Review Article

Is *Saccharomyces boulardii* an ideal probiotic in management of gastrointestinal diseases?: A review

Sagar N. Ande[1]*, Kartikeya R. Mudholkar[1], Ravindra L. Bakal[1], Mahendra D. Kshirsagar[2]

[1]Department of Pharmacology and Toxicology, Dr. Rajendra Gode Institute of Pharmacy, Amravati, Maharashtra, India, [2]Department of Pharmaceutics, P. Wadhwani College of Pharmacy, Yawatmal, Maharashtra, India

Correspondence:
Sagar N. Ande, Dr. Rajendra Gode Institute of Pharmacy, Amravati, Maharashtra, India.
E-mail: sagar986ande@gmail.com

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ABSTRACT

Probiotics are beneficial bacteria. A substance released by one organism that promotes the development of another. As well as living microorganisms that encourage the development of another probiotic as well as live microorganisms that confer a health advantage on the host on condition that in sufficient proportions. Multiple mechanisms of action against infections are among the advantages of probiotic treatment. It includes things such as improving gut barrier function, antimicrobial peptide synthesis, pathogen competitive exclusion, immunological modulation, and tropic impact. The capacity of the probiotic to engage with the host's natural defense system, resulting in increased survival of the mark organ and a favorable risk-benefit ratio. It demonstrated ability to prevent and treat some gastrointestinal infections such as *Helicobacter pylori*, fungemia, ulcerative colitis, and irritable bowel disease. Its effective use in gastric infection, immunocompromised patients, and also decrease patient's exposure to antimicrobials. As well as, it used as good nutritive food for gastrointestinal tract. Clinical studies are clearly showed its safety and efficacy of these agents. Improved gut barrier functioning, pathogen inhibition, antimicrobial peptide production, immunological modulation, and trophic benefits have all been related to its probiotic effectiveness. This research summarizes the significance of *Saccharomyces boulardii* in various pathways, as well as the multifactorial behavior of how yeast affects the host microbiota as well as function of intestine.

Keywords: Mechanism of action, probiotic, treatment, safety etc

Introduction

Escherichia coli, Streptococcus species, and yeast *Saccharomyces boulardii* are often used bacterial probiotics.[1] The precise identification of a microbe (strain and concentration) mentioned on the label of a specific product might provide a first challenge for physicians. It is now widely utilized in clinical practice.[2] *S. boulardii* has phenotypic traits and physiochemical functions that underpin its success as a probiotic, such as optical development temperature, gastric environment resistance, and viability at low pH. It is genetically similar to yeast *Saccharomyces cerevisiae* as a plan to expose capability to host physiological circumstances by probiotic.[3] Its action had been explained as a combination of multiple pathways, including improved gut barrier function, pathogen inhibition, antimicrobial peptide production, immune modulation, tropic effect, and the ability to restore the balance of good bacteria in the intestine, which may be disrupted by antibiotics or intestinal function.[4] There are several items to choose from. Although most goods include at least 1x109 cfu/mg, the quality of these items varies.[5]

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Properties of *S. boulardii*

Genomic properties of *S. boulardii*

Protein synthesis (RPL31A, RPL41A, RPS24B, and RPL2B RSA3) and stress response (HSP26, SSA3, SED1, HSP42, HSP78, and PBS2) are two roles of *S. boulardii* genes with high copy number.[6] It is probable that these genes will help with enhanced growth rate and pseudohyphal switching, as well as greater resilience to high pH.[7] Stress response proteins, elongation factors, ribosomal protein, kinases, transporters, and possibly fluoride export are largely encoded by duplicated and triplicated genes, which may help in *S. boulardii* adaptation under stress conditions.[8] When compared to *S. cerevisiae*, changed gene copy number and mutation (SDH1 and WH12) genes are connected with enhanced acetic acid synthesis by *S. boulardii*, which is coupled with antibacterial action.[9]

Table 1: Doses of *S. boulardii*

Disease	Adult dose	Children dose
Antibiotic-associated diarrhea	500 mg during antibiotic therapy	250–500 mg (2–4 times a day) In case of *Clostridium difficile* of 1g of S.B daily, 4 weeks
Crohn's disease	750 mg	250 mg (3 times a day, 9 weeks) While 1 g use in combination therapy
Ulcerative colitis	205 mg *Saccharomyces boulardii* TD.	As directed by physician
Travelers-diarrhea	250–1000 mg for 5 days before to departure and for the length of the trip	

Thermal stability

One of the most essential factors in assortment research is temperature. In general, *S. boulardii* survives generally at 37°C. In several study, shown that it can be tolerate up to 42°C. According to Hossain *et al*. 2020, it is having thermotolerant ability which is viable up to 45°C.[10]

Bile salt tolerance

Bile is a liquid that comprises bile acids, cholesterol, phospholipids, and biliverdin and is dark green to yellowish brown in color. It has the greatest tolerance for bile salts and can grow in bile salts with a concentration of 2%.[11]

pH resistance

The first important factor in the gut is the acidic condition in gastrointestinal tract. The well-known strains of *S. boulardii* such as C.N.C.M I-745 can be survived at pH 2.0 and pH up to 8.5 of small intestine at alkaline Ph.[12]

Effect of NaCl tolerance

The growing rate of *S. boulardii* must be reduced in these medium.[11,12]

Simulated gastric tolerance

Before administration of this probiotic, it can be survived transit by stomach and exposure to gastric acid constituent which has primer defensive mechanism against most of ingested micro-organism. Mouth mastication, stomach digestion, and small intestine digestive health all took place at 37°C in this example. It can survive up to 80% of the time.[13]

Antibiotic-associated profile

In many recent, probiotic strain is sensitive and its resistance to antibiotics such as Cefotaxime, Ciprofloxacin, and Erythromycin.[14]

Antimicrobial activity

These probiotic having bacteriostatic and bacteriocidal activity against pathogenic Gram-positive bacteria such as *Enteroccous faecalis* and *Bacillus megaterium* and Gram-negative bacteria such as *Shigella flexinery*, *Salmonella* typhi, *and Vibrio parahaemolyticus,* and Fungal species such as *Candida albicans*, *and Rhizopus oryzae*.[14-16]

Mechanism of Action

Mechanism of action of *S. boulardii* is of three kinds as explained below. These major three types are further subdivided as below.

Antimicrobial action

These action are occur within intestinal luminal tract by exerting several antimicrobial activities that could be separated in two classes.[17]

Direct antitoxin effects

Antitoxins generated by *S. boulardii* are mostly owing to tiny peptides synthesized by the yeast. By degrading toxin A on the enterocyte cell surface, a 54 kDa serine protease is able to block enterotoxin and cytotoxic activities of *Clostridium difficile*, whereas other Saccharomyces strains fail to display similar activities. If *Vibrio* cholera decreases cyclic adenosine monophosphate in enterocytes, a 120 kDa protein with little proteolytic activity competes particularly with hypersecretion generated by toxins.[17] Finally, *S. boulardii* develops a phosphatase that may dephosphorylate endotoxins (such as *E. coli* lipopolysaccharide) and render them inactive. This process might explain why people are protected from sepsis.[18]

Inhibition of growth and invasions pathogens

In vitro, *S. boulardii* stops the development of several pathogens (Candida albicans, *E. coli*, Shigella, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Entamoeba histolytica*) as well as *Salmonella* typhyrium cell invasion. *S. boulardii* can also reduce pathogen translocation in rat and pig animal models and interfere with pathogenic *S. boulardii* serves as decay in Enterpathogenic *E. coli* infections by inducing bacterial cells to attach directly to its surface rather than to enterocytes.[18] *C. albicans* adherence to epithelial cell lines is inhibited *in vitro*, and this effect is also seen with *S. boulardii* extracts. Capric acid is a substance released by *S. boulardii* that inhibits *C. albicans* filamentation and partly adhesion and biofilm development, according to several studies.[19]

Tropic action

Normal microbiota is re-established more quickly when these probiotics are assumed to antibiotic-shocked animals or patients having diarrhea, while sb has no impact or microbiota is re-established in healthy people. This action is strongly connected to the stimulation of the formation of short-chain fatty acids, particularly butyrene. In patients taking antibiotics, the synthesis of S.C.F.A is significantly reduced.[17]The effect on butyrate production is especially important given the compound's major role in managing a variety of intestinal functions, having enterocyte growth and differentiation, fluid absorption, immune stimulation, and anti-inflammatory effects, which are particularly important in the treatment of antibiotic-related diarrhea. *S. boulardii* has tropic effects and increases enzyme expression in host microvilli, as well as improving disaccharide activity and D-glucose absorption through the symport glucose cotransporter.[18] *S. boulardii* increases the synthesis of glycoproteins such as hydrolases, transporters, secretory IgA, and polymeric immunoglobin receptors at the brush border of microvilli.[19] One of the most significant and unique mechanisms of action is the formation of intestinal

polyamines generated and promoted by sb. Spermatidine, spermine, and putrescine are polyamines that promote the production of brush border enzymes such hydrolases, proteases, and transport molecules. Furthermore, *S. boulardii* increases the expression of the perioxisomes proliferation activated receptor, which protects the host against gut inflammation and IBD.[20]

Immunoregulation

C. difficile toxin stimulates the MAP Kinases extracellular regulated kinase (ERK) and P38, and the NF-KB (P65/P50) pathway, resulting in the transcription of pro-inflammatory genes such interleukin (IL-8) that increase inflammation. *S. boulardii* reduces IL-8 production and inflammatory diarrhea by inhibiting the MAP kinase and NF-KB signaling pathways.[21] *S. boulardii* conceals a small (1 kDa) thermostable and hydriphilic anti-inflammatory factor in the presence of *C. difficile* toxin, which inhibits NF-KB dependent signaling paths. Modulation of intestinal permeability is another mechanism indirectly implicated in the immune control action produced by sb.[22] Increased intestinal permeability is common in a variety of circumstances, including shock, burns, injuries, obstructive jaundice, intestinal resection, liver transplantation, and intestinal blockage.[23]

Therapeutic Uses of Probiotic

Effect on microbiota

Antibiotic medication increases the numbers of Enterobacteriaceae and Bacteriaceae while decreasing the levels of *Clostridium coccoides* and *Eubacterium rectale*, according to a number of recent research.[24] In dysbiosis, treatment with *S. boulardii* CNCM I- 745 leads to a quicker restoration of a healthy microbiota. After antibiotic treatment, however, the administration of *S. boulardii* CNCM I-745 hastened the return of the intestinal microbiota to its original level. Similarly, ciprofloxacin and metronidazole are used to treat some vaginosis patients. *S. boulardii* CNCM I- 745 was used to swiftly recover their original microbial profiles. In healthy volunteers, it also inhibits the alteration of fecal bile acids metabolism after antimicrobial treatment.[25] After diarrheic dysbiosis, *S. boulardii* CNCM I-745 promotes the regeneration of gut microbiota. They stressed that the most important impacts of this yeast on the fecal microbiota composition are an increase in short chain fatty acid generating bacteria, namely, *Lachnospiraceae* and *Ruminococcaceae*, but also *Bacteroidaceae* and *Prevotellaceae*. In addition, pioneer bacteria are suppressed when they come into close touch with the profile surface. *S. boulardii* CNCM I- 745 improves intestinal barrier function due to anti-inflammatory, migratory, anti-secretion, and adhesion properties.[26] It has anti-inflammatory characteristics, because it suppresses IL-8 production mediated by NF-kB and ERK 12 phosphorylation. Due to the repair of glutathione and a reduction in intestinal permeability, *S. boulardii* CNCM I-745 also recovers epithelium.[27]

Helicobacter pylori infection

Some studies demonstrate that although it may not be efficient enough to eradicate *H. pylori*, the usual triple treatment reduces the negative effects. We know that they are Gram-negative bacteria that infect around half of the world's population.[28] It has a significant part in the expansion of chronic gastritis and duodenal cancer. *H. pylori* has a part in stomach cancer and mucosa-related lymphoid tissue lymphoma (MALT) development. According to certain research, *S. boulardii* CNCM I- 745 is effective in minimizing colonization.[29] It decreases in secretion of cytokines IFN-α, TNFα, and IL-12, which are provide beneficial effects in I.B.D and colitis.[30]

Acute watery diarrhea

Some research suggests that the use of *S. boulardii* compared to controls in healthy infants, children with acute infectious watery diarrhea of viral or bacterial source is associated with moderate therapeutic importance that really is responsible irrespective of the primary outcome researched with duration of diarrhea during certain point interims. Only probiotic strains with shown clinical benefit are used as an adjuvant for diarrhea therapy.[31]

Antibiotic-associated diarrhea

S. boulardii CNCM I-745 is helpful in lowering the risk of antibiotic-associated diarrhea, ulcerative colitis, irritable bowel syndrome,[32] etc. *S. boulardii* CNCM I-745 was given in doses ranging from 50 to 1000 mg/day. In antibiotic and severe diarrhea, however, this effectiveness includes all strains, not only *S. boulardii* CNCM I-745.[33]

C. difficile

A reason leading to CDI following antimicrobial therapy in these situations is the limitation of microbial conversion of primary bile salts into second bile acids.[34] The primary bile acids derived from cholate enhance *C. difficile* sporulation and growth, but secondary bile acids suppress spore germination and outgrowth, according to induced CDI tests. After antimicrobial therapy, *S. boulardii* CNCM I-745 prevents bile acid metabolism disturbance in healthy persons (amoxicillin + clavunate).[34]

Use of *S. boulardii* C.N.C.M I-1079 in new born dairy calves

S. boulardii C.N.C.M I- 1079 is increased endogenous IgA production in the gut of Calves.[35] With addition, it had higher *Lactobacillus* and tended to have higher *Fecalibacterium* in jejunum get positive effect in newborn calves. Direct supplementation of these strains plays a key role in shaping early colonization in the gut of new born calves.[36]

Use of *S. boulardii* Unique 28 strain in diarrhea

In patients with severe diarrhea, this study evaluates the effectiveness and precaution of *S. boulardii* strain unique 28. During the trial, main outcome events such as diarrhea length, frequency of defecation, discomfort in abdomen, and stool consistency were examined.[36] Secondary outcome measures included an assessment of the frequency and kind of opposing events as well as physical examinations. Following these methods, the average length of diarrhea is decreased, as is the frequency of defecation, stomach discomfort, and stool consistency. Therefore these study shows, these strains are useful in alleviating

symptoms of diarrhea without any adverse effect.[35]

S. boulardii in salivary secretion

We know that, Serotonin (5HT) is a unique monoamine hormone as well as neurotransmitter which plays a part in multiple biological Process. It is made from tryptophan, an important amino acid, and then reduced to 5-hydroxyindoleacetic acid for elimination in the urine. It aids in the stimulation of gastrointestinal peristaltic refluxes, as well as the regulation of vascular tone and heart function. A little amount of 5HT is generated, which is present in C.N.S. and seems to reduce psychological reaction. According to author, healthy volunteers supplement with their food of S. boulardii CNCM I-1079 for 30 days, decrease of salivary concentration of 5HT under psychological stress. However, Salivary 5HT in healthy young adult is correlated with sympathetic markers.[37] All therapeutic uses and dose of s. boulardii are mentioned in Table 1.

Other than Therapeutic Uses of *S. boulardii*

Use in ice-cream production

For ice-cream production, well-known probiotics such as *S. boulardii* and *Lactobacillus rhamnosus* are utilized nowadays in ice-cream production. Ice-cream melting properties are critical for stability and customer insight of ice cream in terms of mouth fill, flavoring. Time of onset of ice-cream products is between −13.73 and −15.55°C, which is the lowest value determined by several ice-cream samples. However, when the probiotic *S. boulardii* was combined with *L. rhamnosus*, the Tonset levels were larger than when *S. boulardii* was added alone. Then, the average temperature of ice creams are varied from 8.15°C to 10.37°C, with the lowest and highest temperatures recorded for various ice cream samples.

Beer fermentation of *S. boulardii*

As we all know, the first antilisteral probiotic is *S. boulardii's* leucocin C secretion. *S. boulardii* SAC12 produced much more leucocin C than *S. boulardii* SAC4. Antibiotics are not required for this procedure. The beer produced by *S. boulardii* SAC12 had a mean ethanol level of approximately 4.3% (v/v) in these methods. The amount of ethanol generated by yeast throughout fermenting is usually between 3.5 and 5.0% (v/v). As a result, it seems that utilizing *S. boulardii* SAC12 for beer fermentation is a viable option. Beer brewed by *S. boulardii* SAC12 has an anti-listeral action owing to the buildup of produced leucocin C in the beer. When beer was employed in this approach in a real food matrix, it inhibited *Listeria monocytogenes* contamination in strips of chicken breast by up to 22 log units.[13]

Sugar fermentation

These types of fermentation reaction are to be carried out at higher temperature rate at 37°C aerobic atmosphere than 30°C with some exception. During these method, *S. boulardii* (KT000032) Strain are used. However, when employing raffinose, rhamnose, Sorbitiol, Cellobiose, arabinose, inulin, sucrose, dulcitol, lactose, adonitol, maltose, salicin, mannitol, Galactose, Ionositol, and mannitol, these strains show reduced fermentation, even after 48 h. After 72 h of incubation under shaking conditions, these mild responses and pH ranged from 5.2 to 6.8. However, if fructose, mannose, xylose, dextrose, and trehalose were fermented in 48 h, the results would be different. Xylose is the most often used of the 21 sugars. The fermentation of sugars is equivalent at both 30°C for *S. boulardii* (KT000032) Strain, although the rate of growth was reduced significantly for the first 12 h at 30°C.[12]

S. boulardii fermentation with extraction of rice bran metabolite

Water, rice bran, and probiotic yeast fermentations were approved out utilizing these procedures, which were modified. In this procedure, 1.6 g of rice bran was mixed with 11.4 mL of sterilized water in the presence of *S. boulardii* at a concentration of 6×10^5 cells mL^{-1} and incubated at 37°C for 24 h with moderate shaking. Two distinct solvents are used in these methods: (i) isopropanol: acetonitrile: water for metabolites profiling, and (ii) methanol: water (80:20) for evaluating bioactivity on lymphoma or periphery lymphocytes *in vitro*. After 24 h of fermentation in water, the culture is introduced to isopropanol: acetonitrile or methanol for final 3:2:2 or 80:20 ratios, respectively. The samples were vortexed and kept for 5 min at room temperature. Finally, the modified rice materials and yeast cell was pelleted for 10 min after centrifugation (1500 g) and filtering. The supernatant was taken apart and stored at −80°C and it was subjected to additional chemical and biological examination using gas chromatography.[38]

Conclusion

The *S. boulardii* is must be therapeutically safe, beneficial and nutritive due to its non-pathogenic activity, mechanism of action, properties, and therapeutic uses of each particular strains. On basis of therapeutic use, *S. boulardii* CNCM I-745 is a most widely medicated strains as compared to other strains which are used in Crohn's disease, IBD, Ulcerative colitis, Clostridium disease, and *H. pylori* infection. It keeps its probiotic properties even in case of antibiotic coadministration. Its vitality is not changed during such treatment.

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