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Effects of s. *Cerevisiae var. Boulardii* in gastrointestinal disorders

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Abstract

The increasing interest in the consumption of products containing probiotics is the result of numerous researches on their beneficial influence on human health. The promising one includes the improvement of prevention of various gastrointestinal disorders, the enhancement of immune function and the prevention of recurrent respiratory infections. Probiotics are available in a wide range of products with different benefits. Understanding their functional properties is an important aspect of health and well-being claims. Future studies are necessary to demonstrate the safe character of probiotics. This paper reviews the main effects of probiotic strain *S. cerevisiae* var. *boulardii* on gastrointestinal disorders. It has a beneficial physiological effect by the reduction of gastro-intestinal discomfort. The administration of the yeast, alone or in combination with other treatment, shows anti-inflammatory and immuno-modulatory effects

Keywords: S. cerevisiae var. boulardii, probiotics, gastrointestinal disorders

1. Introduction

Saccharomyces boulardii is a probiotic yeast which was isolated by the scientist Henri Boulard in 1923. It was firstly isolated from lychee fruit and mangosteen fruit in Indochina. At the beginning, in the 1950s, it was used in France to treat diarrhea. It grows at 37°C, at unusually high temperature for yeast strains [1]. *S. boulardii* is different from *S. cerevisiae* through several metabolic, taxonomic and genetic properties [2]. The genes of *S. boulardii*, similar to that of *S. cerevisiae*, are generally used in genetic manipulation such as promoters and resistance markers. A major similarity of the yeasts orthologs has been discovered using sequencing [3]. As we can see in *Fig. 1*, *S. boulardii* is closely related to *S. cerevisiae* strain [4].

Mitterdorfer *et al.* [5] suggested that *S. boulardii* and *S. cerevisiae* species have in common so many molecular clustering characteristics that they cannot be regarded as different species. The term "*boulardii*" is not an accepted taxonomic classification, according to the current nomenclature like the International Code of Botanical Nomenclature (ICBN). The most proper classification is *S. cerevisiae* var. *boulardii*. [6]. Fietto *et al.* [7] showed that *S. boulardii* and *S. cerevisiae* are almost identical as regards their genetic characteristics. However, they have metabolically and physiologically distinct behaviours. *S. boulardii* have essential characteristics for yeast that can be used as a probiotic, like resistance to high temperature and acidic conditions and growth yield [8].

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Probiotics have been defined by the World Health Organization expert group as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host'. They must be capable to tolerate gastrointestinal conditions (acid, bile, enzymes, and low levels of oxygen) and deterring pathogens. In the case of *S. cerevisiae* var. *boulardii*, the main health benefit is correlated with the maintenance of healthy microbiota, by decreasing the numbers or colonization of pathogens. It is also associated with other health benefits like stimulation of immune system, prevention of allergies, prevention of diarrhea, prevention of intestinal infection caused by pathogens, stimulation of digestion and absorption of nutrients [9, 10, 11, 12, 13, 14, 15]. The probiotic yeast is effective if the yeast is used alone, or as a complementary treatment, in a daily dose higher than 10^9/d, for a time interval from 7 days to 6 months [16].

The anti-inflammatory mechanisms of action of *S. cerevisiae* var. *boulardii* are*:* the inhibition of proinflammatory cytokines' development, the inhibition of "bacteria overgrowth" and adhesion to host cells, and the interference with pathogenesis, trapping T cells in mesenteric nodes [17]. *S. boulardii* secretes medium-chain fatty acids and 2-phenylethanol that inhibit the morphological transition and adhesion of *C. albicans* [18]. The decrease of viable and active bacterial cells and the elimination of pathogens, bound to yeast surface within the gastrointestinal tract, limit bacterial growth and infections caused by human pathogens [19].

European Food Safety Authority frequently rejects health claims of probiotics [20]. In order to accept a heath claim, every correlation between a food or a constituent and a claimed effect must form a coherent opinion [21]. Currently, in Europe there is no particular legislation or legal definition of probiotic and functional foods, no class to which they belong [22]. Only Novel Food Regulation regulates the use of microorganisms for human consumption (258/97 EEC). On the other hand, the legislative framework regarding the safety of probiotics in human use is nearly non-existent [23]. In order to offer consumers the confidence in probiotic products, an approach needs to be found to provide the convenient communication for probiotics health benefit.

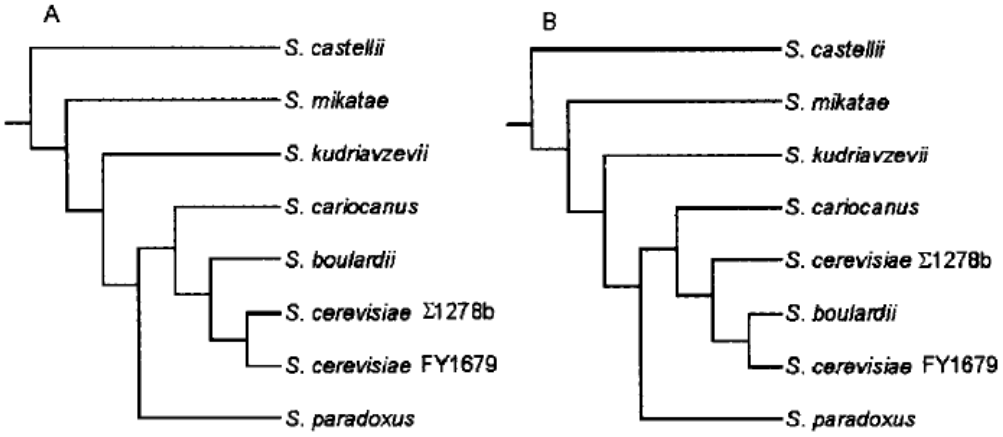

Figure 1. Phylogenetic tree of the *Saccharomyces* sensu stricto complex, (*A*) Construction with the full data set for each species. (*B*)Rearrangement that occurred when Ty-related open reading-frames were removed from the data sets of all species.

2. Prevention and treatment of diarrheal disease

"Diarrhea" is characterized by an increase in the water content and volume of fecal matter. Epidemiologically, it is defined as a decrease in consistency and an increase in frequency of bowel movements to stools per day. Diarrhea can be: "infectious" - diarrhea caused by an infectious etiology; "acute" - an episode of diarrhea of <14 days; "persistent" is the diarrhea lasting >14 days and "chronic" - diarrhea that lasts >30 days [24]. Kotowska *et al.* [25] conclude that *S. boulardii* can be used as complementary treatment in children who

are submitted to antibiotic therapy to prevent the occurrence of antibiotic-associated diarrhea. The effect of *S. boulardii* on the intestinal anaerobe microflora can explain the protective impact of this probiotic on the diarrheal diseases appearing in patients under exclusive enteral nutrition. The use of *S. cerevisiae* var. *boulardii* significantly increases three short-chain fatty acids, i.e. acetic, propionic and butyric acid [26].

Clinical studies support the reduction of diarrhea duration if *S. boulardii* is administered to children within 72 hours after the debut of acute diarrhea [27]. *S. boulardii* can be used as an additional treatment in children, for the oral rehydration in the management of acute diarrhea [28]. In the case of children with persistent diarrhea, it significantly decreases the number of stools, shortening the duration and symptoms of diarrhea [29, 30, 31, 32, 33]. *S. boulardii*, combined with oral rehydration solution, reveals a beneficial response in acute watery diarrhea, especially on the duration of diarrhea, on the consistency and frequency of stools [34].

In the post-antibiotic period, *S. boulardii* had an important influence on the restoration to the normal levels of the *C. coccoides*, *Bacteroides* and *Enterobacteriaceae* strains. The use of *S. boulardii* can restore the balance of the dominant anaerobic microbiota after treatment with amoxicillin-clavulanic acid. The specific immune reaction to microbial-associated molecular patterns can be influenced by the use of the yeast. This result also suggests that *S. boulardii* contributes in keeping the intestinal homeostasis [35]. The antibiotic-associated diarrhea has been shortened significantly by the treatment with *S. boulardii* [36, 37]. It also shows a remarkable effect on the cure and prevention of diarrhea in dogs with lincomycin-induced diarrhea [38].

3. Prevention and treatment of bowel diseases

Inflammatory bowel diseases included two major disorders: ulcerative colitis and Crohn's disease. The diffuse mucosal inflammation is limited to the colon characterized ulcerative colitis. The use of *S. boulardii* during maintenance treatment with mesalazine for 4 weeks resulted in clinical remission, which was endoscopically confirmed in approximately two-thirds of the patients experiencing a clinical flare-up of ulcerative colitis [39].

Crohn's disease may affect any part of the gastrointestinal tract by patchy, transmural inflammation [40]. Dalmasso *et al.* [41] conclude that administration of *S. boulardii* can have a favorable effect in the treatment of inflammatory bowel diseases (IBD). *S. boulardii* may control inflammation and help epithelial reconstruction which is important in IBD [42]. In the case of patients submitted to the maintenance treatment with mesalamine and *S. boulardii*, it was noted that Crohn's disease clinically recurred to a significantly lesser extent (6.25%) than in the case of subjects submitted only to the administration of mesalamine (37.5%) [43]. However, after steroid or salicylate therapies, administration of *S. boulardii* does not appear to have any beneficial effects on patients with Crohn's disease in remission [44].

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by abdominal pain or discomfort, defecation or a change in intestinal [45]. Akhondi-Meybodi *et al.* [46] showed that the use of *Saccharomyces boulardii* can be efficient in improving the symptoms, particularly pain severity, flatulence, belching, diarrhea, and eructation. However, Kabir *et al.* [47] conclude that the use of *S. boulardii* for 30 days was unsuccessful for the treatment of patients with diarrhea- predominant irritable bowel syndrome. *S. boulardii* cannot ameliorate individual symptoms in patients with diarrhea-predominant or mixed-type irritable bowel syndrome, but it can enhance the quality of life, better than placebo [48].

Mucositis is characterized by an increase of intestinal permeability and intestinal inflammation. Studies with *S. boulardii* conclude that it cannot improve the symptoms of mucositis like mucosal lesions, intestinal permeability and sIgA secretion in mice [49].

4. Prevention and treatment of infections

Uncomplicated diarrhea, nonspecific colitis or pseudomembranous colitis characterized the intestinal infection with *Clostridium difficile*. A prospective double-blind study showed that a combination of *S. boulardii* and a standard oral antibiotic can be more effective in preventing

Clostridium difficile infections recurrences than standard therapy alone [50]. Spielholz [51] suggests that the symbiotic tablet, containing *Saccharomyces boulardii* and *Bacillus coagulans*, and a prebiotic, i.e. fructooligosaccharide, can prevent antibiotic-associated diarrhea and *C. difficile* infection in patients submitted to antibiotic treatment within a nursing home.

Infection with *Helicobacter pylori* is one of the most frequent human infections worldwide and its symptoms include a number of critical gastrointestinal conditions such as chronic gastritis, peptic ulcer disease, and gastric malignancy [52]. *Saccharomyces boulardii* seems to be a hopeful treatment that reduces *H. pylori* infections. Regular consumption of the probiotic yeast has been shown capable to eradicate 12% of colonization with *Helicobacter pylori* in infected children [53]. Kyriakos *et al.* [54] conclude that the complementary use of *S. boulardii* and classic therapy (omeprazole 20 mg bid, clarithromycin 500 mg bid and amoxicillin 1 g bid), in order to reduce *H. pylori* infection, lead to higher rates of eradication of this pathogen. *S. boulardii* can reduce treatment-related diarrhea and improve its compliance with the treatment.

One on the most significant causes of neonatal and post-weaning diarrhea in piglets is the infection caused by enterotoxigenic *Escherichia coli*. The treatment with *Saccharomyces cerevisiae* var. *Boulardii*, in combination with β-galactomannan, can be used to prevent *E.coli* K88 infection. The use of an *in vitro* model for pig intestinal cells showed the ability of the probiotic yeast to reduce pathogenic inflammation [55].

5. Control and effect on parasitosis

Toxocariasis is a chronic tissue parasitosis, most commonly correlated with the etiologic agent nematode *Toxocara canis.* It is defined by the migration and permanence of larvae of helminthes in humans. The treatment with *S. boulardii* may differently control this parasitosis, showing a significant decrease in the intensity of toxocariasis [56].

Giardia lamblia is a microscopic single-celled parasite that causes the intestinal infection called giardiasis. The symptoms include diarrhea, pale greasy stools, stomach cramps, gas, nausea, vomiting, bloating, weight loss, and weakness. *S. boulardii* appears to improve clearance of the infecting pathogen [57].

6. Safety

The main risk of consumption of *S. cerevisiae* var. *boulardii* is fungemia [58]. It is defined as the presence of fungi or yeast in blood. Fungemia can appear on patients with high infection risk [59, 60, 61], when the package containing the lyophilized probiotic is opened, without being taken preventive infection control measures in the patient's room. This risk can be reduced by carefully hand washing and changing gloves before the administration of the probiotic product [62].

7. Conclusions

Future studies are necessary to improve reliability of taxonomic classification of *S. boulardii* strain. This can improve the efficiency and activity of products containing probiotics strains. The influence, the mechanisms of action and the functional role of *S. boulardii* in human health must be established. The demonstration of the health claims has to be stable in human intervention studies. It is important to understand the role of probiotics in food matrix related to isolated component. The risk of fungemia should be evaluated before using the *S. cerevisiae* var. *boulardii* strain in the prevention and treatment of diarrheal, infections, parasitosis and bowel diseases.

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Compliance with Ethics Requirements. Authors declare that they respect the journal's ethics requirements. Authors declare that they have no conflict of interest and all procedures involving human / or animal subjects (if exist) respect the specific regulation and standards.

References

1. McFarland, L., Bernasconi, P., *Saccharomyces boulardii*: A Review of an Innovaive Biotherapeutic Agent. *Microbial Ecology in Health and Disease*,**1993**, *6*, 157-171.
2. Łukaszewicz, M. 2012. *Saccharomyces cerevisiae* var. *boulardii* – Probiotic Yeast, *Probiotics*, **2012**, *17*, 385-398, doi:10.5772/50105.
3. Douradinha, B., Reis, V.C.B., Rogers, M.B., Torres, F.A.G., Evans, J.D., Marques, E.T.A. 2014. Novel insights in genetic transformation of the probiotic yeast *Saccharomyces boulardii*. *Bioengineered*, **2014**, *5*, 21–29, doi:10.1371/journal.pone.0112660.
4. Edwards-Ingram, L.C., Gent, M.E., Hoyle, D.C., Hayes, A., Stateva, L.I., Oliver, S.G., Comparative Genomic Hybridization Provides New Insights Into the Molecular Taxonomy of the *Saccharomyces* Sensu Stricto Complex. *Genome Research*, **2004**, *14*, 1043-1051, doi:10.1101/gr.2114704.
5. Mitterdorfer, G., Mayer, H.K., Kneifel, W. Viernstein, H., Clustering of *Saccharomyces boulardii* strains within the species *S. cerevisiae* using molecular typing techniques. *Journal of Applied Microbiology*, **2002**, *93*, 521–530, doi: 10.1046/j.1365-2672.2002.01710.x.
6. Rajkowska, K., Kunicka-Styczyńska A. 2009. Phenotypic and Genotypic Characterization of Probiotic. *Yeasts, Biotechnology & Biotechnological Equipment*, **2009**, *23:sup1*, 662-665, doi: 10.1080/13102818.2009.10818511
7. Fietto, J.L.R., Araújo, R.S., Valadão, F.N., Fietto, L.G., Brandão, R.L., Neves, M.J., Gomes, F.C.O., Nicoli, J.R., Castro, M.I., Molecular and physiological comparisons between *Saccharomyces cerevisiae* and *Saccharomyces Boulardii*. *Can. J. Microbiol*. **2004**, *50*, 615–621, doi: 10.1139/W04-050.
8. Czerucka, D., Piche, T., Rampal, P., Review article: yeast as probiotics – *Saccharomyces boulardii*. *Alimentary Pharmacology & Therapeutics*, **2007**, *26*(6), 767-778, doi: 10.1111/j.1365-2036.2007.03442.x.
9. Buts, J.P., Bernasconi, P. 2005. *Saccharomyces boulardii*: Basic Science and Clinical Applications in Gastroenterology. *Gastroenterol Clin. N. Am*., **2005**, *34*, 515–532.
10. Billoo, A.G., Memon, M.A., Khaskheli, S.A., Murtaza, G., Iqbal, K., Shekhani, M.S., Siddiqi, A.Q. 2006. Role of a probiotic (*Saccharomyces boulardii*) in management and prevention of diarrhoea. World *Journal of Gastroenterology*, **2006**, *12*(28), 4557-4560.
11. Vandenplas, Y., Brunser, O., Szajewska, H., *Saccharomyces boulardii* in childhood. *Eur. J. Pediatr*. **2008**, doi: 10.1007/s00431-008-0879-7.
12. Marcia L. Buck, Pharm.D., *Saccharomyces Boulardii* as a Probiotic for Children. *Pediatr. Pharm*., **2009**, *15*(7)**.**
13. Im, E., Pothoulakis, C. 2010. Progrès récents dans la recherche sur *Saccharomyces boulardii. Gastroentérologie Clinique et Biologique*, **2010**, *34*, 67-75, doi : 10.1016/S0399-8320(10)70010-5.
14. Canani, R.B., Cucchiara, S., Cuomo, R., Pace, F., Papale, F., *Saccharomyces boulardii:* a summary of the evidence for gastroenterology clinical practice in adults and children. *European Review for Medical and Pharmacological Sciences*., **2011**, *15*, 809-822.
15. Feizizadeh, S., Salehi-Abargouei, A., Akbari, V., Efficacy and Safety of *Saccharomyces boulardii* for Acute Diarrhea. *Pediatrics*, **2014**, doi: 10.1542/peds.2013.3590.
16. McFarland, L.V., Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients. *World Journal Gastroenterology*, **2010**, *16*(18), 2202-2222, doi:10.3748/wjg.v16.i18.2202.
17. Pothoulakis, C. 2009. Review article: anti-inflammatory mechanisms of action of Saccharomyces boulardii. *Aliment Pharmacol Ther*., **2009**, *30*(8), 826-833, doi:10.1111/j.1365-2036.2009.04102.x.
18. Murzyn, A., Krasowska, A., Stefanowicz, P., Dziadkowiec, D., Łukaszewicz, M., Capric Acid Secreted by *S. boulardii* Inhibits *C. albicans* Filamentous Growth, Adhesion and Biofilm Formation. *PLoS ONE*, **2010**, *5*(8), doi: 10.1371/journal.pone.0012050.
19. Rajkowska, K., Kunicka-Styczyńska, A., Rygalá, A. 2012. Probiotic Activity of *Saccharomyces cerevisiae* var. *boulardii* Against Human Pathogens. *Food Technol. Biotechnol*., **2012**, *50*(2), 230–236.
20. Katan, M.B.,Why the European Food Safety Authority was right to reject health claims for probiotics. *Beneficial Microbes*, **2012**, *3*(2), 85-89, doi: 10.3920/BM2012.0008.
21. EFSA Panel on Dietetic Products, Nutrition and Allergies, Scientific Opinion on the substantiation of health claims related to *Saccharomyces boulardii* ATY-SB-101 (BCCM/MUCL 53837) (ID 1010, 1011, further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA Journal*, **2012**, *10*(6), 2722.
22. Narayanan, R., Current legislations on probiotic products. *Journal of Agriculture Sciences*, **2013**, *1*(2), 18-24.

23. Wright, A., *Regulating the Safety of Probiotics – The European Approach. Current Pharmaceutical Design*, **2005**, *11*, 17-23.
24. Guerrant, R.L., van Gilder, T., Steiner, T.S., Thielman, N.M., Slutsker, L., Tauxe, R.V., Hennessy, T., Griffin, P.M., DuPont, H., Sack, R.B., Tarr, P., Neill, M., Nachamkin, I., Reller, L.B., Osterholm, M.T., Bennish, M.L., Pickering, L.K. 2001. Practice Guidelines for the Management of Infectious Diarrhea. *Clinical Infectious Diseases*, **2001**, *32*, 331–350.
25. Kotowska, M., Albrecht, P., Szajewska, H. 2005. *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. *Aliment. Pharmacol. Ther.*, **2005**, *21*, 583–590, doi: 10.1111/j.1365-2036.2005.02356.x.
26. Girard-Pipau, F., Pompei, A., Schneider, S., Nano, J.L., Hebuterne, X., Boquet, P., Rampal, P. 2002. Intestinal Microflora, Short Chain and Cellular Fatty Acids, Influence of a Probiotic *Saccharomyces boulardii*. *Microbial Ecology in Health and Disease*, **2002**, *14*, 220–227.
27. Corrêa, N.B.O., Penna, F.J., Lima, F.M.L.S., Nicoli, J.R., A.P. Filho, L.A.P. 2011. Treatment of Acute Diarrhea with *Saccharomyces boulardii* in Infants. *J.P.G.N.*, **2011**, *53*, 497–501, doi: 10.1097/MPG.0b013e31822b7ab0.
28. Cetina-Sauri, G., Basto, G.S., Therapeutic evaluation of *Saccharomyces boulardii* in children with acute diarrhea. *Annales de Pediatrie*, **1994**, *41*(6), 397-400.
29. Gaón, D., Garcia, H., Winter, L., Rodriguez, N., Quitas, R., Gonzalez, S.N., Oliver, G., Effect of *Lactobacillus strains* and *Saccharomyces boulardii* on persistent diarrhea in children. *Medicin*a, **2003**, *63*, 293-298.
30. Ozkan, T.B., Sahin, E., Erdemir, G., Buda, F., Effect of *Saccharomyces boulardii* in Children with Acute Gastroenteritis and Its Relationship to the Immune Response. *The Journal of International Medical Research*, **2007**, *35*, 201 – 212.
31. Folquet, M.A., Saizonou, R., Guedehoussou, T., Vandenplas, Y., *Saccharomyces boulardii* in Acute Gastroenteritis in Children. *WebmedCentral PAEDIATRICS*, **2011**, *2*(11), doi: 10.9754/journal.wmc.2011.001627.
32. Riaz, M., Alam, S., Malik, A., Ali, S.M. 2012. Efficacy and Safety of *Saccharomyces boulardii* in Acute Childhood Diarrhea: A Double Blind Randomised Controlled Trial. *The Indian Journal of Pediatrics*, **79 (4)**, 478-482.
33. Burande, M.A., Comparison of efficacy of *Saccharomyces boulardii* strain in the treatment of acute diarrhea in children: A prospective, single-blind, randomized controlled clinical trial. *Journal of Pharmacology and Pharmacotherapeutics*, **2013**, *4*(3), 205-208, doi: 10.4103/0976-500X.114603.
34. Htwe, K., Yee, K.S., Tin, M., Vandenplas, Y., Effect of *Saccharomyces boulardii* in the Treatment of Acute Watery Diarrhea in Myanmar Children: A Randomized Controlled Study. *Am. J. Trop. Med. Hyg*., **2009**, *78*(2), 214–216.
35. Collignon, A., Sandré, C., Barc, M.C., *Saccharomyces boulardii* modulates dendritic cell properties and intestinal microbiota disruption after antibiotic treatment. *Gastroentérologie Clinique et Biologique*, **2010**, *34*, 71-78, doi : 10.1016/S0399-8320(10)70024-5.
36. Can, M., Beşirbellioglu, B.A., Avci, I.Y., Beker, C.M., Pahsa, A., Prophylactic *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhea: A prospective study. *Med. Sci. Monit.*, **2006**, *12*(4), 19-22.
37. Casem, E.A.O., *Saccharomyces boulardii* in prevention of antibiotic-associated diarrhea in children: a randomized controlled trial. *PIDSP Journal*, **2013**, 13(2), 70-76.
38. Aktas, M.S., Borku, M.K., Ozkanlar, Y., Efficacy of Saccharomyces boulardii as a probiotic in dogs with lincomycin induced diarrhoea. Bull. *Vet. Inst. Pulawy*, **2007**, *51*, 365-369.
39. Guslandi, M., Giollo, P.,Testoni, P.A., A pilot trial of *Saccharomyces boulardii* in ulcerative colitis. *European Journal of Gastroenterology & Hepatology*, **2003**, *15*, 697-698.
40. Carter, M.J., Lobo, A.J., Travis, S.P.L., Guidelines for the management of inflammatory bowel disease in adults. *Gut*, **2004**, *53*(V), 1-16, doi:10.1136/gut.2004.043372.
41. Dalmasso, G., Cottrez, F., Imbert, V., Lagadec, P., Peyron, J.F., Rampal, P., Czerucka, Groux, H., *Saccharomyces boulardii* Inhibits Inflammatory Bowel Disease by Trapping T Cells in Mesenteric Lymph Nodes. *Gasroenterology*, **2006**, *131*, 1812-1825, doi:10.1053/j.gastro.2006.10.001.
42. Thomas, S., Metzke, D., Schmitz, J., Dörffel, Y., Baumgart, D.C., Anti-inflammatory effects of *Saccharomyces boulardii* mediated by myeloid dendritic cells from patients with Crohn's disease and ulcerative colitis. *Am. J. Physiol. Gastrointest*. Liver Physiol., **2011**, *301*, G1083–G1092.
43. Guslandi, M., Mezzi, G., Sorghi, M., Testoni, P.A., *Saccharomyces boulardii* in Maintenance of Treatment of Chron's Disease. *Digestive Diseases*

and Science, **2000**, *45*(7), 1462-1464, doi : 10.1023/A:1005588911207.

44. Bourreille, A., Cadiot, G., Le Dreau, G., Laharie, D., Beaugerie, L., Dupas, J.L., Marteau, P., Rampal, P., Moyse, D., Saleh, A., Le Guem, M.E., Galmiche, J.P., *Saccharomyces boulardii* Does Not Prevent Relapse of Crohn's Disease. Clinical *Gastroenterology and Hepatology*, **2013**, *11*(8), 982-987, 10.1016/j.cgh.2013.02.021.
45. Quigley, E., Fried, M., Gwee, K.A., Olano, C., Guarner, F., Khalif, I., Hungin, P., Lindberg, G., Abbas, Z., Fernandez, L.B., Mearin, F., Bhatia, S.J., Hu, P.J., Schmulson, M. Krabshuis, J.H., Le Mair, A.W., Irritable bowel syndrome: a global perspective. *World Gastroenterology Organisation Global Guideline*, **2009**, 1-20.
46. Akhondi-Meybodi, M., Rahimian, M., Salmanroghani, H., Amirbeigy, M.K., Baghbanian, M., Ghelmani, S.Y., Study of the Effect of Probiotic *Saccharomyces Boulardii* on the Treatment of Irritable Bowel Syndrome. *Journal of Biology and Today's World*, **2014**, *3*(7), 152-156.
47. Kabir, M.A., Ishaque, S.M., Ali, M.S., Mahmuduzzaman, M., Hasa, M., Role of *Saccharomyces boulardii* in diarrhea predominant irritable bowel syndrome. *Mymensigh Med. J.*, **2011**, *20*(3), 397-401.
48. Choi, C.H., Jo, S.Y., Park, H.J., Chang, S.K., Byeon, J.S., Myung, S.J., A randomized, double-blind, placebo-controlled multicenter trial of *Saccharomyces boulardii* in irritable bowel syndrome: effect on quality of life. *J. Clin. Gastroenterol*., **2011**, *45*(9), 679-683, doi : 10.1097/MCG.0b013e318235601c.
49. Maioli, T.U., Silva, B.M., Nobre Dias, M.N., Paiva, N.C., Cardoso, V.N., Fernandes, S.O., Carneiro, C.M., Martins, F.S., Generoso, S.V., Pretreatment with *Saccharomyces boulardii* does not prevent the experimental mucositis in Swiss mice. *Journal of Negative Results in BioMedicine*, **2014**, *13*(6), doi:10.1186/1477-5751-13-6.
50. McFarland, L.V., Surawicz, C.M., Greenberg, R.N., Fekety, R., Elmer, G.W., Moyer, K.A., Melcher, S.A., Bowen, K.E., Cox, J.L., Noorani, Z., Harrington, G., Rubin, M., Greenwald, D., A Randomized Placebo-Controlled Trial of *Sccharomyces boulardii* in combination with Standard Antibiotics for *Clostridium difficile* Disease. *The Journal of American Medical Association*, **1994**, *271*, 1913-1918.
51. Spielholz, C., Efficacy of a synbiotic chewable tablet in the prevention of antibiotic-associated diarrhea. *Health*, **2011**, *3*, 110-115, doi: 10.4236/health.2011.32020.
52. Chey, W.D., Wong, B.C.Y., American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. *American Journal of Gastroenterology*, **2007**, *102*, 1808–1825, doi:10.1111/j.1572-0241.2007.01393.x.
53. Gottland, M., Poliak, L., Crucheti, S., Brunser, O. 2005. Effect of regular ingestion of *Saccharomyces boulardii* plus inulin or *Lactobacillus acidophilus* LB in children colonized by *Helicobacter pylori*. *Acta Paediatr*., **2005**, *94*(12), 1747-1751, doi: 10.1111/j.1651-2227.2005.tb01848.x.
54. Kyriakos, N., Papamichael, K., Roussos, A., Theodoropoulos, I., Karakoidas, C., Smyrnidis, A., Archavlis, E., Lariou, K., Mantzaris, G.J., A Lyophilized Form of *Saccharomyces boulardii* Enhances the *Helicobacter pylori* Eradication Rates of Omeprazole-Triple Therapy in Patients With Peptic Ulcer Disease or Functional Dyspepsia. *Hospital Chtonicles*, **2013**, *8*(3), 127–133.
55. Badia**, R.,** Zanello, G., Chevaleyre, C., Lizardo, R., Meurens, F., Martínez**, P.,** Brufau**,** J., Salmon**,** H., Effect of *Saccharomyces cerevisiae* var. *boulardii* and β-galactomannan oligosaccharide on porcine intestinal epithelial and dendritic cells challenged *in vitro* with *Escherichia coli* F4 (K88). *Veterinary Research*, **2012**, *43*(4), 1-11.
56. Costa de Avilaa, L.F., Conceicão, F.R., Telmo, P.L., Dutra, G.F., Santos, D.G., Martins, L.H.R., Berne, M.E.A., Silva, P.E.A., Scaini, C.J. *Saccharomyces boulardii* reduces infection intensity of mice with toxocariasis. *Veterinary Parasitology*, **2012**, *187*, 337–340, doi:10.1016/j.vetpar.2012.01.002.
57. Besirbellioglu, B.A., Ulcay, A., Can, M., Erdem, H., Tanyuksel, M., Avci, I.Y., Araz, E., Pahsa, A., *Saccharomyces boulardii* and infection due to *Giardia lamblia*. *Scandinavian Journal of Infectious Diseases*, **2006**, *38*, 479–481, doi:10.1080/00365540600561769.
58. Boyle, R.J., Robins-Browne, R.M., Tang, M.L.K., Probiotic use in clinical practice: what are the risks? *American Journal of Clinical Nutrition*, **2006**, *83*, 1256–1264.
59. Cesaro, S., Chinello, P., Rossi, L., Zanesco, L., *Saccharomyces cerevisiae* fungemia in a neutropenic patient treated with *Saccharomyces boulardii*. *Support Care Cancer*, **2000**, *8*, 504 – 505, doi: 10.1007/s005200000123.

60. Riquelme, A.J., Calvo, M.A., Guzman, A.M., Depix,M.S., García, P., Pérez, C., Arrese, M., Labarca, J.A., *Saccharomyces cerevisiae* fungemia after *Saccharomyces boulardii* treatment in immunocompromised patients. *J. Clin .Gastroenterol*., **2003**, *36*, 41–43, doi: 10.1097/00004836-200301000-00013.
61. Thygesen, J.B., Glerup, H., Tarp, B., *Saccharomyces boulardii* fungemia caused by treatment with a probioticum. *BMJ Case Reports,* **2012**, doi:10.1136/bcr.06.2011.4412.
62. Cassone, M., Serra, P., Mondello, F., Girolamo, A., Scafetti, S., Pistella, E., Venditti,M., Outbreak of *Saccharomyces cerevisiae* Subtype *boulardii* Fungemia in Patients Neighboring Those Treated with a Probiotic Preparation of the Organism. *Journal of clinical microbiology*, **2003**, *41*(11), 5340-5343, doi: 10.1128/JCM.41.11.5340-5343.2003