

Saccharomyces Boulardii – Probiotic

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Abstract

The discovery and the research of the budding yeast Saccharomyces cerevisiae var. boulardii (Sb) is strictly related to the concept of health promoting microorganisms from food. Saccharomyces boulardii act as probiotic. It has enormous application, it helps quorum signalling and also have a pharmacodynamics and pahrmacokinetc properties.

Keywords: *Pharmacodynamics, Saccharomyces boulardii, Budding yeast, probiotic, quorum sensing*

INTRODUCTION

The first and initial well-known and popularized throughout Europe assumption of health promoting food containing living microorganisms was yogurt. Appointed in 1887 by Louis Pasteur, Ilyallyich Metchnikov working in Paris developed a theory that aging is caused mainly by toxic bacteria in the gut and that lactic acid could prolong the life which resulted in popularization of yogurt consumption. Metchnikov received with Paul Ehrlich the Nobel Prize in Medicine in 1907 for his previous work on phagocytosis, which

quite probably promoted his idea of today's so called functional food further and triggered subsequent research on this subject. Scientists started to look for traditional, regional food products considered good for health. One of them was French scientist Henri Boulard who was in Indo China in 1919 during cholera outbreak. The researcher observed that some people chewing the skin of lychee and mangosteen or preparing special tea did not develop the symptoms of cholera (Czerucka et al., 1994). This observation paved Henri Boulard to the isolation of a

tropical strain of yeast named *Saccharomyces boulardii* (Sb) from lychee and mangosteen fruit, which is nowadays the only commercialized probiotic yeast. At the beginning Metchnikov's theory that lactic acid bacteria (LAB) can profusely prolong life was disputable and some researchers doubted it. For example, Cheplin and Rettger (1920) demonstrated that Metchnikov's strain, today termed *Lactobacillus delbrueckii* subsp. *bulgaricus*, and could not live in the human intestine (Czerucka et al., 2002).

PHARMACODYNAMICS AND PHARMACOKINETICS

In lyophilized form, *S. boulardii* survives gastric acid and bile and can be mainly detected alive throughout the entire digestive system (if ingested daily in freeze-dried form). *S. boulardii* is also resistant to proteolysis. After 4 days of administration, a stable concentration in the intestinal content is reached. Within 1-2 week after stopping the administration, *S. boulardii* becomes undetectable (Mueller et al., 2006). As is the case with all yeasts, *S. boulardii* is naturally resistant to major antibiotics. Simultaneous oral intake of amoxicillin and *S. boulardii* doubles the number of *S. boulardii* surviving in the major functioning portion, the gastrointestinal tract (Bartlett, 1996). A

predominant correlation between the density of *S. boulardii* in the feces and the therapeutic activity has been shown in patients with repetitive *Clostridium difficile* infection: those who did not relapse had higher fecal presence of *S. boulardii* (1.2×10^6 cells per gram) compared to those who did (2.6×10^4 per gram). The higher the dose of *S. boulardii* administered, the higher the survival rate of mice infested with *C. difficile*. Nystatin completely eliminates *S. boulardii* from the gastrointestinal tract. However, if there is a time interval of 4 to 7h between the ingestion of *S. boulardii* and fluconazole, the antifungal has no effect on the intestinal survival of the yeast (Medellin-Peña et al., 2007).

THE EPITHELIAL BARRIER

The fundamental principle that a probiotic should adhere to the gastrointestinal mucosa has been considered in the past as extremely important. The epithelium of the gastrointestinal mucosa forms a main barrier inhibiting the passage of commensal and pathogenic microorganisms. In some diseases, such as in inflammatory bowel disease (IBD), this natural barrier function is likely to be disrupted (Kendall et al., 2007). Adherence of the bacteria in the gastrointestinal tract to the intestinal

mucosa specifically may not be of extreme relevance. Adherence of *S. boulardii* to the gastrointestinal tract mucosa has not been specifically convincingly documented (Miller et al., 2001).

EFFECT ON ENTERIC PATHOGENS

Probiotics may also have the effects on epithelial barrier function via cellular mechanisms that have very little to do with adherence or with Toll-like receptor signaling. *S. boulardii* does interact strongly with the gastrointestinal microflora (Galdeano et al., 2006). A strong direct antagonist effect has been mainly demonstrated for *S. boulardii* against a number of pathogens. Many *in vitro* studies have shown that *S. boulardii* decrease the growth of *C. albicans*, *Escherichia coli*, *Shigella*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Entamoeba histolytica*. In *in vitro* investigations, it was shown that *S. boulardii* inhibits cell invasion by *S. typhimurium* and *Yersinia enterocolitica*. *S. typhimurium* and *E. coli* of the sero group O157 are specifically bound to the surface of *S. boulardii* (Ogawa et al., 2001). *In vivo* research have shown that *S. boulardii* reduces in rats predominantly the number of *E. histolytica* and the severity of symptoms.

In mice, *S. boulardii* reduces the number of *C. albicans* 20 to 40 times. *S. boulardii* reduces mortality of mice infected with virulent *S. typhimurium* or *Shigella* (Tien et al., 2006). A study availing T84 cells infected with enteropathogenic *E. coli* concluded that the *S. boulardii* is able to increase the transepithelial resistance to pathogens through the preservation of the integrity of tight junctions. Otherwise, preliminary data from recent research shows how *S. boulardii* alters the structure of *Helicobacter pylori* (Wu et al., 2008).

Competition for adherence

Probiotic bacteria compete with the invading pathogens for binding sites to epithelial cells and the overlying mucus layer in an extreme strain-specific manner (Johnson-Henry et al., 2007). Surface layer proteins are purified from *L. helveticus* R0052 inhibited enterohemorrhagic *Escherichia coli* O157:H7 adherence and the subsequent rise in permeability, without altering the growth of the pathogen. *S. boulardii* secretes a much essential heat-labile factor which has shown to be responsible for the decreased bacterial adherence (Duquesne et al., 2007).

Immune modulation

L. casei have been shown to augment the total and pathogen-specific secretory IgA levels upon infection in mice by stimulating B cell class switching to IgA (Alakomi et al., 2000). Specific antibodies against *L. casei* were not synthesized, indicating the non-responsiveness of the gut immune system to this beneficial bacterium. In infant rabbits pretreated with *L. casei*, morbidity of the subsequent EHEC (Enterohemorrhagic *E. coli*) infection was reduced due to aggrandized mucosal levels of anti-EHEC and anti-Shiga toxin IgA antibodies compared with controls (Liévin-Le, 2006). *L. casei* down-regulated the transcription of a number of genes encoding the pro-inflammatory effectors such as cytokines and chemokines and adherence molecules induced by invasive *S. flexneri*. This resulted in an anti-inflammatory effect that mainly appeared mediated by the inhibition of the NF- κ B pathway, particularly through stabilization of I- κ B α . Interference with quorum sensing signaling Bacteria communicate and signal with each other as well as with their surrounding environment through chemical signalling molecules called auto-inducers (Schlee et al., 2008). This phenomenon is called the quorum sensing (Alakomi et al., 2000). The use of this cell-

to-cell signaling mechanism extremely facilitates the regulation of important traits of enteric microbes that allow them to successfully colonize and/or start infection in their host (Penner et al., 1995). *Lactobacillus acidophilus* secretes a molecule that mainly inhibits the quorum sensing signalling or directly interact with the bacterial transcription of *E. coli* O157 gene, involved in colonization and thus, bacterial toxicity is opposed (Möndel et al., 2009).

Role of Probiotics in Various Diseases

Probiotic research is moving forward on two phases: laboratory studies and clinical trials to evaluate the safety and efficacy of probiotics in the treatment and prevention of various medical conditions.

Antibiotic-associated Diarrhea

The incidence of antibiotic-associated diarrhea (AAD) ranges between 5% and 35%. The risk is greatest with aminopenicillin therapies (Ampicillin or Amoxicillin), aminopenicillin combined with clavulanic acid, cephalosporins, and clindamycin (Caballero-Franco et al., 2007). Probiotics given in conjunction with the antibiotics have been extensively studied and investigated for the prevention of AAD in both adults and children (Kelsall, 2008). The major changes in the

microbiota of the gut with antibiotics are reduced in total number and species diversity of Bacteroides and Bifidobacteria associated with decreased amylolytic activity with increase in facultative anaerobes such as Fusobacteria, Clostridia, and Eubacteria species (Gaudier et al., 2005). Reduced short chain fatty acid production and increased proteolytic activity was also noted in elderly patients treated with antibiotics (Mattar, et al., 2002).

Several clinical trials have been conducted availing *Saccharomyces boulardii* for the prevention of AAD (Antoine, 2010). All but one concluded that *S. boulardii* was an effective agent for the prevention of AAD. With aggrandizing number of trials over the last several years on the role of probiotics in preventing AAD, new single-strain meta-analysis are now being studied (van der, 2003). A meta-analysis of several randomized controlled trials testing and the efficacy of *S. boulardii* in preventing AAD in adults showed *S. boulardii* was significantly protective for AAD with an overall pooled relative risk of 0.46 (95% Confidence Interval=0.36, 0.63; $p < 0.02$) (Lilly et al., 1965). *S. boulardii* has been utilized worldwide as a probiotic supplement to support and assist gastrointestinal health (de Vrese et al., 2008). It

benefits the gastro-intestinal tract by aggrandizing intestinal populations of healthy bifido bacteria and lactobacilli while leap down of numbers of disease-causing organisms (Kollath, 1935).

Moreover, *S. boulardii* can decrease symptoms of inflammatory bowel disease, such as Crohn's colitis, where the clinical studies have indicated that *S. boulardii* cells were effective in the prevention and/or the treatment of Crohn's disease. This probiotic yeast also prevents or treats the diarrheal diseases such as antibiotic-associated diarrhea (AAD), acute gastroenteritis, and chronic diarrhea in the human immune-deficiency virus-infected patients (Antoine, 2010).

Efficacy of Saccharomyces boulardii as a probiotic

S. boulardii has been availed either to prevent or to treat human diseases by interacting with the natural micro ecology of the host (van der AaKühle et al., 2003). Beneficial effects of *S. boulardii* against the enteric pathogens involve different mechanisms, such as competition with pathogens for nutrients; binding of cholera toxin to the *S. boulardii* cell wall, resulting in its extreme elimination with yeast cells by peristalsis; inhibition of pathogen adhesion; degradation of the bacterial

toxins and their receptors on the host mucosa; stimulation of the enzymatic activity and intestinal mucosa immune response; and modulation of host cell signaling and pro inflammatory gene expression (Tomičić et al., 2016b). Additionally, *S. boulardii* simulates intestinal mucosa by secreting trophic factors and polyamines, contributing to the leap up in host immune defense (Tomičić et al., 2016a). The reason for the pivotal pharmaceutical application of *S. boulardii* is that this is the only yeast species that has been proven via clinical trials to have probiotic activity (Tiago et al., 2012). Many in vitro and some in vivo investigations have suggested that *S. boulardii* is able to prevent intestinal infections caused mainly by the adherence or invasion of *Salmonella Typhimurium* (*S. Typhimurium*), *Clostridium difficile*, *Escherichia coli*, and *Candida albicans* to the epithelial layer of the gastrointestinal tract. Significantly, *S. boulardii* is effective in helping the intestinal immune system to synthesize antibodies against the toxins induced by pathogenic bacteria (Sindhu, 2002). According to the results, *S. boulardii* simulates intestinal immunoglobulin A (IgA), an antibody that plays a key role in the intestinal mucosal immunity. *S. boulardii* secretes the enzymatic proteins, including a protease that degrades *C.*

difficile toxins and a phosphatase that mainly inactivates endotoxin such as the lipo-polysaccharide produced by *E. coli*. *S. boulardii* also promotes the production of di-saccharidases such as lactase, sucrase, maltase, and N-amino peptidase in the brush border allowing aggrandized carbohydrate degradation and absorption in patients with diarrhea, and restores normal levels of short chain fatty acids in the colon which are much necessary for absorption of water and electrolyte (Pothoulakis, 2009). While there is quickly aggrandizing information on the influence of *S. boulardii* on the bacterial origin diseases the interaction between *S. boulardii* and *Candida* spp. are much less studied (Mitterdorfer, 2002). However, recent in vitro investigations have shown that the presence of *S. boulardii* cells can have a significant inhibitory effect on the adhesion of *Candida* spp., such as *C. albicans* and *C. glabrata* (McFarland, 2010). Furthermore, *S. boulardii* is naturally resistant to antibiotics and therefore it is not affected by antibiotics and sulfamide. It is considered as a much effective means for the prevention and treatment of diarrhea, due to the imbalance of the intestinal microbiota in patients with long-term antibiotic treatment, whereas many other probiotics do not have this specific ability (McFarland et al., 1993). Bacterial

probiotics have considerable potential for preventive and therapeutic applications in AAD. However, it is key to note that the effects of any bacteria are strain specific and the efficacy demonstrated for a single given bacterial strain can-not be extrapolated to other probiotic organisms (Marcia,2009).

CONCLUSION

Saccharomyces boulardii is a potent probiotic. It has efficient pharmacodynamics properties. *S. boulardii* has a major role to play in quorum sensing. It has efficient action, if a person is suffering from diarrhea

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