

Eukaryotic Probiotic *Saccharomyces boulardii* Application in Clinical Trails: A Review

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ABSTRACT

Probiotics are live microbes that assist in restoring the symbiotic intestinal gut flora balance, and thus, bestow health benefits to the host. The most commonly used human probiotics are members of the *Lactobacillus* and *Bifidobacterium* species. Besides these bacteria, *Saccharomyces boulardii*, a yeast strain, is also widely used as a probiotic to treat a variety of conditions, including antibiotics-associated diarrhea and recurrent *Clostridium difficile* infection. A primary advantage of using *Saccharomyces boulardii* as a probiotic is that it can be used by patients undergoing antibiotic regimen due to its natural resistance to antibiotics. The genetic transfer of antibiotic resistance genes, a frequent event between pathogenic and gastrointestinal tract (GIT) bacteria, is not as frequent between yeast and bacteria. Furthermore, *Saccharomyces boulardii* is also tolerant to various local stresses such as the presence of gastrointestinal (GI) enzymes, bile salts, organic acids, etc. and can withstand considerable variations in pH and temperature while transiting through the human GIT. *Saccharomyces boulardii* is known as generally regarded as safe (GRAS) with probiotic activity against a wide range of pathogens. This yeast is often marketed in a lyophilized form, "*S. boulardii* lyo", complete sequence of the genome was performed, and a comparative analysis of the genome was performed. From clinical studies, the results of randomized controlled trials in patients repeatedly confirmed the significant positive effect in the treatment of acute and chronic diseases.

Keywords: Clinical trails, Probiotics, *Saccharomyces boulardii*, Therapeutic yeast.

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INTRODUCTION

The discovery and study of the budding yeast *Saccharomyces boulardii* is strictly related to the concept of health-promoting microorganisms from food; the first most well-known and popularized throughout Europe's assumption of health-promoting food containing living microorganisms was yogurt. Appointed in 1888 by Louis Pasteur, Ilya Ilyich Metchnikov working in Paris developed a theory that toxic bacteria cause aging in the gut and that lactic acid could prolong life, which resulted in the popularization of yogurt consumption. Metchnikov received with Paul Ehrlich the Nobel Prize in Medicine in 1908 for his previous work on phagocytosis, which probably promoted his idea of today's so-called functional food further and triggered subsequent research on this subject.¹ 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 1920 during cholera outbreak; he observed that some people chewing the skin of lychee and mangosteen or preparing special tea did not develop the symptoms of cholera.² This observation lead Henri Boulard

to isolation of a tropical yeast strain named *Saccharomyces boulardii* from lychee and mangosteen fruit, which is nowadays the only commercialized probiotic irrespectively of the assumed probiotic definition, during over half of the last century the conducted research showed that *Saccharomyces boulardii* might be beneficial for human health.³⁻⁷ As mentioned before, the history of the probiotic strain started in 1920. Henri Boulard, after his return to France, patented isolated strain and in 1947 sold it to Biocodex company created for its production. *Saccharomyces boulardii* was registered as a drug for the first time in 1953 and so far it is the only registered eukaryotic probiotic microorganism. While the commercial application of *Saccharomyces boulardii* in diarrhea treatment has been steadily growing since 1953, the scientific interest measured with a number of publications was in a "lag phase" during next 30–40 years, Google Scholar for *Saccharomyces boulardii* has been found out that there were no articles after 1953, with the first appearing in 1977, From 1977 to 1986 only 17 publications were found.⁸⁻¹¹ Recently published papers have recommended further studies on *Saccharomyces boulardii*.¹²

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Antibiotic-Associated Diarrhea (AAD)

Saccharomyces boulardii has been used in different clinical trials against different diarrhoeal diseases and has shown promising results. Treatment with *Saccharomyces boulardii* is well tolerated, except for sporadic reports of fungemia, in immune-compromised patients or patients with severe general or intestinal diseases in most cases infected through an indwelling central venous catheter.¹³ One of the benefits of using *Saccharomyces boulardii* as a probiotic is the natural resistance of that to antibacterial antibiotics. Thus it can be prescribed to patients receiving antibacterial antibiotic therapy. Antibiotic-associated diarrhoea (AAD) is a common complication of treatment with antibiotics caused by disruption of normal gut microbiota and colonization of pathogenic bacteria which results in an acute inflammation of the intestinal mucosa. The most common opportunistic pathogen related to AAD is *Clostridium difficile*.^{14,15} Among other infectious organisms *Staphylococcus aureus*, *Clostridium perfringens*, *Klebsiella oxytoca*, *Candida* species, *E. coli* and *Salmonella* species can be mentioned.¹⁶ *Saccharomyces boulardii* has been comprehensively evaluated for the prevention of AAD and the potential effect of the yeast in decreasing the ADD in adults and children has been proven.¹⁷ Approximately 20% of the patients treated with antibiotics will develop AAD because their intestinal flora, responsible for the natural colonization resistance, is disturbed or reduced.¹⁸ The intestinal flora modification (in particular in the LAB population) could be the cause of diarrhea, dehydration and electrolytic imbalance. Also, the fermentation in the colon can be reduced many preparations have been tested for their preventive efficacy against AAD.¹⁹ Measures to prevent AAD include the use of probiotics of the 10 controlled trials in adults using *Saccharomyces boulardii* for the prevention of AAD, 8 (80%) showed significant efficacy for the prevention of AAD, the protective effect of *Saccharomyces boulardii* and the significant relative reduction in AAD compared with controls ranged between 7.4% and 25%.^{1,20} Other studies failed to demonstrate a significant protective effect of *Saccharomyces boulardii* and this may be secondary to short or no follow-up after antibiotic exposure.²¹ Two RCTs have assessed the ability of *Saccharomyces boulardii* to prevent AAD in children and the relative significant increase in prevention of AAD in the *Saccharomyces boulardii* group compared with controls ranged between 7.6% and 30.1%.^{22,17} A recent meta-analysis of the 10 randomized, controlled trials in adults found that *Saccharomyces boulardii* was significantly protective for AAD with a pooled relative risk (RR) of 0.47 (95% confidence interval (CI) 0.35–0.63, $p < 0.001$).¹ In a double-blind placebo-controlled study examining the preventative effects of *Saccharomyces boulardii* on AAD in adults, 78 patients were given antibiotics plus placebo, while 73 patients were given antibiotics plus *Saccharomyces boulardii* (10 billion CFU/day), in the placebo group, 7 patients (9%) developed diarrhea, while only one (1.4%) patient in the *Saccharomyces boulardii* group developed diarrhea.²² Another double-blind placebo-controlled study which involved 246

children receiving antibiotic therapy for otitis media and/or respiratory tract infections found patients receiving 10 billion CFU/day of *Saccharomyces boulardii* had less occurrences of AAD (4 of 119) compared to those who received placebo (22 of 127).^{17,23} tested 6352 children (3 days to 17 years of age) who were receiving probiotics co-administered with antibiotics to prevent AAD, analyses showed that probiotics are effective for preventing AAD. The incidence of AAD in the probiotic group was 8% (259/3232) compared to 19% (598/3120) in the control group.

***Clostridium Difficile* Infection**

Clostridium difficile is a bacteria that is known to flourish during antibiotic use and is responsible for up to 20% of antibiotic associated diarrhea cases.²⁴ It is also known to be one of the primary causes of pseudomembranous colitis, an infection of the colon. *C. difficile* can be very difficult to treat, approximately 80% of the population responds to typical antibiotic treatment while the other 20% do not and may experience recurrent *C. difficile* infections for many years, a meta-analysis of six RCTs of different probiotics, including *Saccharomyces boulardii* showed that probiotics had a significant efficacy to prevent subsequent recurrences of CDI (RR = 0.59, 95% CI 0.41–0.85, $p = 0.005$).²⁵ Animal models of CDI respond to this yeast and case reports or small case series of patients with recurrent CDI treated with *Saccharomyces boulardii* showed improvement.¹ Evidences suggest that *Saccharomyces boulardii* represents the most effective probiotic that can prevent or, together with other agents, treat antibiotic-associated diarrhea and recurrent CDI. Animal models of CDI respond to this yeast and case reports or small case series of patients with recurrent CDI treated with *Saccharomyces boulardii* showed improvement.²⁵ The significant relative reduction in recurrent CDI in adults taking *Saccharomyces boulardii* compared with controls was evaluated in two RCTs and ranged between 19% and 33.3%, there are only very limited data from one small observational trial in children suggesting that *Saccharomyces boulardii* may be effective in CDI.²⁶ The anti-toxin action elicited by *Saccharomyces boulardii* is mainly due to small peptides produced by the yeast, a 54 kDa serine protease is able to inhibit enterotoxin and cytotoxic activities of *C. difficile* by degradation of toxin A and B, and receptors sites of toxin A on the enterocyte cell surface.²⁷ However, according to guidelines no compelling evidence exists to support routine use of probiotics for prevention or treatment of CDI.^{28,29} Especially since some of these studies did not control the dose or duration of either vancomycin or metronidazole for treatment of CDI.⁴

Acute Diarrhea

Two RCTs using *Saccharomyces boulardii* showed that this probiotic may be effective in treating acute adult diarrhea due to a variety of causes and can significantly lower diarrhea severity score compared with controls, a RCT conducted in 100 hospitalized children showed that *Saccharomyces boulardii* treatment for 5 days significantly reduces the mean duration

of acute diarrhea and frequency of stools, and normalizes stool consistency.³⁰ One RCT regarding the efficacy of *Saccharomyces boulardii* for the prevention of acute diarrhea involved 100 children with acute watery diarrhea and reported a significant difference in the incidence of diarrheal episodes in the group receiving *Saccharomyces boulardii* compared with the control group during 2 months follow up.³¹ Meta-analysis based on 5 RCTs (619 participants) indicated that *Saccharomyces boulardii* significantly reduces the duration of acute childhood diarrhea and the risk of prolonged diarrhea compared with control.³² A meta-analysis of seven RCTs (944 participants) showed a reduction in the duration of acute childhood diarrhea by approximately 1 day in those treated with *Saccharomyces boulardii* compared with placebo, the absence of blinding as well as other factors such as ambulatory care may explain why *Saccharomyces boulardii* had no effect in a European RCT, the findings from RCTs and guidelines from professional pediatric societies indicate that *Saccharomyces boulardii* may be an effective adjunct therapy in managing acute gastroenteritis in children.^{33,34}

Persistent Diarrhea

Results from two clinical trials indicate that *Saccharomyces boulardii* improves outcomes in children with persistent diarrhea.³⁵ The relative significant reduction in persistent diarrhea in the *Saccharomyces boulardii* group compared with controls was approximately 50%.³⁶

Enteral Nutrition-related Diarrhea

Diarrhea is a significant problem in patients on total enteral nutrition (TEN) and may involve changes in intestinal short chain fatty acids (SCFAs), *Saccharomyces boulardii*-induced increase of fecal SCFA concentrations may explain the preventive effects of this yeast on TEN-induced diarrhea.³⁷ In three RCTs, the relative significant reduction in enteral nutrition-related diarrhea in the *Saccharomyces boulardii* group compared with controls ranged between 5% and 8.2%, more studies are needed to elucidate the mechanisms of how *Saccharomyces boulardii* can prevent TEN-induced diarrhea.³⁸

Traveler's Diarrhea

A meta-analysis of 12 RCTs of various probiotics (including *Saccharomyces boulardii*) for the prevention of traveler's diarrhea found a significant reduction in the risk of traveler's diarrhea when probiotics are used (RR = 0.85, 95% CI 0.79–0.91).²⁵

The relative significant reduction in traveler's diarrhea in the *Saccharomyces boulardii* group compared with controls in two RCTs ranged between 5% and 11%, *Saccharomyces boulardii* showed statistically significant efficacy in the prevention of traveler's diarrhea.³⁹

Helicobacter pylori infection

A recent meta-analysis involving 14 RCTs (1671 patients) evaluated the role of probiotics in *H. pylori* eradication, In patients with *H. pylori* infection, probiotic supplementation improved eradication rates and reduced treatment-related

side effects and individual symptoms.⁴⁰ In meta-analysis, only one RCT evaluated *Saccharomyces boulardii* and found that it decreased the risk of diarrhea when given concomitantly to patients receiving triple eradication therapy for *H. pylori*.⁴¹ *Saccharomyces boulardii* induces morphologic changes in *H. pylori* cells consistent with cellular damage.⁴² and was shown to cause reduction in *H. pylori* colonization in infected children by 12%.⁴³ Four RCTs testing *Saccharomyces boulardii* in *H. pylori* infections, two were in children⁴⁴ and two in adults.^{45,46} reported on the efficacy and safety of additional *S. boulardii* and probiotics in eradicating *H. pylori*.⁴⁷ suggested that *S. boulardii* combined with other drugs can gain a synergistic effect which enhance the efficacy and reduce side effects and the supplementation of *S. boulardii* to the standard PPI-based triple therapy is effective in treating peptic ulcer with a low rate of recurrence and low incidence of side effects. Therefore, it may be a safe and valuable therapy for peptic ulcer.⁴⁸ Although there was no significant difference in *H. pylori* eradication between the *Saccharomyces boulardii* and placebo groups, a significantly lower relative rate of AAD (16.1–25%) was observed. In a recent meta-analysis, the *H. pylori* eradication rate in the triple therapy group was 71% and increased significantly to 80% with *Saccharomyces boulardii* supplementation.⁴⁹ *Saccharomyces boulardii* administration can inhibit the formation of gastric lymphoid follicles induced by *Helicobacter suis* infection.⁵⁰ Generally Three clinical trials with *S. boulardii* had a positive effect on patients with inflammatory bowel diseases (IBD), while no effect appeared in one trial showed.⁵¹

Crohn's Disease

Recently, the use of probiotics for maintaining remission from active disease in patients with Crohn's disease was given a 'C' recommendation rating level by a panel of experts evaluating the efficacy of the supplements, mostly due to a scarcity of data.⁵² In a small pilot study of 31 patients with Crohn's disease in remission all patients continued their maintenance medications and were randomized to either *Saccharomyces boulardii* for 3 months or placebo. Those treated with *Saccharomyces boulardii* were found to have a significant reduction in colonic permeability compared with those given placebo, thus reducing the risk of bacterial translocation in these patients.⁵³ Two RCTs tested *Saccharomyces boulardii* for patients with Crohn's disease.⁵⁴ In a small randomized study of 20 patients with Crohn's disease all patients continued their maintenance medications and were randomized to either *Saccharomyces boulardii* for 7 weeks or placebo. Patients treated with *Saccharomyces boulardii* were significantly improved compared with the placebo group.^{55,54} study of 32 patients with Crohn's disease who were in remission, significantly fewer patients treated with *Saccharomyces boulardii* (6%) relapsed than the control group (38%)

Ulcerative Colitis

Probiotics have been used as an adjunct treatment in an attempt to induce remission in patients with active ulcerative colitis.²⁷

In a small pilot study of 25 adults with mild to moderate ulcerative colitis that were treated with a combination of mesalazine and *Saccharomyces boulardii* for 4 weeks, most (68%) of the patients responded to the probiotic treatment.⁵⁵ This pilot study had a promising result, but the implications were uncertain as patients were treated for only a short time, were not followed up for subsequent disease flare ups, and no control group was included. In a small pilot study of 6 patients with ulcerative colitis, a therapeutic regimen including *Saccharomyces boulardii* and rifaximin for 3 months seemed effective in preventing early flare ups of ulcerative colitis.⁵⁶ Further controlled studies on a larger number of patients treated for longer periods with this probiotic agent are warranted. Overall, based upon current consensus, the level of evidence for use of probiotics either to maintain remission or induce remission of ulcerative colitis symptoms is presently limited to a 'C' rating.⁵²

Irritable Bowel Syndrome

Recent evidence suggests a role of the microflora in IBS pathogenesis.⁵⁷ A meta-analysis of 20 RCTs including 1404 subjects found a pooled RR for improvement in global IBS symptoms in 14 probiotic treatment arms (RR = 0.77, 95% CI 0.62–0.94).⁵⁸ In a double-blind trial of *Saccharomyces boulardii* versus placebo in the treatment of IBS patients, the probiotic agent significantly improved the quality of life, but did not improve intestinal symptoms.⁵⁹ These findings are inconsistent with those reported in double-blind, RCTs performed earlier in France.⁶⁰ Along these lines, a recent retrospective analysis suggested that addition of *Saccharomyces boulardii* to mebeverine can provide superior results in IBS treatment and that the probiotic agent does exert beneficial effects on the quality of life and IBS symptoms.^{56,61} reported demonstrates that *Saccharomyces boulardii* contains various heat-sensitive motogenic factors that can improve intestinal restitution. These factors exerted their effect through multiple pathways, including the dynamic fine regulation of integrin-mediated adhesion to the extracellular matrix, this could be of major importance in diseases characterized by severe mucosal injury, as seen in IBD or infectious gastroenteritis.

Parasitic Infections

Saccharomyces boulardii seems to have a beneficial effect in amebiasis, giardiasis and infection with *Blastocystis homini*. In adults, co-administration of lyophilized *Saccharomyces boulardii* with conventional treatment in acute amebic colitis significantly decreased the duration of symptoms and cyst carriage after 4 weeks.⁶² A prospective RCT in patients with amebic colitis showed that addition of *Saccharomyces boulardii* to metronidazole enhanced clearance of cysts and decreased the mean duration of diarrhea, fever and abdominal pain. In a small clinical study of symptomatic children with *Blastocystis hominis* infection *Saccharomyces boulardii* had potential beneficial effects in symptoms and number of parasites.⁶³ The combination therapy of *Saccharomyces boulardii* in addition to metronidazole in patients with

giardiasis resulted in a disappearance of *Giardia* cysts 2 weeks after start of the treatment in contrast to 17.1% of patients treated with 10 days metronidazole as monotherapy who still had *Giardia lamblia* cysts in the stool.⁶⁴ In another clinical trial of 40 children who received tinidazole for giardiasis of 3 or 4 weeks duration, the percentage of children with only one to three bowel movements per day was significantly higher in the *Saccharomyces boulardii* group compared with the placebo group (65% versus 15%).⁶⁵

HIV-related Diarrhea

Patients with HIV-associated diarrhea seem to be one group that requires a higher than typical dose of *Saccharomyces boulardii*. In a blinded, placebo-controlled study in 11 HIV-positive patients who had chronic diarrhea, lower doses of *Saccharomyces boulardii* were not as effective compared with 6 patients who reported that diarrhea was controlled while taking 3 g/day *Saccharomyces boulardii* after 1 month.⁶⁶ In a RCT of 35 adult patients with acquired immune deficiency syndrome (AIDS) and chronic diarrhea, 61% of patients given *Saccharomyces boulardii* had their diarrhea resolved compared with patients on placebo (12%).⁶⁷ In the patient with AIDS-associated diarrhoea, the efficacy of *Saccharomyces boulardii* has been proven by a randomized, double-blind trial^{68,9} using the probiotic yeast *Saccharomyces boulardii* to modify gut microbiome composition in 44 HIV virologically suppressed patients, half of whom (n = 22) had immunologic non-response to antiretroviral therapy (<270 CD4+Tcells/ μ L despite long-term suppressed viral load.

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