

Beneficial effects of *Saccharomyces boulardii* CNCM I-745 on clinical disorders associated with intestinal barrier disruption

Chloe Terciolo^{1,2}
Michel Dapoigny³
Frederic Andre⁴

¹INRA, UMR 1331 Toxalim, Research Center in Food Toxicology, F-31027 Toulouse, France; ²Aix-Marseille Université, INSERM, UMR 911, CRO2, Marseille, France; ³Médecine Digestive, CHU Estaing, CHU Clermont-Ferrand, Université Clermont Auvergne, INSERM UMR 1107, Neuro-Dol, Clermont-Ferrand, France; ⁴Centre de Recherche en Cancérologie de Marseille (CRCM), INSERM U1068, CNRS UMR 7258, Aix-Marseille Université and Institut Paoli-Calmettes, Parc scientifique et technologique de Luminy, Marseille, France

Abstract: Intestinal barrier defects lead to “leaky gut syndrome”, defined as an increase in intestinal permeability that allows the passage of luminal content into intestinal tissue and the bloodstream. Such a compromised intestinal barrier is the main factor underlying the pathogenesis of inflammatory bowel disease, but also commonly occurs in various systemic diseases such as viral infections and metabolic syndrome. The non-pathogenic yeast *Saccharomyces boulardii* CNCM I-745 has demonstrated its effectiveness as a probiotic in the prevention and treatment of antibiotic-associated, infectious and functional diarrhea. Via multiple mechanisms of action implicated in intestinal barrier function, *S. boulardii* has beneficial effects on altered intestinal microbiota and epithelial barrier defects in different pathologies. The well-studied probiotic yeast *S. boulardii* plays a crucial role in the preservation and/or restoration of intestinal barrier function in multiple disorders. This could be of major interest in diseases characterized by alterations in intestinal barrier function.

Keywords: *Saccharomyces boulardii* CNCM I-745, apical junctional complex, leaky gut syndrome, intestinal barrier function, intestinal permeability, tight junctions

Introduction

In the human body, the gastrointestinal tract represents the largest surface area exposed to the external environment. The intestinal epithelium has a dual function, acting on one hand as an exchange surface between luminal nutrients, molecules produced by the intestinal microbiota and intestinal tissue, and on the other hand as a barrier to prevent the entry of and protect the tissue from external harmful substances such as pathogenic toxins and antigens.¹ This barrier is formed by the interconnection of epithelial cells via the apical junctional complex and desmosomes.² Its disruption leads to an increased intestinal permeability that facilitates translocation of luminal contents into the intestinal tissue and bloodstream, a situation referred to as “leaky gut syndrome”.³ A significant body of evidence indicates that such disruption plays a crucial role in intestinal diseases such as inflammatory bowel diseases (IBDs) and irritable bowel syndrome (IBS), but more research evidence highlights that it also occurs in certain systemic diseases, including type 2 diabetes, obesity and HIV infection. The maintenance of intestinal barrier integrity is essential to the preservation of gastrointestinal homeostasis and could be of major importance in the treatment of various diseases and in the prevention of severe complications.^{3,4} The lack of published studies on the beneficial effects of other strains of *Saccharomyces boulardii* prompted us to focus on a specific strain of *Saccharomyces boulardii*, CNCM I-745 (*S. boulardii*). We

Correspondence: Chloe Terciolo
INRA Toxalim, 180 chemin de
Tournefeuille, 31300 Toulouse, France
Tel +33 60 146 2483
Email chloe.terciolo@gmail.com

summarize the clinical effects of *S. boulardii* on intestinal barrier function in gastrointestinal and systemic diseases, followed by a discussion of the mechanisms by which *S. boulardii* modulates intestinal permeability.

Intestinal barrier function

The intestinal epithelium functions as a barrier, preventing and controlling the penetration of food and bacterial antigens into the tissue. At the same time, it has to be permeable to allow the translocation of nutrients, electrolytes and water. This intestinal permeability allows the exchange of solutes and fluids between the intestinal lumen and tissue⁵ and is mediated by two pathways: the transcellular pathway, which is generally associated with the transport of solutes by specific transporters present in the cell membrane, and the paracellular pathway, which is associated with the transport of small molecules in the space between epithelial cells.⁶ Permeability can be assessed by different techniques in vitro and in vivo, in animal and human studies, respectively. In vitro assessments include the measurement of transepithelial resistance (TER) or macromolecular flux in Ussing chambers, morphological measurements of tight junction (TJ) components, and measurement of the polyethylene glycol profile to characterize pore pathways. In vivo approaches consist of the oral ingestion of probes (lactulose/mannitol) followed by their measurement in urinary excretion.⁵ The integrity of the intestinal barrier is essential for intestinal homeostasis and is maintained by the presence and correct functioning of several components (Figure 1A).

Intestinal microbiota

Bacteria, fungi, archaea, viruses and protozoa compose the gut microbiota and inhabit the gastrointestinal tract. Bacteria are the major component of the human microbiota, with more than 400 species hosted by the human gut.⁷ Gene sequencing data show that three phyla predominate in the human microbiota (Bacteroidetes, Firmicutes and Actinobacteria), with a large diversity in bacterial species but functional homogeneity.⁸ Freter et al showed that bacterial competition for nutrients and adhesion sites limits the colonization by external bacteria. Indeed, exogenous bacteria must have an ecological advantage, compared to residing bacteria, to occupy an ecological niche,⁹ which reveals a barrier effect induced by microbiota. Bacteria also act as modulators of intestinal permeability. *Escherichia coli* Nissle 1917 increases the TER by stimulating the TJ protein zonula occludens-2 (ZO-2). By contrast, *E. coli* C25 increases intestinal permeability.^{10,11} In addition, the microbiota protects intestinal tissue by secreting into the

intestinal lumen bacterial toxins, known as bacteriocins, that inhibit the growth of other bacteria, thus reducing bacterial invasion.¹² In addition, some bacteria transform primary into secondary biliary acids, which protect against some pathogens.¹³ Short-chain fatty acids (SCFAs), produced by microbial fermentation, promote intestinal barrier function by enhancing TJ assembly and the establishment of the TER.¹⁴ Together, these findings demonstrate the active role played by commensal bacteria in intestinal barrier integrity.

Mucus

The mucus is both a physical and a chemical barrier which spatially delineates the lumen from the epithelium by the presence of antimicrobial peptides and trefoil peptides.¹⁵ The gastrointestinal mucus is mainly composed of highly glycosylated proteins called mucins, synthesized and secreted by goblet cells into the lumen, but also of carbohydrates, lipids and water. In humans, the major component is mucin-2, followed by the trefoil factor-3.^{15,16} These components confer the viscoelastic properties displayed by mucus, and in humans allow the formation of a two-layered mucus coat several hundreds of micrometers thick.^{16,17}

Epithelium

Although single layered, the epithelium is the physical living boundary between exterior and interior. The passage of molecules and ions across the epithelium and the cohesion between cells are regulated by the presence of two types of junctional complexes: apical TJs and below them adherens junctions (AJs).² The TJs are multiprotein complexes that seal cells together, maintaining membrane polarity and regulating the selective paracellular permeability of ions, nutrients and water. Transmembrane proteins (occludins, claudins, junctional adhesion molecules and tricellulin) link to actin microfilaments by cytoplasmic proteins called zonula occludens (ZO-1, ZO-2 and ZO-3). Every component contributes towards the assembly and/or the maintenance of the TJ and plays a role in the regulation of intestinal barrier function.^{6,18,19} AJs are localized below the TJs and participate in both the integrity of the epithelial layer and cell-cell communication. AJs consist of calcium-dependent transmembrane proteins, called cadherins, which interact via their C-terminal domain with scaffold proteins, p120-catenin and β -catenin. In the intestinal epithelium, the major component is E-cadherin. The anchorage of the E-cadherin/catenins complex with actin cytoskeleton is mediated by α -catenin.²⁰ Within the epithelial cells, the tightness of both TJs and AJs is regulated through signal

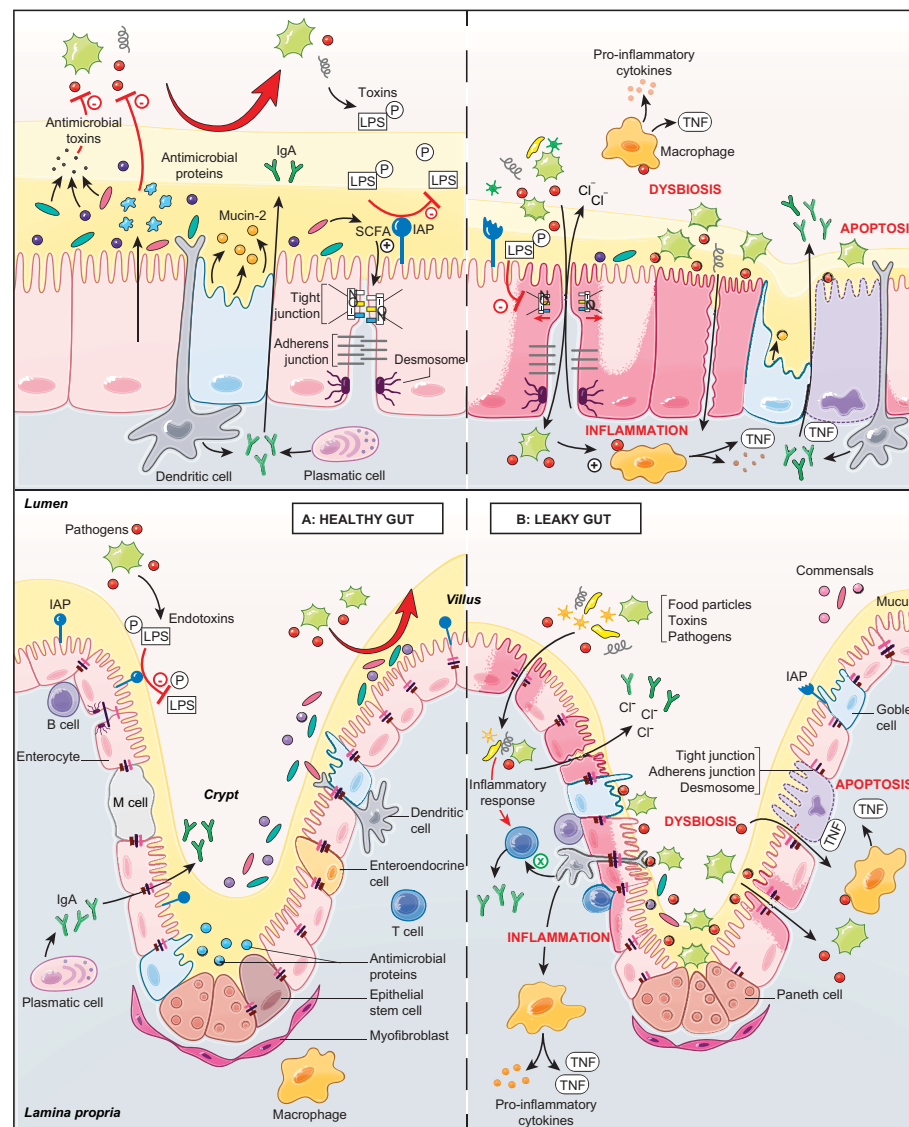


Figure 1 Role of the intestinal barrier components in a healthy gut and a leaky gut.

Notes: The top panels show the components of the intestinal barrier: the microbiota (pale yellow), mucus (dark yellow), the epithelial layer (pink) and the immune layer (gray). The bottom panels show the intestinal barrier on the crypt–villus axis. **(A)** The healthy gut is characterized by an intact intestinal barrier. Commensal bacteria secrete antimicrobial toxins, which protect against pathogenic invasion and SCFAs produced by bacterial fermentation and participate in the formation of tight junctions. The epithelial cells secrete a variety of endogenous molecules, such as antimicrobial proteins and mucins (mucin-2), which make up the mucus layer, and IAPs, which protect the tissue against luminal toxins. The epithelial cells also mediate selective permeability by the apical junctional complex formed by tight and adherens junctions and desmosomes. The immune components include plasmatic cells, which secrete IgA, and the dendritic cells, which sense the luminal environment. **(B)** The leaky gut is characterized by a damaged intestinal barrier. Microbial dysbiosis leads to the interaction of luminal pathogens with intestinal epithelial cells via the bacterial lipid structures. Attachment of pathogens to the epithelial surface impairs the apical junctional complex and increases the intestinal permeability. As a consequence, food particles, toxins and pathogens penetrate into the tissue and provoke an inflammatory response, resulting in cell apoptosis. Increased intestinal permeability also increases the secretion of electrolytes and ions into the lumen, resulting in diarrhea.

Abbreviations: IAP, intestinal alkaline phosphatase; LPS, lipopolysaccharide; M cell, microfold cell; SCFA, short-chain fatty acid.

transduction proteins, such as myosin light chain kinase (MLCK), RhoGTPases, protein kinase C (PKC) and mitogen-activated protein kinase (MAPK), in response to various stimuli.²¹ The expression level of junctional proteins is also controlled by mechanisms including transcriptional and post-transcriptional regulation, transport or recycling at the cell membrane.²²

Lamina propria

Below the intestinal epithelium, the lamina propria contains immune cells and contributes toward protection against potentially harmful molecules or pathogens while tolerating the presence of commensal bacteria. One immune response is demonstrated by intestine-specific IgA, which is secreted by B cells and binds to

microorganisms, forming a complex, which is cleared by bowel movement.³ In case of infections, kinase signaling cascades are activated, which induce nuclear factor- κ B (NF- κ B), leading to the secretion of pro-inflammatory mediators including IL-6, IL-8, IL-12 and TNF- α .²³ The secretion of anti-inflammatory cytokines, such as IL-10, by T lymphocytes is crucial to maintain the balance between tolerance and immune response.⁶

Disruption of intestinal barrier function

The entry of bacteria, food contaminants and luminal antigens through damaged intestinal epithelial cells (IECs), dendritic cells or microfold cells poses a risk to the maintenance of intestinal integrity (Figure 1B).²⁴ Intestinal barrier disruption induces a systemic inflammatory response and causes increased permeability, functional impairment and disease.² Intestinal alkaline phosphatases (IAPs) protect intestinal tissue against luminal endotoxins such as lipopolysaccharide (LPS) by dephosphorylation, resulting in a reduction of the inflammatory response.²⁵ Loss of intestinal integrity with increased permeability plays a major role in the pathogenesis of multiple intestinal and extraintestinal disorders (eg, IBD, IBS, viral or bacterial infections, obesity, type 2 diabetes and non-alcoholic steatohepatitis). Increased intestinal permeability can also be iatrogenic following treatment with antibiotics or NSAIDs, leading to leaky flux diarrhea. Different factors can increase intestinal permeability, including genetic alterations or abnormal regulation of TJ function, dysbiosis of microbiota and chronic inflammation.²⁶ Such TJ alterations can lead to the relocalization of TJ proteins or to their disruption by phosphorylation state regulation. For example, the phosphorylation of occludin is essential for a functional TJ complex.²⁷ TJ alterations also include indirect mechanisms implicating actin cytoskeleton reorganization.²² Such actin cytoskeleton alterations occur through myosin light chain (MLC) phosphorylation by MLCK, alteration in RhoGTPase activity or PKC activation. In physiological conditions, MLCK regulates TJ dynamics but in pathological conditions, secretion of pro-inflammatory cytokines can induce MLCK activation and disruption of TJs.²¹ For example, interferon- γ or TNF- α was found to induce protein relocation and MLC phosphorylation, which facilitated actin contraction and caused the opening of TJs and extension of the intercellular space.²⁸

Modulation of intestinal epithelial barrier function by the probiotic *Saccharomyces boulardii* CNCM I-745

Definition and properties of *S. boulardii* CNCM I-745

Saccharomyces boulardii CNCM I-745 (*S. boulardii*) is a non-pathogenic yeast discovered in 1923 by a French microbiologist in Indochina. It has since been widely used as probiotic in the prevention and treatment of gastrointestinal disorders. As a yeast, *S. boulardii* is distinct from bacterial probiotics, in particular because of its intrinsic resistance to antibiotic treatment.²⁹ In addition, *S. boulardii* can adapt to and survive in the gastrointestinal tract owing to its ability to grow at 37°C, and its resistance to low gastric pH^{30,31} and to bile acids.^{30,32,33} Once in the gastrointestinal tract, *S. boulardii* reaches a maximum concentration within 2 days and is cleared in the stools within 3–5 days after oral administration.³²

Intestinal permeability alterations due to enteric pathogens and corrective effects of *S. boulardii*

The IECs act as a physical barrier via TJs to protect tissue from invasion by pathogens. The bacterial recognition occurs by pattern recognition receptors such as Toll-like receptors (TLRs).³⁴ The TLRs are type I membrane proteins that protect mucosal and commensal homeostasis but also induce adaptive immune signaling in response to bacterial invasion.³⁵ They bind a variety of bacterial lipid structures and bacterial cell wall components. For example, TLR-2 signaling enhances the TJ-associated barrier through activation of the PI3K/Akt pathway.^{34,36} During invasion, enteric pathogens (bacteria and viruses) use TJs as receptors to attach to the cell membrane in order to become internalized, or they disrupt the TJ first before penetrating into the tissue. Alterations in TJs are implicated in diarrhea through a “leaky flux” mechanism, which allows the passage of ions and water toward the lumen after the impairment of intestinal barrier integrity. The *S. boulardii* CNCM I-745 strain is registered in many countries for the treatment of diarrhea in adults and children. Its efficacy has been proven through many randomized clinical trials and its use recommended by numerous scientific societies.³⁷ *S. boulardii* owes its clinical efficacy to a wide variety of actions counteracting numerous pathogen-induced deleterious effects. The modes of action of *S. boulardii* can be summarized as follows:³⁸ 1) luminal

action, referring to the action of *S. boulardii* within the lumen: antitoxic effect, notably against cholera toxin and *E. coli* LPS, antimicrobial activity, modulation of intestinal flora and metabolic activity; 2) trophic action at the villi, ie, secretion of digestion-enhancing enzymes and induction of host digestive enzymes³⁹ and 3) mucosal action, referring to the action of *S. boulardii* deeper within the mucosa, including anti-inflammatory activity. Altogether, the various modes of action of *S. boulardii* act in concert to counteract infections and to support barrier function and regeneration of damaged intestinal tissue. A broad spectrum of non-clinical data supports the beneficial effects of *S. boulardii* counteracting the pathogenicity of various pathogens (Table 1).

E. coli

Enteropathogenic *E. coli* (EPEC) and enterohemorrhagic *E. coli* (EHEC) are pathogenic strains of attaching and effacing bacteria. The interaction between bacterial toxins and IECs leads to intestinal barrier disruption and intestinal permeability alterations.⁴⁰ This type of invasion (for *E. coli* strains HB101 and LF82) is followed by alterations in electrolyte transport, chloride secretion and diarrhea.^{41,42} In various intestinal cell models, pathogenic effector proteins delivered into enterocytes have caused TJ disruption by MLCK and PKC activation, and increased intestinal permeability.²¹ EPEC and EHEC cause gastroenteritis, with different mechanisms being responsible for the increased intestinal permeability. More precisely, EPEC infection stimulates phosphorylation of MLC by MLCK, inducing TJ disruption and the stimulation of cytoskeletal contraction. This event causes a drop in TER and thus increased intestinal permeability. EPEC infection is also associated with an alteration of occludin distribution (shift from TJ to cytosol) by a dephosphorylation of this protein, essential to this localization in the TJ complex.⁴⁰ In contrast to EPEC, EHEC infection is promoted by an alteration in ZO-1 distribution.⁴³ In EHEC O157:H7, the regulation of the dynamic of the actin cytoskeleton is also impaired in the paracellular permeability via a PKC-dependent mechanism which inactivates the RhoA/Rac/Cdc42 pathway and in turn increases actomyosin contractility.⁴⁴ Furthermore, *E. coli* O157:H7 strain has been shown to induce secretion of pro-inflammatory cytokines (IL-8) mediated by MAPK and NF- κ B activation.⁴⁵ IECs treated with *S. boulardii* before infection by EPEC strain E2348/69 display a reduced level of secreted pro-inflammatory cytokines and a preserved TJ structure due to the abolition of MLC phosphorylation.⁴ Administration of *S. boulardii* in mice reduced *C. rodentium* strain DBS100-induced colitis by a decrease in

intestinal permeability and a reduction in chloride secretion and mannitol flow.⁴⁶ *S. boulardii* also modulates bacterial attachment of 055B5 *E. coli* to enterocytes by secreting a 63 kDa alkaline phosphatase.⁴⁷ Endotoxins such as LPS are dephosphorylated by this phosphatase, causing a reduction in bacterial attachment and a 60% decrease in the TNF- α level in the bloodstream.⁴⁷

Shigella

Invasion by *Shigella* requires two events that decrease barrier function: TJ disruption and E-cadherin intracellular domain cleavage.⁴⁸ An increased intestinal permeability facilitates *Shigella* invasion into IECs, leading to bacterial dysentery. In T84 cells, modification of the phosphorylation status of occludin and reduction in claudin-1 expression mediated TJ disruption.²⁷ In both in vitro and in vivo models, *S. boulardii* has shown to restore partially this claudin-1 expression and the barrier integrity. It also exerted anti-inflammatory effects by inhibiting IL-8 secretion mediated by NF- κ B and ERK1/2 phosphorylation.⁴⁹

Salmonella

Salmonella species belong to the family of proteobacteria. The subtype *Salmonella enterica* serovar Typhimurium is a major cause of gastroenteritis. Translocation of effector proteins is a key event in *S. enterica* Typhimurium invasion. Translocation is caused by decreased expression of ZO-1, modified phosphorylation status of occludin and activation of RhoGTPases. The resulting alteration in TJ and AJ localization causes a drop in TER as well as an increase in intestinal permeability, allowing bacterial invasion and amplified diarrhea.²⁸ Invasion by *S. enterica* Typhimurium also induces IL-8 secretion by NF- κ B activation. *S. boulardii* protects mice during *S. enterica* Typhimurium infection and preserves epithelial barrier function in IECs. It was found to interfere with signaling pathways implicated in the invasion, in particular by reducing activation of RhoGTPases, which are implicated in actin cytoskeleton rearrangement and modulation of TJ proteins. It also decreased activation of MAPKs and reduced the level of inflammatory cytokines while up-regulating the secretion of anti-inflammatory cytokines such as IL-10 and TGF- β .^{50,51} In addition, *S. boulardii* adheres to *S. enterica* Typhimurium and, thus, prevents contact of the pathogen with the epithelial surface, decreasing the bacterial translocation to almost 50%.⁵¹ Adhesion of *S. enterica* Typhimurium to yeast cells is mediated by type I fimbriae and this interaction uses mannose from yeast cell walls.⁵² Furthermore, *S. boulardii* trapped *S. enterica* Typhimurium

Table 1 Deleterious actions of pathogens in the gut and beneficial effects of *S. boulardii* CNCM I-745

	Deleterious actions of pathogens	Beneficial effects of <i>S. boulardii</i> CNCM I-745
<i>Escherichia coli</i>		
Barrier integrity	Epithelium disruption: <ul style="list-style-type: none"> • MLC phosphorylation and PKC activation lead to TJ disruption²¹ 	Epithelium restoration: <ul style="list-style-type: none"> • Inhibition of MLC phosphorylation⁴ • Restoration of barrier integrity through TJ protection
Diarrhea	<ul style="list-style-type: none"> • Alterations in electrolyte transport • Chloride secretion^{41,42} 	<ul style="list-style-type: none"> • Reduction of intestinal permeability • Reduction of chloride secretion and mannitol flow⁴⁶
Inflammation	<ul style="list-style-type: none"> • IL-8 secretion mediated by MAPK and NF-κB activation⁴⁵ 	<ul style="list-style-type: none"> • Reduced levels of secreted pro-inflammatory cytokines⁴ • Decrease in TNF-α level⁴⁷
Invasion	<ul style="list-style-type: none"> • Pathogenic strains of attaching and effacing bacteria⁴⁰ 	<ul style="list-style-type: none"> • Modulation of bacterial attachment to enterocytes by secreting alkaline phosphatase⁴⁷
<i>Shigella</i>		
Barrier integrity	Epithelium disruption: <ul style="list-style-type: none"> • Modification of phosphorylation status of TJ proteins²⁷ • TJ disruption due to reduction in claudin-1 expression²⁷ • AJ disruption induced by E-cadherin intracellular domain cleavage⁴⁸ 	Epithelium restoration: <ul style="list-style-type: none"> • Partial restoration of claudin-1 expression⁴⁹ • Restoration of barrier integrity through TJ protection
Inflammation	<ul style="list-style-type: none"> • IL-8 secretion 	<ul style="list-style-type: none"> • Inhibition of IL-8 secretion mediated by NF-κB and ERK 1/2 phosphorylation⁴⁹
<i>Salmonella</i>		
Barrier integrity	TJ disruption due to: <ul style="list-style-type: none"> • Decrease in ZO-1 expression²⁸ • Modified phosphorylation status of occludin²⁸ • Activation of RhoGTPase²⁸ 	Epithelium restoration: <ul style="list-style-type: none"> • Reduction of RhoGTPase preserves TJ^{50,51}
Diarrhea	Decrease in TER ²⁸	Restoration of barrier integrity through TJ protection
Invasion	<ul style="list-style-type: none"> • <i>Salmonella typhimurium</i> invasion led by translocation of effector proteins²⁸ 	<ul style="list-style-type: none"> • Deviated trajectory of <i>Salmonella</i> and modified motility in the gastrointestinal tract by trapping of <i>Salmonella</i> by <i>S. boulardii</i>^{53,54} • Increase in bacterial elimination in feces^{53,54}
Inflammation	<ul style="list-style-type: none"> • NF-κB and IL-8 secretion^{50,51} 	<ul style="list-style-type: none"> • Up-regulation of anti-inflammatory cytokines (IL-10 and TGF-α)^{50,51} • Reduction in activation of MAPK and reduced level of inflammatory cytokines^{50,51}
<i>Vibrio cholerae</i>		
Barrier integrity	Epithelium disruption: <ul style="list-style-type: none"> • Zonula occludens toxin⁵⁵ • 84 kDa cholera enterotoxin⁵⁵ 	Epithelium restoration: <ul style="list-style-type: none"> • Reduction of intestinal damage and mucosal lesions⁵⁸
Diarrhea	Hydroelectrolytic diarrhea due to: <ul style="list-style-type: none"> • cAMP stimulation⁵⁵ • Chloride secretion⁵⁵ • Cell adhesion leakage⁵⁵ 	Antidiarrheic effects by: <ul style="list-style-type: none"> • 120 kDa protein secretion, which decreases cAMP^{56,57} • Decrease in chloride secretion^{56,57}
Rotavirus		
Barrier integrity	Epithelium disruption: <ul style="list-style-type: none"> • Drastic reduction in TER³⁸ • Alteration in TJ protein localization (ZO-1, occludin and claudin-1)^{38,59} 	Epithelium restoration: <ul style="list-style-type: none"> • Restoration of glutathione, which inhibits ROS production⁶⁰ • Decrease in intestinal permeability⁶⁰
Diarrhea	<ul style="list-style-type: none"> • Noxious substance penetration⁴⁰ • Alteration of redox balance enhanced by ROS production leads to chloride secretion⁶⁰ 	<ul style="list-style-type: none"> • Inhibition of chloride secretion and reduction of diarrhea⁶⁰

Abbreviations: AJ, adherens junction; cAMP, cyclic adenosine monophosphate; MAPK, mitogen-activated protein kinase; MLC, myosin light chain; NF- κ B, nuclear factor- κ B; PKC, protein kinase C; *S. boulardii*, *Saccharomyces boulardii*; TER, transepithelial resistance; TJ, tight junction; ZO-1, zonula occludens-1.

within the intestinal lumen, thereby deviating its trajectory and modifying its motility, thus increasing the fecal elimination of the pathogenic bacteria. These two mechanisms limit

bacterial invasion.^{53,54} Intestinal epithelial barrier alterations have only been studied in animal models and need to be confirmed in humans.

Vibrio cholerae

V. cholerae is an enteropathogen responsible for cholera epidemics. Two toxins are produced: zonula occludens toxin, which alters the barrier function of TJs, and the 84 kDa enterotoxin cholera toxin, which modulates membrane channels. Cyclic adenosine monophosphate (cAMP) stimulation resulting from toxin catalytic activity induces chloride secretion into the intestinal lumen and causes hydroelectrolytic diarrhea.⁵⁵ Cell adhesion leakage allows the diffusion of water and ions into the lumen, causing diarrhea. A pre-incubation with *S. boulardii* was shown to dose-dependently decrease the cAMP level by up to 50% in male rats and rat epithelial intestinal cell lines (IRD 98 and IEC 17). The preventive role of *S. boulardii* is mediated by secretion of a 120 kDa protein which interferes with the cAMP-dependent induction of chloride secretion and decreases diarrhea caused by *V. cholerae*.^{56,57} Pretreatment by *S. boulardii* was shown to reduce intestinal damage and lesions in a rat model of *V. cholerae* infection.⁵⁸

Rotavirus

Rotavirus infection is associated with a drastic reduction in TER (from 325 to 22 Ω .cm² in 24 hours).³⁴ An increase in intestinal permeability stems from a deregulated secretion and absorption of ions. Thus, noxious substances can penetrate into the intestinal tissue, inducing diarrhea and morbidity.³⁵ Rotavirus produces the enterotoxin non-structural protein-4 (NSP-4), which alters the localization of TJ proteins (ZO-1, occludin and claudin-3), leading to the disruption of intestinal barrier integrity and blockade of epithelial barrier formation in MDCK cells.⁵⁹ In addition, NSP-4 alters redox balance by enhancing ROS production in the mitochondrial compartment of enterocytes, with the potential to cause damage to intestinal barrier integrity. The generation of ROS also induces chloride secretion and diarrhea. In a study with infected IECs, *S. boulardii* restored glutathione levels, which in turn inhibited ROS production, leading to a decrease in intestinal permeability.⁶⁰

Intestinal permeability alterations due to antibiotics and preventive and corrective effects of *S. boulardii*

While antibiotic treatment does result in the destruction of pathogens, it also destroys commensal bacteria, leading to osmotic diarrhea and the promotion of intestinal permeability, associated with potential bacterial and viral translocation. The *S. boulardii* CNCM I-745 strain has proven efficient in the prevention of such antibiotic-induced diarrhea, independent

of the specific antibiotic (Figure 2).^{39,61} In addition, by reducing the occurrence of diarrhea, *S. boulardii* is an effective adjunctive therapy for *H. pylori* eradication during antibiotic treatment.⁶² Owing to its multiple modes of action, it is also effective in the treatment of *Clostridium difficile* infection and in the reduction of recurrence.³⁹ Finally, concomitant treatment by *S. boulardii* was recently shown to prevent the huge shifts in the microbiome composition observed following use of antibiotics alone.⁶³ Infection by *C. difficile*, responsible for diarrhea or even pseudomembranous colitis, can occur further to antibiotic treatment (Figure 2). It is associated with frequent stools of liquid consistency during or after the antibiotic treatment, and sometimes a fever. Some evidence suggests a higher incidence of *C. difficile* infections among older adults, in particular those with multiple associated pathologies.⁶⁴ This kind of infectious diarrhea has a high risk of relapse even in the absence of antibiotic retreatment. *C. difficile* produces two toxins (A and B; enterotoxin and cytotoxin, respectively) which alter the assembly and maturation of TJs.⁶⁵ Such TJ alterations lead to a reduction in TER and an increase in intestinal permeability, a key element in the pathological progression, as reflected by antibiotic-associated diarrhea (30% of cases) or pseudomembranous diarrhea (95%).^{66,67} In hamsters and gnotobiotic mice, *S. boulardii* reduced the rate of clindamycin-induced mortality caused by pseudomembranous colitis or *C. difficile* infection. The reduction in mortality was highest when *S. boulardii* was administered preventively.^{68–70} These effects were correlated with a reduction in the number of *C. difficile* bacteria as well as a lowered toxin expression.⁷¹ Moreover, *S. boulardii* was found to increase the concentration of IgAs directed against bacteria by 57%,⁷² induce proteolysis of toxins A and B, and inhibit the interaction with enterocytes by secretion of a 54 kDa serine protease.^{73,74} This serine protease blocks JNK and ERK1/2 kinase activation, inhibits MLC phosphorylation and prevents TJ disruption. *S. boulardii* secretes another factor, named *S. boulardii* anti-inflammatory factor (SAIF; <1 kDa), which exerts anti-inflammatory effects by blocking NF- κ B activation and IL-8 secretion mediated by IL-1 β .⁷⁵ Altogether, *S. boulardii*-secreted factors exert anti-inflammatory and barrier-protective/restorative effects.

Gut response during childhood

Children's gut responses to noxious agents are very different from adults' because of the immaturity of the intestinal epithelial barrier in children. The development of the intestinal epithelial barrier occurs in utero and postnatally with the formation of AJ complexes, and then with the development

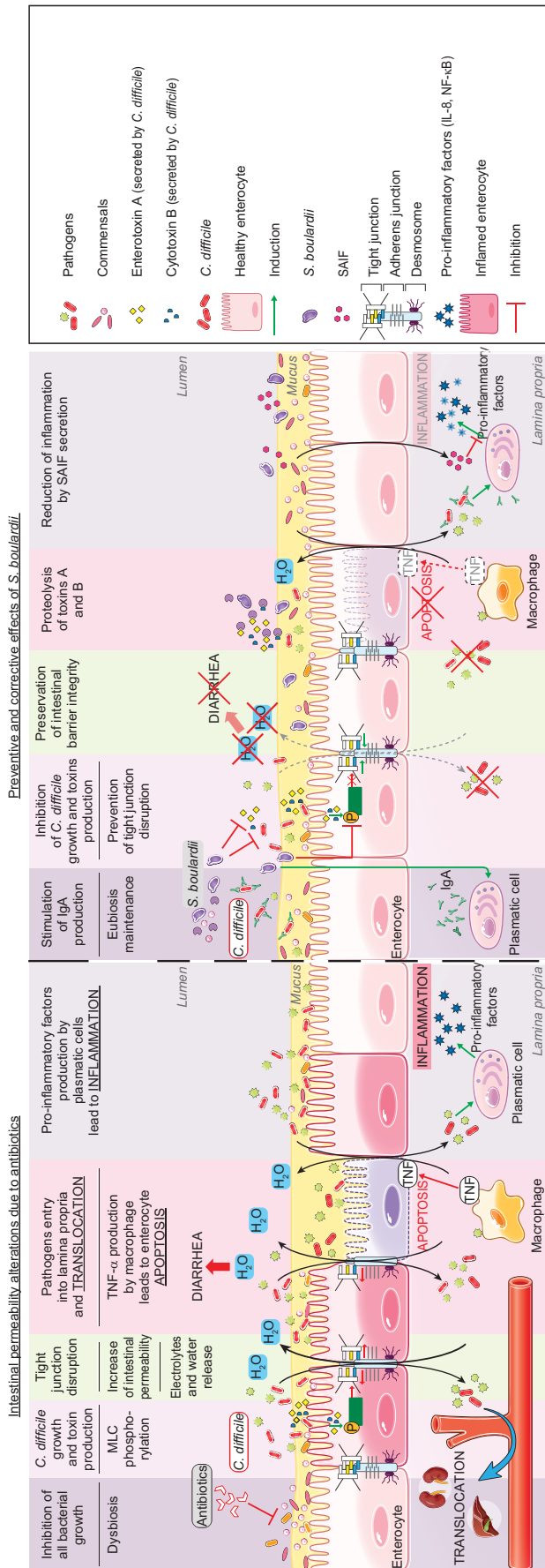


Figure 2 Proposed model for the effects of *S. boulardii* on intestinal permeability due to antibiotics.

Notes: Administration of antibiotics leads to multiple intestinal alterations. For example, antibiotic administration reduces all bacterial growth and this reduction leads to *C. difficile* growth and to the production of these toxins, which alter the formation of tight junctions. Intestinal permeability and the entry of pathogens into the lamina propria lead to different responses from the intestinal tissue: passage of electrolytes and water to the lumen, TNF- α production by macrophages leading to enterocyte apoptosis, and secretion of pro-inflammatory cytokines leading to inflammation. *S. boulardii* has a variety of preventive and corrective effects on antibiotic alterations: it stimulates the secretion of IgA directed against toxin A, and inhibits pathogen growth and toxin production. Besides, *S. boulardii* inhibits MLC phosphorylation and preserves the tight junction at the cell membrane. The restoration of intestinal barrier decreases the passage of electrolytes and water to the lumen. *S. boulardii* induces proteolysis of toxins A and B by secretion of serine protease (54 kDa) and secretes a factor named SAIF which exerts anti-inflammatory effects.

Abbreviations: *C. difficile*, *Clostridium difficile*; MLC, myosin light chain; NF- κ B, nuclear factor- κ B; *S. boulardii*, *Saccharomyces boulardii*; SAIF, *S. boulardii* anti-inflammatory factor.

of physical and chemical barriers (eg, defensins, lysozymes and mucins). The development in utero and the maturation postnatally are under the control of multiple factors, especially the development of the microbiota.⁷⁶ The first colonizers create a new environment that promotes colonization, such as *Bacteroides*, *Clostridium* and *Bifidobacterium*.⁷⁷ For many years, it was thought that uterine life was sterile and that newborns acquired a microbiota during delivery. In the past decade, investigations have shown bacterial transmission through the placental barrier and have detected bacteria in the placenta, umbilical cord blood, amniotic fluid and fetal membranes.^{78–81} These findings suggest that the placenta is not sterile and that mother-to-child efflux of commensal bacteria exists, which influences both the microbiota and the immune system in utero. It is currently held that the maturation of microbiota begins during delivery and ends at 3 years old, at which timepoint it achieves the adult characteristics. During the maturation stage, several environmental factors may influence and affect the establishment and diversity of intestinal microbiota, including gestational age, mode of delivery (vaginal or cesarean), diet (breast milk or formula) and antibiotic treatment.⁸² It has been reported that birth mode influences the level of bacterial species in the first 6 months until complete maturation of the microbiota.⁸³ Yassour et al described the influence of birth mode on the diversity and maturation of microbiota in 39 children aged 3–36 months. They observed multiple similarities in the composition of microbiota over time between birth modes (succession of bacterial populations in the gut communities); they also found a distinct microbial signature of *Bacteroides* in the first 6 months in babies born by cesarean section compared to vaginal delivery.⁸³ This can be explained by the fact that cesarean delivery transfers a large part of the commensal bacteria from the skin microbiota instead of the vaginal and fecal microbiota. Cesarean delivery increases by 20% the risk of acute gastroenteritis, and this risk is increased by 62–78% when cesarean section is combined with preterm delivery and exclusive formula feeding.⁸⁴

Diet is another major factor that influences the development of the microbiota. Investigations have shown that breastfeeding influences the growth of microbes and improves the intestinal barrier.⁸⁵ Components of the breast milk may improve the epithelial intestinal barrier and stimulate the immune system.⁸⁶

Other substances, such as prebiotic and probiotic compounds, may stimulate the production of various immunoglobulins (IgG, IgM and secretory IgA).⁸⁴ The development of a mature immune system is correlated with

the development of the microbiota.⁸⁷ The SCFAs produced by microbes can affect the inflammatory response by binding to and stimulating G-protein coupled receptor-43 (GPR43).⁸⁸ The presence of *Bacteroides fragilis* in commensal bacteria is capable of suppressing inflammation by down-regulation of IL-17. It can also convert CD4⁺ T cells in regulatory T cells, which produce an anti-inflammatory cytokine (IL-10).⁸⁹ Exposure to postnatal antibiotics, total parental nutrition and delay in breastfeeding are factors responsible for the impairment of intestinal colonization and favor the overgrowth of pathological microorganisms.^{90–93} Disruption of the gut barrier accompanied by altered microbiota and/or intestinal inflammation with impaired immune-regulatory mechanisms has been shown in many gastrointestinal diseases with onset in childhood (eg, celiac disease,⁹⁴ IBD and infectious diarrhea) but also in numerous extraintestinal pathological, non-communicable diseases (eg, asthma, allergy, eczema, diabetes and cystic fibrosis with cirrhosis).^{80,95–100} Furthermore, several studies have shown that the gut microbiota has a role in the development of non-communicable diseases. Some bacteria are correlated with the onset of allergy, eczema or type 1 diabetes while others protect against these pathologies. For instance, *Lactobacilli*, *Bacteroidetes*, *Bifidobacteria* and *Proteobacteria* taxa are decreased in children who develop allergy.^{88,96,101} With regard to non-communicable diseases, meta-analyses of clinical trials using probiotics for allergy prevention demonstrate a reduced incidence of eczema, but mechanistic pathways to understand how probiotics mediate these beneficial effects are still to be investigated. Furthermore, no studies have analyzed the effectiveness of *S. boulardii* in non-communicable diseases.⁹⁵

Only a few studies have specifically focused on the effects of *S. boulardii* on gut permeability in children. One important difference between bacteria and yeast is their cell wall composition, which is responsible for the modulation of the mucosal immune response.²⁹ In children with acute gastroenteritis, Ozkan et al showed that blood levels of IgA and of CD8 lymphocytes increased at day 7 while both C-reactive protein and complement C4 decreased in reaction to *S. boulardii* treatment.¹⁰² These modifications in blood immune parameters are in line with the findings of Caetano et al in adults.¹⁰³

Leaky gut in gastrointestinal diseases

Luminal contents, diarrhea, dysbiosis and allergy can cause damage to IECs and lead to alterations in cell–cell junctions and finally to impaired intestinal permeability, known as

the “leaky gut”. The leaky gut allows molecules, drugs or toxins to penetrate into the bloodstream and create chronic inflammation and further increases in intestinal permeability. This condition is responsible for many complications in gastrointestinal disorders, such as diarrhea or IBS, but also in non-gastrointestinal diseases. For example, the leaky gut observed in HIV patients can lead to cardiovascular disease or chronic kidney disease. In obesity, intestinal permeability can induce visceral obesity and/or type 2 diabetes.²⁷ More precisely, alterations in intestinal function are associated with the pathogenicity of type 2 diabetes. Several causes are responsible for the decrease in intestinal barrier in type 2 diabetes. Among them, changes in the dietary composition (from high carbohydrates to western diet) are important factors which allow a rapid modification of the microbiota community.¹⁰⁴ The nutritional imbalance along with changes in microbiota composition/activity contributes to the increase in intestinal permeability. The paracellular permeability allows the passage of bacterial lipoproteins such as LPS and their binding to TLR-4. Secretion of pro-inflammatory cytokines is induced after the activation of TLRs. The inflammatory cascade promotes the phosphorylation of the receptor insulin substrate and impairs insulin signaling.¹⁰⁵

Intestinal permeability is also believed to play a crucial role in some liver diseases, such as alcoholic or non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma.^{106,107}

IBDs

IBDs are multifactorial diseases with two main subtypes: Crohn’s disease (CD) and ulcerative colitis (UC). The etiology is still unknown but IBDs are driven by an immune activation against the host microbiota in genetically predisposed patients.¹⁰⁸ IBDs have a prevalence of 1/1,000 and clinical morphological features that differ between CD and UC.¹⁰⁹ The microbiota (composition and diversity) and environmental factors are important in the pathogenesis of either IBD subtype.¹¹⁰ While smoking increases the frequency of CD relapse, it shows no effect in UC patients. While all UC patients display AJ abnormalities, only 50% of patients with CD show such abnormalities. Impairment of intestinal permeability causes “leaky flux” diarrhea and an easier uptake of noxious substances, which could be of importance in IBD patients suffering from transit disorders and abdominal pain despite complete mucosal healing of their intestinal disease.¹¹¹ Alterations in intestinal barrier integrity cause a deregulation in the immune response with secretion of pro-inflammatory cytokines.¹¹² The impact of probiotics, including *S. boulardii*, in IBDs has been rigorously studied,

with controversial results to date. A clinical study with 159 IBD patients treated with steroids or salicylates showed no significant effects of *S. boulardii* regarding CD relapse rate;¹¹³ however, *S. boulardii* was effective on intestinal permeability, as shown by the decrease in the lactulose/mannitol ratio (33.33%).¹¹⁴ Experimental studies on the effect of *S. boulardii* supernatant on mucosal lesions found that it accelerates the migration of enterocytes compared to control conditions by modulating $\alpha_2\beta_1$ - and $\alpha_v\beta_5$ -integrin activation states.^{115,116} Another study showed, both ex vivo and in vitro, that *S. boulardii* accelerates the expression of E-cadherin at the cell membrane by inducing E-cadherin recycling in Rab11A-dependent recycling endosomes.²⁰ These experimental studies indicated that *S. boulardii* could have beneficial effects in the treatment and prevention of intestinal permeability in patients with IBDs.

IBS

IBS is a functional gastrointestinal disorder affecting more than 10% of the population across the world.¹¹⁷ It is defined by the Rome IV criteria and characterized by intermittent abdominal pain, transit disorders such as diarrhea, constipation or alternating diarrhea/constipation, and is associated with bloating during the symptomatic periods. While no detectable structural or biochemical abnormalities have been found and despite many studies on motility, psychology, diet, visceral hypersensitivity and microbiota in IBS patients, the physiopathology remains unclear.¹¹⁸ Nevertheless, some evidence does suggest the involvement of interactions between the gut, immune system and nervous system in the pathogenesis. In addition, increased intestinal permeability has been noted in patients with IBS, associated with a lower expression of ZO-1 and a decrease in TER.^{119,120} Increased intestinal permeability can contribute to more severe symptoms and hypersensitivity. In a mouse model, TJ alterations were found to originate from MLCK-dependent activation. While IBS is not lethal, patients do suffer from an altered quality of life and have increased health care costs. Clinical trials on probiotic efficiency have given controversial results. Some have suggested that *S. boulardii* can restore intestinal epithelial barrier function in IBS patients by modulating the intestinal immune response.¹²¹ This could affect IBS symptoms and the hypersensitivity associated with an impaired intestinal barrier. These results need to be validated in larger studies.

The gut microbiota plays a major role in the pathogenesis of IBD and IBS. A dysbiosis characterized by an decrease in protective species and correlated with an increase in inflammatory species has been found in the

mucosa and feces of IBD patients. Even if probiotics, and especially *S. boulardii*, do represent a plausible treatment, further studies are necessary to better characterize the exact role of *S. boulardii* in IBD and IBS and its specific mechanisms of action, including the modulation of microbiota. More evidence on the beneficial effects of *S. boulardii* in IBD and IBS needs to be validated with further placebo-controlled clinical studies.

New pathways to prevent intestinal permeability alterations in obesity and metabolic syndrome

The composition of the diet has a critical role in the colonization, maturation and stability of the microbial community. Dietary changes induce changes in the microbiota and lead to negative effects such as dysbiosis and low-grade inflammation. In non-obese humans, overfeeding leads to rapid changes in the composition of the gut microbiota and decreases nutrient absorption.¹²² High-fat or high-sugar diets modify the composition of the microbiota by increasing the proportion of Firmicutes and reducing the proportion of Bacteroidetes.¹²³ Furthermore, a western diet can have long-term consequences and can lead to the permanent loss of bacteria and induce inheritable metabolic changes.¹²⁴ Obesity is associated with chronic diseases such as diabetes, cardiovascular disorders and liver diseases. These pathologies are induced by a high-fat, high-sugar diet and are characterized by low-grade inflammation and the secretion of pro-inflammatory factors such as TNF- α or IL-1 β , which in turn enhance the dysbiosis associated with intestinal permeability.

Impairments of epithelial barrier function are correlated with alterations in the structure and localization of TJ proteins, ZO-1 and occludin.¹²⁵ In addition, an imbalance in the Firmicutes/Bacteroidetes ratio contributes to alterations in the expression of TJ proteins.¹²⁶ In “leaky gut” patients, modifications of the intestinal microbiota composition lead to metabolic endotoxemia and to the translocation of commensal bacteria or bacterial products such as LPS into the circulation, contributing to a chronic systemic low-grade inflammation.¹²⁷

In a preclinical study evaluating the impact of *S. boulardii* on obesity, *S. boulardii* administered daily to 6-week-old obese, type 2 diabetic mice (*db/db*) for 4 weeks led to reductions in body weight, fat mass, hepatic steatosis and secreted pro-inflammatory cytokines (IL-1 β , -4 and -6). In addition, *S. boulardii* was found to alter the microbial composition of the gut-affecting bacterial species known to be associated with diabetes, inflammation and intestinal permeability. This may

have contributed to restoring intestinal barrier function.¹²⁸ However, in humans results are rare and inconsistent. Further investigations are required to determine whether *S. boulardii* has beneficial effects in the treatment of obesity and type 2 diabetes.

Excessive alcohol consumption is associated with alcoholic liver diseases (steatosis, acute alcoholic hepatitis and cirrhosis) and can lead to hepatocellular carcinoma. Alcohol was found to decrease the level of defensins, the expression of TJs and the number of immune cells within the intestinal wall.¹²⁹ Such defects associated with hepatic “micro-inflammation” play a role in the pathogenicity of liver diseases and bacterial translocation. In addition, a newly identified regulator of intestinal permeability (FoxO4) is increased by alcohol.¹³⁰ The relationship between intestinal permeability and liver disease is still speculative, and any factor found to restore intestinal barrier function could be of interest. Methionine–choline-deficient diet-induced non-alcoholic steatohepatitis in a mouse model highlights that gut microbiota and overnutrition are other major factors involved in the pathogenicity of non-alcoholic fatty liver disease. The use of probiotics in that case prevents liver steatosis and inflammation induced by the diet and improves high-fat diet-induced insulin resistance and steatosis.¹³¹

Leaky gut due to enteral feeding

Enteral nutrition is responsible for major changes in intestinal nutrient uptake. These changes produce a deficiency in SCFAs, which are known to participate in TJ assembly, and thus SCFA deficiency contributes to a loss of epithelial barrier function and alterations in intestinal permeability.¹³² In a mouse model, enteral nutrition was associated with reduced expression of E-cadherin and β -catenin.¹³³ In addition, reduced SCFA levels caused diarrhea, the most frequent complication observed in ill, tube-fed patients. Schneider et al showed that treatment with *S. boulardii* increased the total fecal content of SCFAs, mostly in terms of butyrate level, in patients receiving long-term enteral nutrition (150.2 ± 27.2 vs 107.5 ± 18.2 mmol/kg, $P=0.02$) but not in controls (129 ± 28.6 vs 113 ± 15.2 mmol/kg, not significant).¹³² An absence of luminal nutrition is associated with deleterious consequences to the intestinal barrier. In human intestinal Caco-2 cells, butyrate promoted barrier function by increasing AMP-activated protein kinase activity, accelerating TJ assembly and inhibiting NF- κ B activation.¹⁴ By increasing SCFA concentrations in patients with enteral nutrition, *S. boulardii* was shown to contribute to the restoration of the intestinal epithelial barrier, thereby preventing diarrhea in these patients.

Leaky gut in immunocompromised HIV patients

About 50–60% of HIV patients in western countries suffer from diarrhea. In HIV patients, the HIV envelope glycoprotein gp120 induces a reduction in intestinal TER. In addition, HIV caused alterations in TJ protein expression (claudin-1, occludin and ZO-1) and induced a pro-inflammatory response (IL-1, IL-6 and TNF- α), resulting in increased intestinal permeability.¹³⁴ Impairment of intestinal barrier function causes increased entry of LPS into the bloodstream along with a systemic immune activation, but also contributes to the translocation of HIV into tissue, both leading to faster disease progression.¹³⁴ Recent studies have focused on developing therapies that control bacterial translocation by decreasing intestinal permeability. In a double-blind, randomized, placebo-controlled trial, Villar-García et al assessed the impact of *S. boulardii* on microbial translocation. Among 44 antiretroviral therapy-treated patients receiving *S. boulardii* or placebo for 12 weeks, supplementation with *S. boulardii* significantly decreased serum levels of LPS and IL-6, which are responsible for pore-forming claudin-2 expression.^{135,136} After 12 weeks of treatment, patients receiving *S. boulardii* showed increased levels of *Megamonas* and *Desulfovibrionales* species and decreased levels of certain pathogenic species (*Clostridiales* and *Catenibacterium*) known to correlate with IL-6 and TNF- α secretion.^{135,137} Analysis of the microbiota profile by 16s rDNA did not establish the mechanisms underlying the modulation of gut microbiota by *S. boulardii*, but these data suggest that rather than acting directly on TJ barrier function, *S. boulardii* instead modulated the intestinal microbiota composition. More precisely, it is known that TNF- α and IL-6 secretion increases intestinal permeability through mechanisms involving TJs. IL-6 impairs ZO-1 apical localization and increases actin cytoskeleton contraction.¹³⁸ TNF- α increases MLCK protein levels and RhoA activation, correlated with an increase in intestinal permeability.¹³⁸ The change in microbial community after *S. boulardii* treatment restores a homeostatic microbiota and reduces pathogenic-related species.¹³⁹ Moreover, *S. boulardii* restored the production of certain SCFAs (acetate and propionate) to normal levels in an ex vivo model of the pig fecal microbial ecosystem disturbed by clindamycin.¹⁴⁰ We can speculate that *S. boulardii* has similar effects on the microbiota in HIV patients. Further studies are needed to explore the role of *S. boulardii* in TJ function in HIV infection, while taking into account the safety warning regarding the use of probiotics in patients with central venous catheters and in immunocompromised or critically ill patients. Modifications in bacterial

diversity and the reduction of pro-inflammatory cytokines by *S. boulardii* may restore intestinal barrier and prevent microbial translocation in HIV patients.

Conclusion

The intestinal epithelial barrier plays a major role in tissue defense and intestinal homeostasis. Disruption of this barrier is a key element in various gastrointestinal disorders and systemic diseases, and occurs through complex cross-talk between signaling pathways and TJ/AJ complex regulation. Understanding the mechanisms implicated in intestinal permeability is essential for the development of new therapeutics that may prevent or restore intestinal epithelial barrier function. *Saccharomyces boulardii* CNCM I-745, already used in the prevention and treatment of diarrhea of differing etiology (antibiotic-associated or infectious), has proven protective effects on the barrier function in various diseases. In this review, we have summarized the impact of *S. boulardii* on various gastrointestinal and systemic diseases associated with intestinal epithelial barrier defects. Through anti-inflammatory, anti-secretion, pro-migratory and adhesive effects, *S. boulardii* preserves and restores intestinal barrier function. Possibly, a yeast-induced general metabolic activation may enhance barrier function by the acceleration of enterocyte turnover.

This review opens new perspectives for various pathologies associated with impaired gut permeability, in which *S. boulardii* treatment could be investigated.

Abbreviations

AJ, adherens junction; cAMP, cyclic adenosine monophosphate; CD, Crohn's disease; EHEC, enterohemorrhagic *Escherichia coli*; EPEC, enteropathogenic *Escherichia coli*; IAP, intestinal alkaline phosphatase; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IEC, intestinal epithelial cell; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MLC, myosin light chain; MLCK, myosin light chain kinase; NF- κ B, nuclear factor- κ B; NSP-4, non-structural protein-4; PKC, protein kinase C; SAIF, *Saccharomyces boulardii* anti-inflammatory factor; SCFA, short-chain fatty acid; TER, transepithelial resistance; TJ, tight junction; TLR, Toll-like receptor; UC, ulcerative colitis; ZO-1, zonula occludens-1.

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The authors report no conflicts of interests in this work.

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