intestinal barrier and balanced microbiota is crucial for maintaining health and preventing a person from tissue injury and diseases. It is evident that dietary modifiers, including the consumption of live bacteria (probiotics) and ingestible food constituents such as prebiotics, as well as polyphenols or synbiotics (combinations of probiotics and prebiotics) have been demonstrated to influence the gut health and the overall well-being of the host. Since the intestinal barrier is a very complex environment, it is important to understand the interaction between different components of the intestinal barrier when developing preventive or therapeutic strategies for enhancing barrier integrity and maintaining gut microbiota composition using dietary components.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

None

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Table 1. Polyphenol-mediated TJ regulation, *in vitro*, *ex vivo* & *in vivo*

PPs (Dosages)	**Cells/ Models** **(Stimulants, if any)**	**Effects/ Key findings**	**Refs.**
Quercetin	Caco-2	● Quercetin (>100 µM) increases TEER significantly.	(Amasheh et al. 2008)
(50, 100, 150 & 200 µM)		● It increases claudin-4 protein expression.	

Quercetin, Myricetin (10, 30 & 100 µM)	Caco-2	● Quercetin (not myricetin) enhances intestinal barrier function through assembly of claudin-1, ZO-2, & occludin by inhibiting PKC; & increases claudin-4 protein expression.	(Suzuki and Hara 2009)
Apple PPs	T84	● They increase TEER in both stimulated & non-stimulated cells.	(Rogoll et al. 2010)

(Catechin, Epicatechin, Quercetin, Phloretin etc.)	(Sodium caprate)	● They alternate gene expression of ZO-1, occludin & claudin-4.	
(10–80 μM)			
Berberine	HT29/B6	● Berberine prevents TNFα-induced claudin-1 disassembly and upregulation of claudin-2.	(Amasheh et al. 2010)
(50 μM)	(TNF-α)		

Berberine	Mice	● Berberine reduces the permeability of the gut barrier in endotoxinemia	(Gu et al. 2011)
	(Lipopolysaccharide)	● It partially reverses the redistribution of claudin-1, claudin-4, ZO-1 and occludin.	

Kaempherol	Caco-2	● Kaempherol increases TEER dose-dependently.	(Suzuki et al. 2011)
(10, 30 & 100 µM)		● It promotes assembly of ZO-1, ZO-2, occludin, claudin-1, 3 & 4.	
		● It increases ZO-2 & claudin-4 protein expression.	

Chrysin, Daidzein,	Caco-2	● Chrysin decreases TEER; daidzein, hesperetin, naringenin & morin increase TEER; luteolin and genistein increase or normalize TEER after a transient decrease.	(Noda et al. 2012)

Hesperetin, Naringenin,		● They affect distribution and expression of ZO-1, ZO-2, occludin, JAM-1 & claudins differentially.	
Morin, Luteolin, Genistein			
(100 µM)			
Quercetin	HT-29/B6	● Quercetin does not affect TEER of unstimulated cells.	(Amasheh et al. 2012)

(50, 100 & 200 µM)	Rat intestine *ex vivo*	● It reduces claudin-2 protein expression.	
	(TNFα)	● It partially restores TNFα - induced mucosal resistance drop by inactivating claudin-2 promoter activity.	

		● It increases resistance in rat intestine *ex vivo*.	
Quercetin (33 & 66 µM),	Caco-2	● Quercetin, EGCG & resveratrol (but not rutin) prevent indomethacin-induced TEER drop.	(Carrasco-Pozo et al. 2013)

EGCG (218 µM),	(Indomethacin)	● Quercetin prevents downregulation of ZO-1 & occludin gene expression; & inhibits ZO-1 redistribution induced by indomethacin.	
Rutin (164 µM),			
Resveratrol (438 µM)			

Naringenin	Mice	● Naringenin partially reduces DSS-induced symptoms by preventing downregulation of occludin, JAM-A & claudin-3 expression.	(Azuma et al. 2013)

(diet of 0.3% wt/wt)	(Dextran sulfate sodium)	● It ameliorates DSS-induced colitis by modulating expression of cytokines.	
Curcumin, Quercetin,	Mice	● They ameliorate DSS-induced colitis by restoring ZO-1, occludin, JAM-A & claudin-3 expression.	(Shigeshiro et al. 2013)
Naringenin, Hesperetin	(Dextran sulfate sodium)		
(diet of 0.3% wt/wt)			

Berberine	Caco-2	● Berberine significantly attenuated IFN-γ and TNF-α induced TEER decrease and paracellular permeability increase.	(Cao et al. 2013)

	(IFN-γ and TNF-α)	● Berberine could prevent the reorganization of ZO-1, occludin and claudin-1 induced by IFN-γ and TNF-α.	
Biochanin A, prunetin	Caco-2	● They improves TEER.	(Piegholdt et al. 2014)

	(TNF-α)	● They reduced tyrosine phosphorylation of scaffolding protein ZO-1.	
6-gingerol	Caco-2	● 6-ginerol improved TEER.	(Chang and Kuo 2015)
(0, 1, 5, 10, 50, and 100 μM)	(Dextran sulfate sodium)		
Theaflavins-3'-O-gallate	Caco-2	● Theaflavins-3'-O-gallate significantly increases both the mRNA and protein expression of TJ-related proteins (occludin, claudin-1, and ZO-1)	(Parka et al. 2015)
(20 μM)			

Resveratrol (50 μM)	IPEC-J2	● RES could protect DON-induced bacteria translocation because of enhanced of intestinal barrier function by restoring the DON-induced decrease in transepithelial electrical resistance and increase in paracellular permeability	(Ling et al. 2016)

	(Deoxynivalenol)	● RES protects against DON-induced barrier dysfunction by promoting assembly of claudin-4 to the TJ complex	

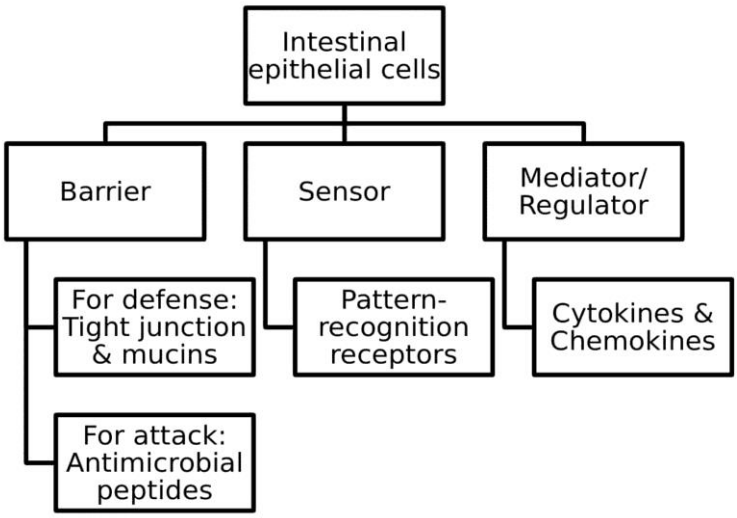

Figure 1. Basic functionalities of IECs in immune defense responses.

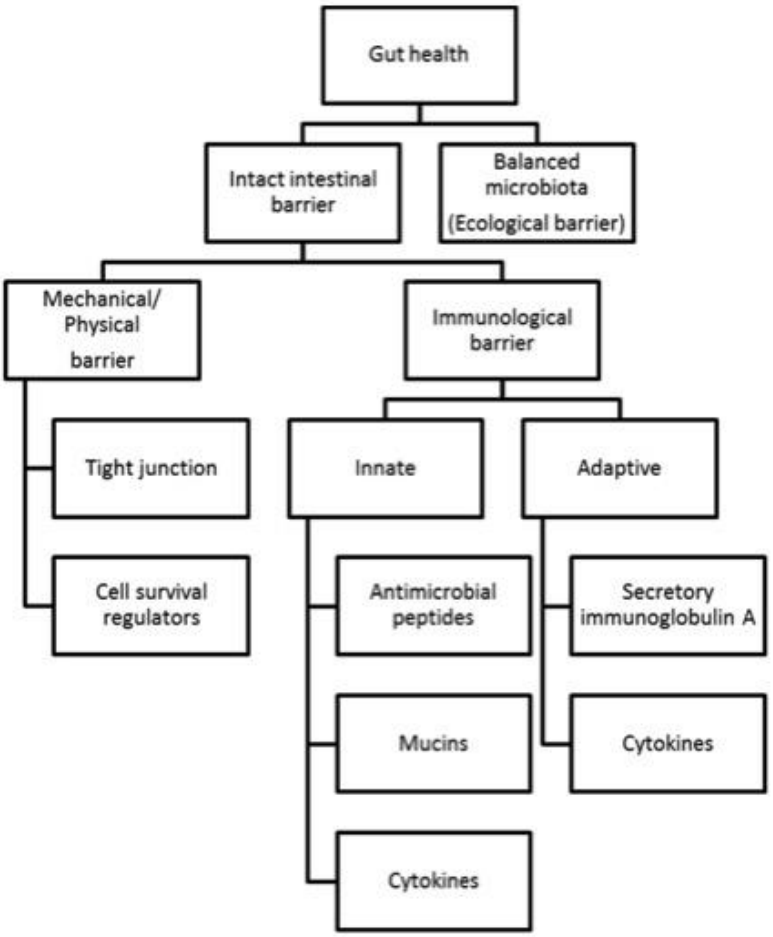

Figure 2. Functional entities of intestinal barrier.

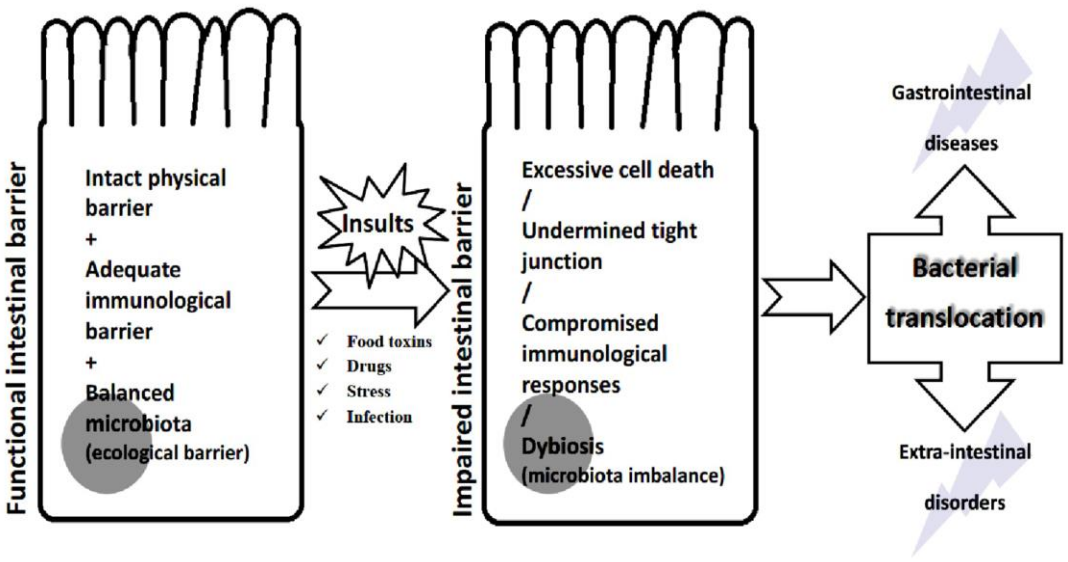

Figure 3. Schematic causation of bacterial translocation.

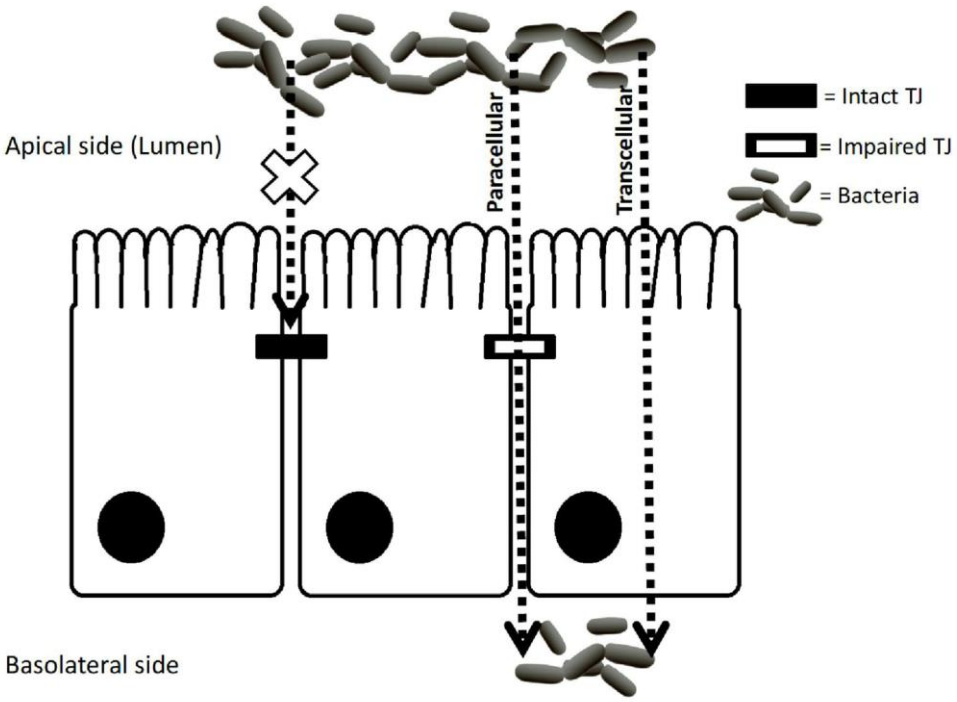

Figure 4. Routes of bacterial translocation.