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Role of *Saccharomyces boulardii* in inflammatory bowel disease.

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Abstract

The health benefits of probiotics have been discussed from the decades in various health disease. For the management of chronic diseases these probiotics showed positive response. Recently, by various research groups, the beneficial effects have been obtained. *Saccharomyces boulardii* is only yeast base probiotic approved for use in human with pathogenesis of inflammatory bowel disease. The basic probiotic mechanisms of action, related to inflammatory bowel disease *Saccharomyces boulardii* , a well-studied probiotic, can be effective in inflammatory gastrointestinal diseases. Such as inflammatory bowel disease (IBD), and inflammation. In this review clinical and in-vitro and animals trial has been discussed.

Keywords: *Saccharomyces boulardii*, Yeast, Inflammatory bowel disease, Ulcerative colitis, Crohn's disease.

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Introduction

Probiotic is defined as the living cells of any type of organism which is harmless to the individual but show deteriorate effect to the bad bacteria and increase the growth of helpful bacteria in the gut. These can be used to treat G.I.T inflammation. The Gastrointestinal (GI) microflora ('microbiota') is a tremendously complex ecosystem that coexists in symmetry with the host. When this symmetry is interrupt, clinical disorders may arise. Microbiota has an important role in infectious G.I.T diseases. Current research has linked intestinal microbiota disequilib-rium to such Inflammatory Bowel Disease (IBD), Irritable Bowel Syndrome (IBS) and colon cancer etc. Additionally, the microbiota has been proposed while a main monitor of the immune system outside the gut. Various attempts have been made to progress the health condition of affected individuals by adjusting the intestinal flora by means of living microbial adjuncts called 'probiotics'. Probiotics have been defined as viable micro-organisms having a positive effect in the prevention and treatment of specific pathological conditions such as IBD [1]. In recent years, the description of a probiotic has changed, primarily because of the recognition that probiotic bacteria can control the physiological outcomes, distant from the G.I.T lumen. Furthermore, the activation of local mucosal protective mechanisms and the modulation of adaptative immune effector functions can persuade safety levels and the degree of inflammation at the site of mucosal [2]. It is important that the probiotic should be capable to survive the host's natural barriers adjacent to ingested microorganisms. The majority of probiotic micro-organisms are bacteria. Strains of *Lactobacillus rhamnosus* and Lactobacillus acidophilus strain most likely have the greatest history of application as pro-biotics because of their evidence based health benefits, although there is much type of probiotic species available from variety of species with their dose and action variability. So specific probiotic should play important role in the particular type of complications. Major marketed probiotic species are lactobaccilus, *saccharomyces boulardii* etc. [3].

Saccharomyces Boulardii as yeast probiotic

Saccharomyces boulardii is the specie of yeast which is occurring widely in the tropical region and it's a fungus. Generally it doesn't show any pathogenic effect like other of *saccharomyces* type which may be harmful [4]. Due to its non-pathogenic effect and probiotic action it is used as supplement for treating variety of diseases. It has positive effects in inflammatory bowel disease, various research teams are working on this yeast based probiotic [5].

Clinical efficacy of *saccharomyces boulardii* as a probiotic in chronic gastrointestinal diseases

For several types of chronic diseases, clinical efficacy of probiotic *saccharomyces boulardii* can be determined by evaluation. *Saccharomyces boulardii* is probiotic yeast that has been shown to have beneficial effects on the intestinal epithelial barrier and digestive immune system shown in figure 1 [6].

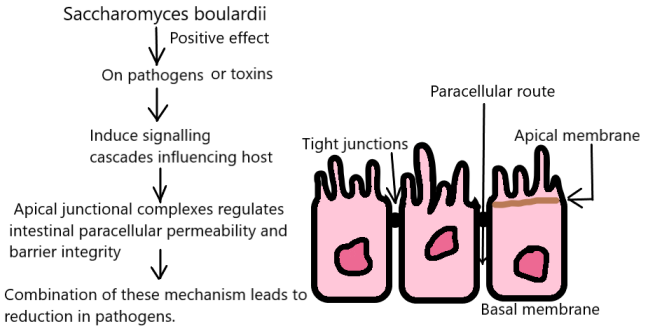

Figure 1. *Positive effect of saccharomyces boulardii leads to decrease in the permeability and barrier integrity.*

Inflammatory bowel disease

A chronic course interfered by acute episodes consisting of phases of remissions with variable period of time. The two main forms are crohn's disease and ulcerative colitis [7]. Multifactorial etiologies, IBD as shown in Figure 2.

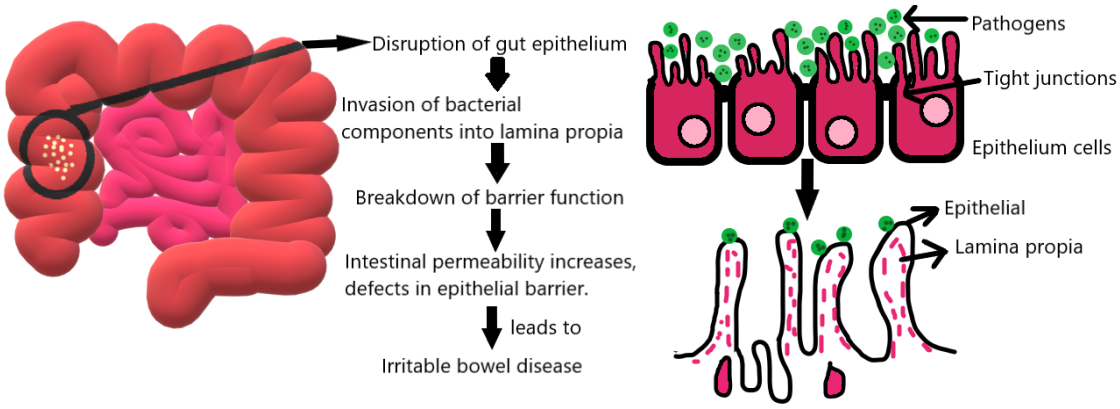

Figure 2. *Pathogenesis of irritable bowel disease.*

Including ulcerative colitis and Crohn's disease, are chronic inflammatory diseases called as relapsing remitting [8]. Prevalence rates are higher for women than for men and younger people are more likely to be affected than those older than age 50 years [9]. Focusing on risk stratification and early use of highly effective therapy in high-risk patients, treat to target using Patient-Reported Outcomes (PROs), biomarkers, endoscopy, and therapeutic drug monitoring [10]. Inflammatory bowel symptoms were present in 16.3% of patients with IBD and mucosal healing (15.4% of patients with CD, 17.4% with UC) [11]. Gut colonization and inflammatory NCDs and gut microbiota modulation strategies for their treatment and prevention [12]. *S. boulardii* exhibits its positive effect by the direct effects on pathogens or their toxins as well as by influencing the host's infection-induced signaling cascades and its innate and adaptive immune system. Intestinal paracellular permeability and barrier integrity are regulated by apical junctional complexes, comprised of tight junctions and adherens junctions (Figure 2). During episodes of inflammation, these apical junctional complexes in the gut are often compromised, increasing epithelial permeability [13]. The combination of these mechanisms results in a reduction of the pathogens' ability for adhesion or colonization and an attenuation of the overreacting inflammatory immune response [14]. Although, genetic susceptibility, environmental factors, and immune dysregulation all contribute to disease pathogenesis [15] *S. boulardii* treatment was shown to inhibit inflammatory bowel disease by suppressing CD4þ T-cell number and interferon-g production within the colon bacterial infections and inflammatory bowel disease, through modulation of host pro-inflammatory responses by controlling inflammation at different levels, such as the NF-kB and the mitogen-activated protein kinase pathways [16]. Included Animal trials and cell assays describes different anti-inflammatory mechanisms of *S. boulardii* supporting a possible effect when treating IBD patients [17].

Crohn's disease

According to this disease, intestinal inflammation effects the whole gastrointestinal tract. Anti-inflammatory effects of *Saccharomyces boulardii* mediated by myeloid dendritic cells from patients with Crohn's disease and ulcerative colitis. Dendritic cells (DC) are thought to be critically involved in inflammatory T cell polarization and activation observed in human IBD, the mechanism of action of inflammation in crohn's disease as shown in Figure-2 [18].

Clinical Trials on *Saccharomyces boulardii*

There are both clinical trials and non-clinical studies has been done using *saccharomyces boulardii* on both human and animal.

Clinical trials: First clinical trial was done by Garcia vilela amd her team. She took 34 patient with clinical remission. in her study she included 18 men and 13 women. In the total of 34 patient only 31 completed the study while other 3 hindered the treatment. This patient having age between 18 to 54 (Figure 3). she separate the patient in three group in which group A group B and Group C in group A there was 19 patient who took lacebo and in Group B 15 patient getting the saccharoyces boulardii capsule. And in group C there was 15 healthy individual who does not took any treatment and acted as control group and the entire individual ratio of mannitol and lactulose was calculated and it come to be 0.005+ or-0.0037. After getting the therapy in placebos individual this value increased to 0.004+ or – 0.010 and in the *saccharomyces* persons the value decreased to 0.008+ or – 0.006. This value indicate the *saccharomyces boulardii* has role in the IBD disease treatment and also it increase the barrier function of the gut so very important role in the ulcerative colitis and crohn disease [19-25].

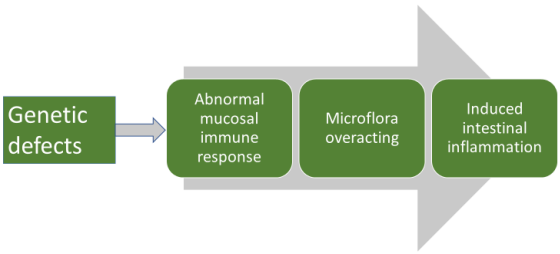

Figure 3. *Shows mechanism of action of inflammation in crohn's disease.*

Another trial is done by Gulsandi et al. Another research on the *saccharomyces* yeast was done by this researcher. These patients were on steroid therapy and included localized fistula, allergy and intestinal disease. The patients grouped into group A and Group B. Group A was treated with mesalazine 500 mg twice while group B was treated with *saccharomyces* 500 mg and mesalazine twice in the morning. All the subjects successfully performed the study. Results were seen that in a Group A people 6/16 people had

clinical relapse while only 1/16 in group B. So this study showed that beneficially effect of the yeast in IBD disease [26]. The third trial pilot scale study done by McFarlandetal. In his study he took patient of ulcerative colitis with symptoms. He gave 250 mg *saccharomyces* capsule to 25 people three times a day for weeks (Table 1). In his study he took 14 men and 11 women. Mesalazine also given concurrently one patient leave the study because of condition became critical. Other 24 successfully done the study. Rachemilewitz's indexes were calculated. At last 17 were attained remission [27].

Table 1: *Various studies for saccharomyces boulardii in the treatment of crohn's disease.*

Evaluation of the efficacy of probiotic *saccharomyces boulardii* in the treatment of crohn's disease	
Study	Result
Patient with crohn's disease were randomized for three months or placebo with *saccharomyces boulardii* [19].	Effective in reducing acute intestinal inflammation managing colitis, by reducing intestinal inflammation and accelerating the recovery and attenuating the relapse.
Study	Result
In the patient with crohn's disease two randomized controlled trial were tested with *saccharomyces boulardii* in this randomized study of 20 patients with crohn's disease managed their medications with *saccharomyces boulardii* or placebo for 7 weeks [20].	Those which are treated with *saccharomyces boulardii* were found to have decrease in colonic permeability as comparing with placebo.

In one more study by Ganji et al. in his study he gave *s. boulardii* capsule dose 1 gm this study goes 52 weeks. Total 196 patients were taken for study in which 165 were random. Out of these 59 subjects received s (Table 2). boulardii capsule cc while other received placebo. After study it was noted that 38 patient relapsed in *saccharomyces* and 42 in placebos in his study he said *s. boulardii* is not beneficially in ulcerative colitis [28].

Table 2: *Various studies for saccharomyces boulardii in the treatment of ulcerative colitis.*

Evaluation of the efficacy of probiotic *saccharomyces boulardii* in the treatment of ulcerative colitis	
Study	Result
In 25 patient having mild to moderate ulcerative colitis they were treated for the period of four months with a combination therapy of mesalazine and *saccharomyces boulardii* [21].	68% of patient responded to treatment. In another study with six patients in which combination given was rifaximin and *saccharomyces boulardii* for three months showed the reduction in occurrence of the ulcerative colitis flares.

Animal trials: this type of study is done on animal specially mice. One of the animal study include bacterial like Escherichia coli, Rumnicocuscdays animals were sacrificed and intestinal samples were taken and it is noted that *saccharomyces* strain upgraded to angiogenesis' while this effect is opposite. Generally it should inhibit angiogenesis while it increasing. This study was opposite to clinical studies. Angiogenesis have role in inflammation. Goal is to inhibit it whether to increase. So result is opposite to the wanted effect [29].

Another animal study was done by Chen et al. His goal was to see whether sachharomyces inhibit VEGFR (vascular endothelial growth factor receptor). So to perform this he induces colitis and then injected *saccharomyces*. After that he saw that it induce vascularisaton and increased mucosal was aim to see. To further confirm this he injected adenovirus carrying VEGF into ear of mice and *saccharomyces* were given to mice after 1 hour of adenovirus injection (Table 3). After 24 hour second dose of *saccharomyces* was given. Approximately after 7 days of treatment he saw that vessel formation reduced in right ear compared to the left. From this study it was confirmed [30].

Table 3: *Various studies for saccharomyces boulardii in the treatment of irritable bowel syndrome.*

Evaluation of the efficacy of probiotic *saccharomyces boulardii* in the treatment of irritable bowel syndrome	
Study	Result
In double bind placebo-controlled study of 34 patients having several episodes of diarrhea [22].	Treated with *saccharomyces boulardii* shows the result of decrease in number of occurrence of stools as well as consistency. [24].
Study	Result
19 RCTs in 1650 patients with IBS were identified. There were 10 RCTs involving 918 patients providing outcomes as a dichotomous variable [23].	Probiotics were statistically significantly better than placebo (RR of IBS not improving=0.71. There was significant heterogeneity and possible funnel plot asymmetry. Fifteen trials assessing 1351 patients reported on improvement in IBS score as a continuous outcome (SMD=−0.34; 95% CI −0.60 to −0.07).

One more study was done by it. So to perform this he took five animal groups in which no colitic, with treatment of doxycycline, colitic mice treated with *saccharomyces* and last one colitic mice treated with both doxycycline and ulcerative colitis. After this he seen that mice treated with both doxycycline and sachharomyces show good result and thus *saccharomyces* bolardii has good role in IBD [31].

In vitro trials

In this type of study experiment were performed outside the body mainly in laboratory in cells or animal [32]. He took 10 specimens from IBD patient and sees that they are deficient from E-cadherin and after treating with *s. boulardii* they increase with E-cadherin and showing its effect in ulcerative colitis. A study by Thomas et al. in his study see that IBD patient has increased expression of CD40 and CD80 on dendritic cells and *saccharomyces* decrease its expression showing once again its role [33].

Future aspects

From the extensive literature review it has been confirmed that *saccharomyces* bolardii has benefical role in the IN the inflammatory bowel disease, this yeast probiotic can be combined with the other probiotic to synergies the effect in IBD. Till now there is no drug combination is available with yeast probiotic.

Improved characterization of probiotic strains at the genomic level is required, along with more clear explanation of mechanisms of action in different clinical scenery. In the future thoroughly controlled clinical trials will be necessary in different settings. Indeed, probiotic efficacy should be defined in terms of the preferred health benefit or function, for example, anti-inflammatory or anti-antioxidant or both. Additionally, there are clinical subsets of IBD such as Crohn's disease and ulcerative colitis, the effect of different strains on the specific disease should be evaluated [34].

Conclusion

S. boulardii in the management of ulcerative colitis proved beneficial but due to only small pilot scale studies on this we are lacking more data on this yeast effect on the management of the ulcerative colitis. Many study proved the anti-inflammatory effect of it. But we can't confirm from existing study that *S. boulardii* is fully beneficial for the management of Ulcerative colitis. But from the existing data it may possible that it can be best treatment for treating IBD especially ulcerative colitis. For its better understanding I suggest that more large scale studies should be conducted to seek full result. Studies has been done only person with reemission so i suggest that both remission and active state diseased condition should be taken for proper study. Probiotic can be useful alternative in the condition like inflammation except Ulcerative colitis. Due to their many effects probiotic are under the eyes of many researcher. Except for that these are useful in managing the microbiota and maintaining the integrity of the epithelial layer.

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