Saccharomyces boulardii: Basic Science and Clinical Applications in Gastroenterology

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Saccharomyces boulardii is a nonpathogenic yeast widely prescribed in a lyophilized form in many countries of the world and used in adults and children as a biotherapeutic agent [1,2]. Controlled clinical trials have demonstrated the efficacy of S boulardii for preventing or treating several intestinal disorders including antibiotic-associated diarrhea [3,4], recurrent Clostridium difficile disease [5,6], C difficile-associated enterocolopathies in infants and children [7], acute diarrhea in children [8] and in adults [9], traveler’s diarrhea [10,11], diarrhea in tube-fed patients [12], AIDS-related diarrhea [13], and relapses of Crohn’s disease [14] or ulcerative colitis [15].

S boulardii differs from S cerevisiae by several taxonomic, metabolic, and genetic properties [16,17]. Lyophilized S boulardii is obtained by cryodessication, a technique that allows it to preserve viability and stability. The pharmacodynamic properties of S boulardii are linked mostly to the revitalization capacity of the yeast after oral administration to the host. S boulardii is genetically resistant to all antibacterial antibiotics [18,19], gastric acidity [18,19], and proteolysis. After oral administration of lyophilized S boulardii, steady-state concentrations of viable yeast cells are achieved within a mean of 3 days, and the cells are cleared from the stools within 2 to 5 days after discontinuation. Thus, S boulardii reaches rapidly in the gastrointestinal (GI) tract high concentrations and remains in a viable (Fig. 1) form throughout the bowel [20]. S boulardii exerts several beneficial effects on the host GI tract including protective effects against enteric pathogens such as Vibrio cholerae [21], C difficile [22,23] and Escherichia coli [24,25], lysis of enterotoxins and their binding to intestinal receptors (C difficile) [22], stimulation of immune host

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defenses [26], inhibition of the inflammatory response induced by enterotoxins [25], and enhancement of trophic factors such as brush border membrane enzymes and nutrient transporters [27,28]. A summary of these beneficial effects is shown in Table 1.

According to these pharmacological and clinical data, *S. boulardii* is a biotherapeutic medication clearly distinct from nutrient probiotic foods containing various species of microorganisms or of substances able to modify the microflora and given in fermented milks or in yogurts to improve host physiology [11].

This article focuses on the clinical applications of the administration of lyophilized *S. boulardii* and explains its beneficial effects on the basis of basic experimental studies.

![Fig. 1. Scanning electron micrograph of the cecum of mice treated with *Saccharomyces boulardii*.](image)

**Table 1**

Mechanisms of action of *Saccharomyces boulardii*  

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production of antimicrobial substances</td>
<td>Not known</td>
</tr>
<tr>
<td>Interaction with host microflora</td>
<td>Yes</td>
</tr>
<tr>
<td>Inactivation of bacterial toxins</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibition of toxins binding to their intestinal receptors</td>
<td>Yes</td>
</tr>
<tr>
<td>Antisecretory effects (Na⁺, Cl⁻)</td>
<td>Yes</td>
</tr>
<tr>
<td>Stimulation of host immune system</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibition of the inflammatory response induced by enterotoxins</td>
<td>Yes</td>
</tr>
<tr>
<td>Trophic effects on intestinal mucosa</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Effects have been assessed on different models of intestinal infections or colonization by different pathogenic microorganisms. They have been reviewed recently by Czerucka and Rampal [29].

Clostridium difficile
Administration of S boulardii significantly reduces mortality caused by C difficile colitis in hamsters treated with clindamycin [30] and in mice inoculated orally with C difficile [31] or directly with toxin A and B of this pathogen [32].

The absence of intestinal or colonic lesions in animals protected by S boulardii has been observed using optical [33] and electron [34] microscopy and has been confirmed on an in vitro model of a cell line (IRD 98) belonging to rat epithelial intestinal cells [35]. The protective effect against C difficile enterotoxigenicity is more marked when S boulardii is given preventively and continuously [30,31,36]. This protective effect disappears when yeast cells are killed by amphotericin-B or by heating and is proportional to the oral dose administered and to the viability of S boulardii in the GI tract [36]. Elmer and Corthier have documented a significant correlation between the survival rates of mice infected with C difficile and the oral dose of S boulardii given [36]. If the dose of S boulardii was increased from $3 \times 10^8$ to $3.3 \times 10^{10}$ cells/mL drinking water, survival rates increased linearly from 0% to 85% [36].

In addition, the protective effect of S boulardii was correlated with the intestinal concentration of C difficile and the levels of toxin A or toxin B [37]. The protective effect of S boulardii against intestinal infections due to C difficile results from several complementary mechanisms. The first of these mechanisms is the secretion in vivo by the yeast of a 54 kDa protease, which inhibits the enterotoxinic and cytotoxic effects of toxins A and B. The intestinal receptor for toxin A of C difficile is a glycoprotein of high molecular weight, sensitive to proteases. Pothoulakis and colleagues [22,37] have demonstrated that S boulardii produces in vivo an original protease of 54 kDa, able to decrease intestinal hydroelectrolytic secretions in an isolated loop of rabbit but being without effect on the lesions caused by C difficile on other cell lines than intestinal epithelial cells, such as lung fibroblasts (SMR-90) or basophilic leukemia cells of rats (RBL). This protease of S boulardii inhibits binding of purified [H³]-enterotoxin A to brush border membranes by 37%, reduces by 55% hydroelectrolytic secretions induced by enterotoxin A, and decreases by 93% intestinal permeability to mannitol. In addition, after oral administration of S boulardii to rats, during 3 days oral administration, enterotoxin A had no effect on hydroelectrolytic secretions and on intestinal permeability. Castagliulo and colleagues [23,37] have confirmed that the partially purified 54 kDa protease could lyse toxin A promptly and specifically and partially destroy the intestinal receptor, resulting in an inhibition of binding of toxin A and B on their intestinal receptors.
The second mechanism is the stimulation of the immune response against toxin A. In mice inoculated orally with a toxoid of toxin A, administration of *S. boulardii* results in an important stimulation of the specific immune response of secretory IgA and IgM antitoxin A in the serum [38].

The third mechanism is inhibition of the adherence of *C. difficile* to intestinal cells by *S. boulardii*. This has been documented in vitro on a cell line [39].

**Vibrio cholerae**

In a model of the isolated jejunal loop of rats, administration of *S. boulardii* reduced hydrosaline hypersecretion induced by cholera toxin significantly [40]. This inhibitory effect has been confirmed in vitro on several intestinal epithelial cell lines of rats IRD 98 [35], IEC 17 [35] and IEC6 [21]. This effect of *S. boulardii* is associated with a 50% decrease in the activity of cyclic adenosine monophosphate (AMP) induced by the cholera toxin. The protective effect disappears after destruction of the yeast by heating. The supernatant of the culture media of *S. boulardii* (also called conditioned medium; CM) is able by itself to decrease, c-AMP activities induced by cholera toxin in IEC 6 cells in a dose-dependent fashion. This effect disappears when the medium is denatured by heating, hydrolyzed by trypsin, or treated with trichloroacetic acid, suggesting the presence of a protein secreted by the yeast in the medium. This protease has been identified on polyacrylamide gels as a 120 kDa protein [21]. This protein and the CM, however, do not change the binding parameters of iodinated cholera toxin on the intestinal receptor [41] and do not show a proteolytic activity on the cholera toxin [21]. These observations have prompted Czerucka and colleagues [42] to study the effects of CM of *S. boulardii* on the intracellular signal pathway regulating the secretion of chloride.

This effect of CM on the transport of chloride has been studied on T84 cells derived from a human carcinoma. These cells present the characteristics of crypt cells secreting chloride by the Na\(^+\) pump, K\(^+\) ATPase, the co-transporter Na\(^+\)/K\(^+\)/Cl\(^-\) and the K\(^+\) channel located at the basolateral side of the cell and the chloride channel located at the apical side. All of these exchange mechanisms play a role in the secretion of chloride induced by agonists acting by means of the c-AMP such as forskolin, vasoactive intestinal polypeptide (VIP), and prostaglandins (PGE), or by means of the Ca\(^{2+}\) pathway such as carbachol [43]. Chloride secretion induced 60 minutes after exposure to cholera toxin has been quantified by the technique of Venglarik and colleagues [44].

In the presence of *S. boulardii* CM, chloride secretion and the levels of c-AMP stimulated by cholera toxin in T84 cells were reduced to the control level. Furthermore, CM of *S. boulardii* decreased chloride secretion enhanced by VIP and PGE2 only if cells had been exposed during 60 minutes to CM preparation of *S. boulardii* before the incubation with the agonists. One hour incubation with CM of *S. boulardii* was also necessary to decrease chloride secretion induced by carbachol without decrease in the intracellular concentration of inositol-triphosphate. CM of *S. boulardii* seems to generate in T84 cells a mediator able to dissociate ionic channels and intracellular calcium levels. In summary, these
data suggest that *S. boulardii* secretes a 120-kDa protein that acts directly on enterocytes and regulates in the cell the pathways controlling chloride secretion.

**Escherichia coli**

On the model of acute diarrhea induced in mice by the thermostable enterotoxin of enterotoxigenic *Escherichia coli* (ETEC), the administration of a suspension of *S. boulardii* exerts a significant inhibitory effect on intestinal hydroelectrolytic secretion [45].

Enteropathogenic *E. coli* (EPEC) are bacterial pathogens predominating in infantile gastroenteritis, especially in developing countries. Enterohemorrhagic *E. coli* (EHEC) are implicated in alimentary contaminations occurring in industrialized countries (United States, Canada, Japan) and produce hemorrhagic colitis associated in some cases with the hemolytic-uremic syndrome [45]. These pathogens secrete a shiga-like toxin that inhibits protein synthesis in intestinal cells but does not seem to be involved in the intestinal pathology caused by EHEC. The pathogenic sequence of EPEC and EHEC begins with their adhesion to the intestinal mucosa resulting in patchy destructions of microvillus membranes, accumulation of actin fibers under the site of bacterial attachment [46], and, as a result, disruption of the tight junctions leading to an increase in intestinal permeability with disappearance of the intestinal barrier [46].

These changes are associated with a translocation and migration of polynuclear cells and with the synthesis of proinflammatory cytokines (interleukin [IL]-8) [47]. Some responses of the enterocytes to infection have been correlated with the activation of the phosphorylation of intracellular signal proteins. For instance, phosphorylation of the myosin light chain (MLC) has been implicated directly in the disruption of tight junctions during acute infections by EPEC [48].

Oral administration of *S. boulardii* during infection of T84 cells with EPEC producing a shiga-like toxin (strain EDL 931) reactivates the barrier function as measured by the transepithelial resistance, the absorption of inulin, or the immunolocalization of protein ZO-1.

In addition, cleavage of caspase 32 shows that *S. boulardii* is able to delay the apoptosis processes resulting from the infection of T84 cells by EPEC pathogens. The yeast has no effect on the amount of EPEC or EHEC bacteria adherent to enterocytes. By contrast, *S. boulardii* inhibits the phosphorylation of several signaling molecules, normally phosphorylated in the response of an infection [24,49].

Infection of T84 cells by EPEC or EHEC pathogens induces the activation of the three pathways of MAP (mitogen activating protein) kinases: the extracellular-regulating protein kinase 1 and 2 (ERK-1 and ERK-2), p38 MAP kinase, and cJUN-kinase. The activation by phosphorylation of ERK-1,2 is associated directly with internalization of the pathogens. The presence of *S. boulardii* significantly decreases the number of bacteria internalized and modulates the phosphorylation levels of ERKs-1,2 [25,50] on serine–threonine residues. Under normal physiological conditions, activation of ERK-1 and -2
by diphosphorylation is the result of a growth factor such as the action of insulin or IgF-1 [51,52]. Diphosphorylation of p38 MAP kinase is involved in the process of apoptosis [51]. During the infection of invasive pathogens such as Salmonella typhimurium [53] and Listeria monocytogenes [54], synthesis and activation of MAP-kinases have been incriminated in the invasion process and in the synthesis of inflammatory cytokines. Czerucka and colleagues [25] have demonstrated that the MAP-kinases pathways stimulated by EPEC and EHEC infection and the activation of the transcription factor NF-kB induced by EHEC are involved in the synthesis of IL-8. S boulardii inhibits these pathways and the synthesis of IL-8 during intestinal infection by these pathogens [25,50]. The yeast also inhibits apoptosis induced by EHEC and reduces the production of TNF-α.

Other enteropathogenic bacteria
Administration of a single dose of 10 mg S boulardii to gnotobiotic mice first inoculated with a suspension of Shigella flexneri or Salmonella typhimurium produced a protective effect against mortality (Shigella flexneri) and severity of intestinal lesions (Salmonella typhimurium) induced by these enteropathogens [53–55].

EFFECTS OF SACCHAROMYCES BOULARDI\ \ON THE GASTROINTESTINAL TRACT
These effects have been reviewed recently [11,19].

Trophic effects
Oral administration of S boulardii to human volunteers during 8 days had no effect on intestinal morphology, villus height, crypt depth, or cellularity of the lamina propria [27]. Likewise, electron microscopy of intestinal epithelial cells of rats treated with S boulardii showed no intracellular translocation of yeasts and no morphological change of microvilli, villus, and crypt structures [27]. Using a three-dimensional technique of microdensification on human intestinal biopsies, Jahn and colleagues [56] confirmed the authors’ findings that after an oral treatment with S boulardii, there was no change in villus surface, microvillus structure, and crypt depth. In a study conducted in human volunteers and in growing rats, Buts and colleagues [27] showed that compared with the initial biopsies taken at day 0, the biopsies of human volunteers treated with S boulardii presented significant increases in the specific and total activity of sucrase–isomaltase (+82%), lactase (+77%), and maltase–glucoamylase (+75%) after 8 days of oral treatment. Likewise, in 30-day-old growing rats treated during 14 days with S boulardii, the specific and total activities of these enzymes were significantly increased compared with a control group treated with a placebo. In agreement with the authors’ findings, Jahne and colleagues [56], using an in situ technique to measure microvillus enzyme activities on histological specimens from frozen intestinal biopsies, reported that after treatment with S boulardii, lactase, α-glucosidases, and alkaline phosphatase
activities were increased by +22% to +55% compared with the basal enzyme activities measured before treatment. From these findings, it appears that *S. boulardii* enhances, in human volunteers and in rats, intestinal enzyme activities that assume nutrient degradation and absorption that are frequently altered in acute or chronic enteropathies. *S. boulardii* secretes in the endoluminal compartment a sucrase at levels of activities so high that *S. boulardii* may be an efficient treatment of congenital sucrase–isomaltase deficiency [57]. A recent study from the authors’ laboratory [58] demonstrated that oral administration of *S. boulardii* also produces a leucine aminopeptidase that belongs to the family of zinc-metalloproteases and that enhances proteolysis of small N-terminal peptides in the intestinal lumen. This enzyme could help reduce the occurrence of allergenization to dietary proteins, especially during the healing phase of acute gastroenteritis, thereby reducing the likelihood of developing chronic persistent or protracted diarrhea after an acute intestinal infection.

In another recent study [28], the authors showed that oral administration of *S. boulardii* to rats during 8 days after a proximal enterectomy of 60% not only enhanced the activity of disaccharidases but also enhanced the absorption of D-glucose coupled to Na\(^+\) by the symport glucose/Na\(^+\).

The absorption of D-glucose measured in vitro on preparations of brush border vesicles was enhanced markedly in relation to the incubation time and glucose concentration in the incubation media, compared with resected rats placebo-treated and with rats that underwent a single transection. In addition, the expression of sodium-glucose cotransporter-1 (SGLT-1) in the brush border membrane, a protein of 70-kDa, when measured by autoradiographic screening, was much more marked in rats resected and treated with *S. boulardii* than in the two other groups. These data underline the interest of *S. boulardii* for acute gastroenteritis when SGLT-1 is used to reabsorb water and electrolytes with salt replacement therapy to prevent or to treat moderate dehydration. Similar data have been published by Zaouche and colleagues [59].

In addition to the stimulation of brush border enzymes and transporters, *S. boulardii* enhances expression of the receptor for polymeric immunoglobulins [26] and the secretion of secretory IgA [26] (s-IgA), whose intraluminal function and intracellular synthesis differ quite totally. Because yeast cells do not penetrate into enterocytes [27] the authors have assessed the potential influence of trophic factors secreted by *S. boulardii* cells during their intestinal transit.

Table 2 summarizes the intestinal functions stimulated by oral administration of *S. boulardii* and the enzymatic and trophic factors secreted by the yeast during its transit identified up to now.

As shown in Table 3, determinations by high-performance liquid chromatography (HPLC) of polyamines on lyophilized preparations of yeast cells revealed substantial amounts of these substances, totaling 679 nmol/100 mg of lyophilized *S. boulardii*, mainly spermidine (55%) and spermine (43%), with very low concentrations of putrescine (1.4%) [60]. Theoretically, these amounts of polyamines can influence the intestinal expression of brush border glycoproteins such as hydrolases, proteases, and transport carriers. Indeed,
a marked stimulation of disaccharidase activity, aminopeptidase and the endoluminal secretion of secretory IgA has been observed in the small intestine of infant rats before weaning in response to oral ingestion of spermine and spermidine equal to 1000 nmol of purified polyamines per day [60]. When rats were treated with an amount of spermine (500 nmol/d) equivalent to the content of polyamines of the yeast lyophilized preparation (679 nmol/100 g), similar enzymatic responses were observed, including significant increases in the specific and total activities of sucrase (2.5-fold increase) and of maltase (+24%). In response to 1000 nmol spermine, the stimulation of the enzyme activities was proportionally greater with increases in the activity of sucrase (4.6-fold increase) and of maltase (+70%). Likewise, weaned rats treated with *S boulardii* or with equivalent amounts of spermine (500 nmol) presented parallel

<table>
<thead>
<tr>
<th>Factor</th>
<th>Stimulated</th>
<th>Secreted</th>
</tr>
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<tbody>
<tr>
<td>Sucrase</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Maltase-glucoamylase</td>
<td>+++</td>
<td>No</td>
</tr>
<tr>
<td>Lactase</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>Aminopeptidase</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Protein phosphatase</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>Trehalase</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Carboxypeptidase</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Angiotensinase</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>DPP IV</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>SGLT-1</td>
<td>+++</td>
<td>No</td>
</tr>
<tr>
<td>Receptor of polymeric immunoglobulins</td>
<td>+++</td>
<td>No</td>
</tr>
<tr>
<td>s-IgA</td>
<td>+++</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: DPP IV, dipeptidyl peptidase IV; SGLT-1, sodium-glucose cotransporter-one; s-IgA, secretory IgA.

- +++ markedly.
- ++ moderately.
- + slightly.

### Table 3

Polyamine concentrations in lyophilised preparation of *Saccharomyces boulardii*

<table>
<thead>
<tr>
<th>S boulardii nanomoles/mg</th>
<th>S boulardii nmol/mg protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 8</td>
<td>n = 8</td>
</tr>
<tr>
<td>Putrescine</td>
<td>0.095 ± 0.014</td>
</tr>
<tr>
<td>Spermidine</td>
<td>3.766 ± 0.328</td>
</tr>
<tr>
<td>Spermine</td>
<td>2.930 ± 0.268</td>
</tr>
<tr>
<td>Total</td>
<td>6.790</td>
</tr>
</tbody>
</table>

Values are means ± SD [77].
and significant increases in the specific activity of sucrase (+157%) and of maltase (+47.5%) [60].

Thus, oral administration of 100 mg lyophilized S boulardii containing 679 nmol of polyamines compared with 500 nmol of purified spermine given to suckling rats or to weaned rats results in similar enzymatic responses. The stimulation of sucrase and maltase by oral administration of spermine is a dose-dependent effect that for sucrase and maltase is more sensitive than for lactase, aminopeptidase, and alkaline phosphatase, and which becomes detectable for doses of spermine exceeding 250 nmol/d. In addition, both S boulardii [60] and purified spermine given at 500 nmol per day can stimulate significantly the intestinal production of the intestinal receptor for immunoglobulins in weanling rats between postpartum days 20 and 40.

Besides changes in enzyme activities, oral treatment with S boulardii produced parallel changes in the concentrations of polyamines in intestinal mucosa (+21.4%) and in endoluminal fluid (+48% to +316% in the jejunum and +60.8% to +150% in the ileum). Variations in concentration of the three polyamines measured by HPLC in the intestinal mucosa were proportional to their respective concentrations measured in the lyophilized preparation of the yeast. Indeed, spermine and spermidine, which represented respectively 44% and 55% of the total of polyamines produced by S boulardii, were increased in similar proportions in the intestinal mucosa (+21.4% and +21.9%).

In concordance with the very low amounts of putrescine produced by the yeast (1.4%), putrescine concentrations in the small bowel mucosa varied very little and were not affected by the oral treatment.

Experimental data indicate that the transepithelial transport of polyamines by brush border membrane vesicles is a selective and saturable process, largely dependent upon intraluminal concentrations [60].

In samples of jejunal and ileal endoluminal fluid rinsed and filtered to discard yeast cells, spermidine and spermine levels were increased after oral treatment by +48% to +316% in treated rats compared with controls, while the levels of putrescine were not enhanced significantly.

In summary, the data show that at the doses used, the lyophilized preparation of S boulardii exerts trophic effects on the small intestinal mucosa that likely are mediated, at least in part, by the endoluminal production of spermine and spermidine. These polycationic substances seem to be released by yeast cells during their catabolic phase rather than being secreted by viable yeast cells during their endoluminal transit. Indeed, only traces of putrescine have been detected in the culture media of yeast after 96 hours of exponential growth without evidence of spermine or of spermidine in the media. Because the physiological effects of exogenous polyamines on intestinal cell maturation, intestinal enzyme expression, transport mechanisms, crypt cell division, DNA synthesis and gene transcription are established, the substantial amount of polyamines delivered by S boulardii could have important clinical implications. Although the use of S boulardii as a biotherapeutic agent has been documented in acute gastroenteritis, in antibiotic-associated diarrhea, and in enterocolopathies
caused by *C. difficile*, the potential trophic effects of the yeast for preventing chronic persistent diarrhea, chronic protracted diarrhea, allergenization to dietary proteins, and for the substitutive treatment of congenital enzymatic deficiencies (sucrase–isomaltase, trehalase) warrant further investigations.

Besides the trophic effects mediated by polyamines, an important matter of study has been raised by the effects of *S. boulardii* on the metabolism of short-chain fatty acids (SCFAs), especially butyrate, acetate, and propionate. SCFAs are among the most important metabolites produced by the anaerobic colonic microflora, and they play a major role in colonic reabsorption of water and electrolytes [61]. In a porcine model of bacterial ecosystem, administration of *S. boulardii* was able to restore the production of SCFA, at normal levels, which were depressed by the decrease of bacterial mass due to clindamycin treatment [62].

This property can play a role in acute gastroenteritis and explain in part the antidiarrheal effect of *S. boulardii*, because SCFA are decreased in relation to microflora alterations in antibiotic-associated diarrhea and diarrhea occurring during continuous enteral feeding.

**Antisecretory effects**

*S. boulardii* reduces hydroelectrolytic secretions (–39%) and permeability of the mucosa to mannitol (–65%) induced by toxin A of *C. difficile* in the rat ileum [22,23].

Furthermore, *S. boulardii* inhibits the secretion of chloride induced by the signal transduction pathway of cyclic AMP and the calcium pathway in epithelial villus cells [42,63].

Lastly, when administered preventively in rats, *S. boulardii* exerts a marked effect on the secretory diarrhea induced by castor oil, the effect being dose-dependent [64]. This effect is inhibited by L-arginine, suggesting a role of the nitric oxide (NO) pathway in this mechanism.

**Immunological effects**

In growing rats, *S. boulardii* produces a marked increase (+57%) in the concentrations of secretory s-IgA in the intestinal lumen and the concentration of the receptor for polymeric immunoglobulins in crypt cells (+63%) [26]. A similar effect has been documented in BALB/c mice orally treated by a toxoid of *C. difficile* toxin A, resulting in a strong increase in total s-IgA production (1.8-fold) and in the levels of secretory s-IgA specifically directed against toxin A (4.4-fold) [38].

**Anti-inflammatory effects**

Studies on the protective mechanisms of *S. boulardii* on infections EPEC and EHEC have shown that *S. boulardii* inhibited the pathways of MAP kinases and of NF-kB, leading to apoptosis and secretion of proinflammatory cytokine IL-8 [49]. Likewise, Sougioultzis and colleagues [65] have shown the production by the yeast of a hydrosoluble factor that is able to inhibit NF-kB when intestinal cells are exposed to the toxin A of *C. difficile*. These findings emphasize the
importance of developing clinical studies of *S boulardii* for treating inflammatory bowel diseases (IBDs).

In summary, the mechanisms of the antidiarrheal effects of *S boulardii* may be attributed to two main pharmacodynamic properties of the yeast cells: (1) inhibition of some bacterial toxins or of their pathogenic effects and (2) direct effects on intestinal mucosa, including trophic effects, antisecretory effects, a stimulation of intestinal immunity, and an anti-inflammatory effect.

The clinical efficacy of lyophilized *S boulardii* has been assessed in several intestinal diseases.

**ANTIBIOTIC-ASSOCIATED DIARRHEA AND CLOSTRIDIUM DIFFICILE ENTEROCOLOPATHIES**

Antibiotic-associated diarrhea (AAD) occurs between 5% and 30% of the time during antibiotic treatment. Symptoms range from simple diarrhea without dehydration or hydroelectrolytic disturbances to severe secretory diarrhea that is potentially lethal, with in extreme cases pseudomembranous colitis or enterocolitis. *C difficile* is thought to be responsible for 10% to 30% of AAD and for 95% of pseudomembranous colitis [66]. *C difficile* is also the cause of protracted chronic enterocolopathies in infants [7]. Beside their potentially lethal outcome, AADs caused by *C difficile* overgrowth are characterized by a high frequency of clinical relapses: 20% of relapses after the initial affection and 60% after the first relapse. In some cases, another pathogen, especially *Klebsiella oxytoca* [67], has been incriminated. The risk factors to develop AAD now are understood better. They are linked either to the type and duration of antibiotherapy (long treatments, multiple antibiotics, antibiotics excreted in the bile, antibiotics acting on anaerobes, broad-spectrum antibiotics) or to factors linked to the host (eg, very young or very old persons, surgery, chronic digestive diseases, severity of the causal infection, immunosuppression) [68].

The existence of one or of a combination of these factors of risk may justify prophylactic treatment.

**Prevention of antibiotic-associated diarrhea**

Three prospective, randomized, placebo-controlled clinical studies have confirmed the efficacy of *S boulardii* for preventing AAD.

In a first study, conducted in 180 hospitalized patients [3], *S boulardii* was given at the dose of 1 g/d during the period of antibiotherapy up to 2 weeks after discontinuation of antibiotics. The occurrence of AAD was 21.8% in the placebo group versus 9.5% in the treated group (*P* = .038).

In a second two-center study of 193 hospitalized patients receiving a β-lactam in combination with another antibiotic or not [4], *S boulardii* was administered at the dose of 1 g/d and was continued during 3 days after discontinuation of antibiotics. Occurrence of AAD was 14.6% in the placebo group versus 7.2% in the group treated with *S boulardii* (*P* = .03).

These data confirm those recorded in a preliminary study conducted in 388 ambulatory patients [69]. Treatment with *S boulardii* at the dose of
200 mg/d during the antibiotic therapy (β-lactams or cyclines) decreased the percentage of AAD from 17.5% to 4.5% [69].

**Treatment of recurrent diarrhea and colitis due to Clostridium difficile**

Several clinical trials aiming to assess the efficacy of *S. boulardii* for treating relapses of colitis and diarrhea caused by *C. difficile* have been performed.

In a preliminary open study, conducted in 13 patients presenting multiple relapses of pseudomembranous colitis caused by *C. difficile* [70], administration of *S. boulardii* at 1 g/d during 1 month in association with vancomycin prevented further relapses in 11 patients.

A multi-center prospective, randomized, placebo-controlled study in 124 patients treated with vancomycin or metronidazole for an episode of colitis or diarrhea caused by *C. difficile* [5] has assessed the effect of *S. boulardii* on the occurrence of further relapses. In patients having had at least one relapse (n = 60), administration of *S. boulardii* reduced the occurrence of further relapses significantly: 64.7% relapses in the placebo group versus 34.6% relapses in the group treated with *S. boulardii* (P = .04).

Another multi-center, prospective and placebo-controlled study has been conducted in 170 patients presenting a chronic intestinal infection caused by multi-resistant *C. difficile* strains. That study has shown that the treatment of choice was the combination of high doses of vancomycin with *S. boulardii* [6].

**Treatment of enterocolopathies caused by Clostridium difficile in infants**

In infants and children, intestinal overgrowth of a pathogenic strain of *C. difficile* rarely results in pseudomembranous colitis. More often, it produces an acute enteritis or a chronic enterocolopathy. In an open trial of 19 infants and children presenting with chronic diarrhea or chronic protracted enterocolopathy caused by toxinogenic resistant *C. difficile*, *S. boulardii* treatment at the dose of 500 to 1000 mg/d during 15 days resulted in a prompt disappearance of clinical symptoms in 18 patients, with negativation of toxin B in 16 patients [7]. Most of the patients had been treated before with one or several antibiotics.

**ACUTE GASTROENTERITIS**

A prospective, randomized, placebo-controlled study evaluated *S. boulardii* at 500 mg/d in acute gastroenteritis of moderate intensity occurring in young children [71]. At day 1 and day 4 in the treated (n = 19) and in the control group (n = 19), there was a significant difference in four criteria: number, weight, consistency of stools, and transit time measured by the red carmine method [71].

In another placebo-controlled study of 130 children aged from 3 months to 3 years, administration of *S. boulardii* at 300 mg/d significantly reduced the frequency of stools after 48 hours of treatment. At 48 and 96 hours of treatment, the amount of clinical healing was significantly higher in the treated group [9] than in the placebo group.
In adults, a prospective placebo-controlled study was performed in 92 patients with acute gastroenteritis [8]. Administration of *S boulardii* reduced symptoms and diarrhea significantly after 48 hours (*P* = .035), measured by a score integrating symptoms, number, and consistency of stools.

**TRAVELER’S DIARRHEA**

This is the most frequent disorder occurring in people traveling in tropical or subtropical countries.

The efficacy of *S boulardii* for preventing traveler’s diarrhea has been demonstrated in a large cohort of travelers going to different continents. A total of 1016 persons have been questioned to evaluate the efficacy of *S boulardii*. Treatment with yeast cells has been assumed 5 days before the travel and during all the trip.

Patients were assigned to one of three groups. The first group received a placebo; the second group received *S boulardii* at 250 mg/d, and the third group received *S boulardii* at 1000 mg/d.

The incidence of diarrhea was 39.1%, 34.4% (*P* = .019 versus placebo), and 28.7%, respectively (*P* = .005 versus placebo) [10].

**DIARRHEA ASSOCIATED WITH CONTINUOUS ENTERAL FEEDING**

Three randomized, prospective and placebo-controlled studies have documented an efficacy of *S boulardii* for preventing diarrhea that occurs during continuous enteral feeding.

In patients hospitalized in a high care medical unit, administration of *S boulardii* at 500 mg/l of nutritive solution reduced the incidence of diarrheal days from 16.9% to 8.7% (*P* < .001) [72].

In another study of patients hospitalized in a sterile unit burn, preventive treatment with *S boulardii* at the dose of 2 g/d reduced the incidence of diarrheal days from 9.1% to 1.5% (*P* < .001), with a significant improvement in digestive tolerance to the enteral diet and a significant increase in caloric intake [73].

Lastly, a multi-center study (11 centers) conducted in 128 patients has confirmed the efficacy of *S boulardii* given at 2 g/d for preventing diarrhea in patients hospitalized in an intensive care unit and nourished with enteral feeding [12]. The authors observed a significant reduction of the number of days with diarrhea (14% versus 19% in the placebo group, *P* < .01) in the group treated with *S boulardii* (relative efficacy of 29%).

**DIARRHEA IN PATIENTS WITH AIDS**

In an open study on 17 patients presenting chronic diarrhea associated with AIDS, *S boulardii* given at 3 g/d during 15 days exerted an antidiarrheal effect, with diminution of the mean stool output from 9.0 to 2.1 per day [13]. A double-blind, placebo-controlled study conducted in 35 patients has confirmed these results. After 1 week of treatment, diarrhea was controlled in 61% of...
treated patients compared with 12% in the placebo group (<.002). The number, weight, and volume of stools; abdominal pain; body weight; and the Karnofsky quality of life index also were improved significantly in patients treated with *S. boulardii* [74].

**IRRITABLE BOWEL SYNDROME**

A prospective placebo-controlled, clinical trial composed of 34 patients with irritable bowel syndrome with predominant episodes of diarrhea has shown that treatment with *S. boulardii* has a significant effect on the number and consistency of stools (*P* < .05) after 1 month of treatment [75].

**CHRONIC INFLAMMATORY BOWEL DISEASES**

A prospective randomized clinical trial has assessed the efficacy of *S. boulardii* (1 g/d) with mesalamine (2 g/d) versus mesalamine alone (3 g/d) for preventing relapses of Crohn’s disease [14] in adults in remission for the disease. After 6 months, the incidence of relapses reached 37.5% in the group receiving mesalamine alone (*n* = 16) versus 6.25% in the group treated with mesalamine and *S. boulardii* (*n* = 16, *P* = .04).

A recent pilot study showed interesting data for treating moderate forms of ulcerative colitis [15].

**SAFETY OF USE**

Lyophilized *S. boulardii* is tolerated well under usual conditions of use. In very rare cases, *S. boulardii* fungemias have been reported. In documented cases, all patients had an indwelling central venous catheter [76].

*S. boulardii* fungemia disappeared, either spontaneously with discontinuation of the product or as a result of antifungal treatment. In some cases, the removal of the central venous catheter was necessary. Colonization of the central venous catheter during handling of packets or capsules appears to be the most likely involved mechanism. Consequently, administration of lyophilized *S. boulardii* is contraindicated in patients with an indwelling central venous catheter [77].

**SUMMARY**

Because of major advances in understanding in intestinal physiology and in the role of intestinal microflora, many of the mechanisms of action of *S. boulardii* have been elucidated: secretion in vivo of proteases and substances inhibiting bacterial toxins or their pathogenic effects, trophic effects, antisecretory effects, immunostimulatory effects and anti-inflammatory effects.

The efficacy of lyophilized *S. boulardii* has been established by clinical studies, conducted prospectively and placebo-controlled, in several pathological conditions such as AAD, *C difficile* enterocolopathies, pseudomembranous enterocolitis, acute gastroenteritis, traveler’s diarrhea, chronic diarrhea of patients with AIDS, and IBDs.
The recent discovery of a clear anti-inflammatory effect of this biotherapeutic agent warrants further scientific studies and clinical trials in IBD.

References


