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Review

The Role of *Saccharomyces boulardii* over Probiotics in Prevention and Treatment of Colorectal Cancer and Gastrointestinal Disorder in Potential High-Risk Individuals, Review of Current Evidence

Potansiyel Yüksek Riskli Bireylerde Kolorektal Kanser ve Gastrointestinal Bozuklukların Önlenmesi ve Tedavisinde Probiyotiklere Kıyasla *Saccharomyces boulardii*'nin Rolü: Mevcut Kanıtların Gözden Geçirilmesi

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ABSTRACT

Saccharomyces boulardii, a widely used non-pathogenic yeast used as a probiotic in different regions of the world,was first isolated from litchi fruit *(Litchi chinensis)* in 1923 by Dr. Henri Boulard. From that time, it became well known tool in prevention and treatment of many gastrointestinal tract diseases like inflammatory bowel disease, *Clostridium difficile* infections, antibiotics associated with diarrhea, eradication of *Helicobacter pylori* and irritable bowel syndrome, this is done usually by two major ways, first, *Saccharomyces boulardii* founded to inhibit release or inhibit the effect of bacterial toxins, second; it founded to have direct effect on intestinal mucosa, The aim of this systematic review is to focus on recent studies about probiotic, then addresses the role *Saccharomyces boulardii* in prevention and treatment of various intestinal tract pathologies like inflammation and cancer by providing recent clinical based trials with numerous meta-analysis studies. Multiple studies from PubMed and Google Scholar, including clinical trials, meta-analyses, and experiments published from (2010-2025), suggest a beneficial effect of *Saccharomyces boulardii* in the prevention and treatment of colorectal cancer and various acute or chronic intestinal disorders. Despite the risk of fungemia, previous studies have not reported other adverse effects.

Keywords: *Saccharomyces boulardii*, colorectal cancer, gastrointestinal disorder

ÖZ

Saccharomyces boulardii, dünyanın farklı bölgelerinde probiyotik bir unsur olarak yaygın olarak kullanılan patojenik olmayan bir mayadır ve ilk olarak 1923 yılında Dr. Henri Boulard tarafından liçi meyvesinden (*Litchi chinensis*) izole edilmiştir. O zamandan beri, enflamatuvar barsak hastalığı, *Clostridium difficile* enfeksiyonları, antibiyotik kaynaklı ishal, *Helicobacter pylori* eradikasyonu ve irritabl bağırsak sendromu gibi birçok gastrointestinal sistem hastalığının önlenmesi ve tedavisinde bilinen bir araç haline gelmiştir. Bu genellikle iki ana yolla yapılır: Birincisi, *Saccharomyces boulardii*'nin bakteriyel toksinlerin salınımını veya etkisini inhibe ettiği bulunmuştur; ikincisi, barsak mukozası üzerinde doğrudan bir etkiye sahip olduğu bulunmuştur. Bu sistematik incelemenin amacı, probiyotikler hakkındaki son çalışmalara odaklanmak ve ardından *Saccharomyces boulardii*'nin enflamasyon ve kanser gibi çeşitli barsak sistemi patolojilerinin önlenmesi ve tedavisindeki rolünü, çok sayıda meta-analiz çalışmasıyla desteklenen son klinik çalışmalar sunarak ele almaktır. PubMed ve Google Schoolar'da (2010-2025 yılları arasında yayınlanan) klinik çalışmalar, meta-analizler ve deneyler de dahil olmak üzere çok sayıda çalışma, *Saccharomyces boulardii* kolorektal kanser ve çeşitli akut veya kronik bağırsak rahatsızlıklarının önlenmesi ve tedavisinde faydalı etkisini göstermektedir. Bu çalışmalar, fungemi riski olmasına rağmen, önceki çalışmalarda bildirilen herhangi bir yan etkiye dair kanıt bulunmamaktadır.

Anahtar Kelimeler: *Saccharomyces boulardii*, kolorektal kanser, gastrointestinal bozukluklar

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INTRODUCTION

Colorectal carcinomas considered as the third cancer in incidence over the world and second most killer especially after 50 years of age with 10% incidence rate (1,2). There are various risk factors that help in development of colorectal cancer like genetic predisposition, lifestyle, diet, eating processed meat, low fiber diet like fruits, vegetable, also alcohol consumption and cigarettes smoking considered as important variables (3).

Numerous microorganisms are also reported to be influenced positively or negatively in the development of colorectal cancer (4). It accounts for about one hundred trillion microorganisms living digestive tract from mouth to rectum, so it is important to rule out the function of these organisms in immune, absorption, and metabolism of intestinal tract, these organisms called gut microbiome or gut flora (5).

Any change or disruption in gut microbiome may predispose to colorectal cancer by modifying metabolism, epithelial lining, immune response and deoxyribonucleic acid (DNA) change or damage, all these factors leading to abnormal cellular events and function of colorectal cells (6), Conditions such as malnutrition, obesity, diabetes mellitus, and chronic inflammatory bowel disease are considered important leading causes of colorectal cancer (7,8).

The gut microbiome is a dynamic complex system of microorganism that inhabits the gastrointestinal tract in planned matter, according to multiple factors including age, lifestyle, antibiotic treatment, genetic predisposition in addition to environmental factors and exposure to pathological agents (9-11).

Bioactive material that is consumed by population like probiotics is very important, where recent studies showed the benefit of these materials upon human health (12-14). So, probiotics are considered an important alternative pathway in treatment and prevention of various pathological diseases of intestinal tract (15).

The aim of this review is to focus on recent studies on probiotics, especially *Saccharomyces boulardii,* and their role in the prevention and treatment of various intestinal tract pathologies, such as inflammation and cancer.

Probiotics

The probiotics define as "live microorganisms which when administered in an adequate amount, confer health benefits on the host" (16). This definition established by Food and Agriculture Organization of the united nation and World Health Organization (WHO) 2001 (17). Where the probiotic term came or derived from Greek word "for-life," the FAO and WHO discuss the anti-disease activity of probiotic in few areas of effectiveness (16). We will review the latest evidence.

Saccharomyces boulardii

A widely used non-pathogenic yeast as probiotic element in number of regions of world, first isolated from litchi fruit (*Litchi chinensis*) in 1923 by Dr. Henri Boulard (18). From that time, it became well known tool in prevention and treatment of many gastrointestinal tract diseases like inflammatory bowel disease, *Clostridium difficili* infections, antibiotics associated with diarrhea (ADD), due to *Saccharomyces boulardii* had resistance to all antibacterial antibiotics making it typical antibiotic companion agent in treatment various GIT pathologies and in same time regarded as cost-effective treatment (19). *Saccharomyces boulardii*, considered a safe agent for use in children and the elderly, sometimes requires 2-3 days to reach a viable concentration in the gut and 2-5 days to be cleared after oral use (20). The mood of action of this yeast by two major ways, first, *Saccharomyces boulardii* founded to inhibit release or inhibit the effect of bacterial toxins, second; it founded to have direct effect on intestinal mucosa (21).

Role of Probiotics in Colorectal Cancer In Clinical Trials on Humans

There are myriad studies focused on the role of probiotics in colorectal cancer that conducted beyond *in vitro* or *in vivo* levels but as clinical trials such what examined by Hibberd et al. (22). In this trial he studied the influence of probiotics on gut microbiomes in patients with colorectal carcinoma staged from I-III, where the participants received probiotics doses of [$7x10^9$ colony forming unit (CFU)] of *Lactobacillus acidophilus* and 1.4x10 (10) CFU of *Bifidobacterium lactis* with as two tablet with 630 mg of inulin daily for 8-78 days based on date of their surgery, after which he collected biopsies from all groups of participants (probiotics with colorectal cancer patients, patients with colorectal cancer without probiotics supplementations and normal control group) also he took fecal samples from all participants during colonoscopy, he conclude after the trial have been completed; the colorectal cancer patient have different microbial signature in cancerous tissue and normal mucosa of safe margin that have been alter after probiotics treatment (2,22).

The probiotics enhance the quality of life in patients who survive from cancer as suggest by another study of Lee et al. (23). Also, multiple studies explained the role of probiotics in infections after routine therapy of cancer due to immune suppression which can be lethal where probiotics can improve the rate of infection and complication after surgery (24).

In Laboratory Design Studies

After appearance of potential effect of probiotics in modulating cell immunity, myriad studies and research focused on effects of probiotics on colorectal cancer and the ways in which they act (25). From standpoint of nature of cancerous cells to proliferate and migrate; some laboratory design studies focused on proliferation, that explore the effects of probiotics (*Enterococcus faecium* and *Lactobacillus fermentum*) on caco-2 cancer cells, where they suggest there was antiproliferative effect of aforementioned bacteria on cancerous cells by about 21-29% (26).

In terms of migration and spreading, recent data refer; introducing the probiotics CT26 cells line derived from mouse and fed them to mice with BALB/c tumor and follow them for 21 days, they suggest that; there was reducing in CT26 cells ability to proliferate, invade and migrate in comparing to control cells, also he found the tumor in mice that fed with probiotics was statistically significant smaller in size than control group (27).

At the molecular level, several studies explore the probiotics effects and alteration in apoptotic activity of CRC cells, where recent study examined and explore the effect of probiotics (*Lactobacillus acidophilus, Lactobacillus casei*) on LS513 cell line and suggest that, there was increase in activity of apoptotic factors after increasing in dose also there was increase in Caspase-3 activity and decreased in P21 expression (28). Other studies using diverse types of bacteria reported similar results. Similar studies at the molecular level revealed decreased expression of CD166, CD44, CD133, and ALDH1 in addition to decrease in formation of colon spheres and increase the activity of caspase-3 (29-31).

In general, most used way to treat colorectal cancer is curative chemotherapy (32,33). Chemotherapy induced mucositis (CIM) nearly happen in 40-100% of patients undergo chemotherapy treatment for CRC, those patients may need supportive measures like parenteral feeding, fluid replacement therapy, and preventive measure against infections (34).

Saccharomyces boulardii Over Probiotic in Treatment of CRC

Recent studies have focused on using *Saccharomyces boulardii* in the treatment of CIM because of its stability at low pH, resistance to antibiotics, and ability to withstand normal body temperature, allowing prolonged residence in the gastrointestinal tract. In treatment of CIM, The *Saccharomyces boulardii* affects the GIT lumen through restoring gut dysbiosis in addition to production of spermidine, spermine, polyamines that stimulate enzymes production, protein synthesis and DNA replication that promote cell growth, regeneration control apoptosis through mitogen-activated protein kinase and nuclear factor kappa B (35). *Saccharomyces boulardii* increases the strength of the mucosal barrier by increasing mucosal production which protects the intestinal mucosa from physical and chemical damage (36).

Immune System of Gastrointestinal Tract and Probiotics

Probiotics can adhere to intestinal mucosa by about 80%, so it is considered a crucial factor in modulating immune response of intestinal tract and preventing serious illness, such as intestinal infections, inflammatory bowel disease and relieving lactose intolerance (37,38).

Probiotics can stimulate both innate and adaptive immune response, by enhancing phagocytosis and increasing the cytotoxicity of NK cells leading to inhibiting tumor and infection development (39).

Different studies have shown that probiotics increase the expression of immunoglobulin A (IgA) and IgM, thereby enhancing adaptive immunity. These studies also suggest probiotics can enhance production and differentiation of T1 helper lymphocytes and alter the balance of Th1 and Th2 lymphocytes as a results probiotic's supplementation can enhance both innate and adaptive immunity (37,40).

Saccharomyces boulardii Over Probiotics in Immune Modulation

Early studies on *Saccharomyces boulardii* showed this yeast can triggered the complement and reticuloendothelial systems that lead to migration of monocyte and granulocyte in addition to enhancing number of Kupffer cells, these studies indicate that *Saccharomyces boulardii* stimulate innate immunity of gastrointestinal tract (41,42).

Qamar et al. (43) found that after oral administration of *Saccharomyces boulardii* to rat, there was increasing in production in secretory IgA in duodenal fluid by 56.9% and in other study increase by 62.8%, also IgA increased in villous cells by 69% and in the crypt cells by 80%, so these study conclude that *Saccharomyces boulardii* can stimulate and triggered the adaptive immunity.

Recent studies show that *Saccharomyces boulardii can decrease* pro-inflammatory molecules in response to infections such as *Salmonella typhimurium,* including interleukin-8 (IL-8), nuclear factor kappa B, and mitogen-activated protein kinase (44). In the same manner the *Saccharomyces boulardii* can increase anti-inflammatory cytokines like (IL-4, IL-10) and decrease pro-inflammatory

factors (IL-8) in response to *Escherichia coli* infection, likewise it found to increase in IgA and IgG in response to *Clostridium difficili* toxins (45).

Another study showed that *Saccharomyces boulardii* can induce pro-inflammatory cytokines like (interferon-γ) in early *Salmonella typhimurium* infection and suppress production of anti-inflammatory cytokines (IL-10) in small intestine but increase production of both cytokines in cecum as a result, *Saccharomyces boulardii* can modulate immune response throughout GI in different manner (46,47).

Saccharomyces boulardii in Chronic Inflammatory Bowel Diseases

The efficacy of *Saccharomyces boulardii* has been assessed in multiple inflammatory bowel diseases, such as ulcerative colitis, Crohn's disease (CD), irritable bowel syndrome, and other illnesses related to diarrhea.

Saccharomyces boulardii Role in Ulcerative Colitis

Saccharomyces boulardii used as a complementary therapy in ulcerative colitis patients to achieve remission state in active disease (47). Recent data suggest that treatment with *Saccharomyces boulardii* and rifaximin for 3 months seems to be effective in prevention of disease relapsing early, this study was a pilot study with small sample size and short duration of treatment time with no control group or follow up measures (48).

Saccharomyces boulardii supplementation in UC can restore normal gut flora and diminished development of harmful flora leading to restoring normal intestinal environment (49,50).

Very recent studies proposed that additive treatment of *Saccharomyces boulardii* to sulfasalazine in UC patients promote remission in active disease in addition to relief associate symptoms and restore normal mucosal barrier furthermore enhancing quality of life, then using sulfasalazine alone (50-52).

Saccharomyces boulardii Role in Crohn's Disease

Recent studies mentioned CD incidence increased since 1990 in previous century with 3.5 per 100,000 persons\year specially in newly industrialized countries in Africa, Asia, and south America (52).

Most of systematic review of literatures mentions the role of *Saccharomyces boulardii* as probiotics in treatment of CD and they mentioned there was a marked reduction in clinical relapses of CD after six months of treatment with *Saccharomyces boulardii* in combination with Mesalamine, also there was increase in function of intestinal barrier by decreasing of lactulose\mannitol ratio in other studies (53-55).

Compared with *Lactobacillus rhamnosus* GG, which was not found to improve or prolong remission nor to be effective in reducing relapse, *Saccharomyces boulardii* showed effectiveness in prolonging remission in CD and in improving the permeability of the intestinal wall when combined with standard therapy (36,56).

Saccharomyces boulardii in Irritable Bowel Syndrome

Irritable bowel disease (IBS) considered as most common disease identified in people attending gastroenterologist clinics with about 12% of all cases, the prevalence of IBS differs from one country to another where myriad studies reach to incidence of 10-15% of population have IBS (57). IBS had no sure treatment, the most drug modalities merely had supportive and palliative role in treatment of IBS (58).

Different studies declare that the IBS result as changing in gut micro-flora superimposed by enteric infection, so the best treatment is to restore normal microflora by using probiotic (59,60). As IBS characterized by disturbance in normal function of GI tract so its manifestation as abdominal pain or changing in intestinal habits (61).

Recent data suggest that *Saccharomyces boulardii* can improve the abdominal pain, diarrhea and eructation and gas release from stomach, also there was no benefit on using probiotics upon flatulence (57), while other studies suggest that using *Saccharomyces boulardii* along with Mebeverine can exert an additional benefit on treatment of IBS (49).

Role of *Saccharomyces boulardii* in Antibiotic Associated Diarrhea

This type of diarrhea is considered the most common complication of using antibiotics that result from disruption of normal intestinal microbiome (62,63).

Moreover, the antibiotics ADD can display or lead to *Clostridium difficili* infection that is present in more than 50% of infants, 10% of hospitalized patients and 1-5% of normal adults (64). Treatment of *Clostridium difficili* with antibiotics can lead to more turmoil, so the goal of treatment is to restore normal gut microtropia through completion of clinically improve antibiotic course and time with suitable supportive probiotics (65). The European Society for Pediatric Gastroenterology, Hepatology and Nutrition, The World Gastroenterology Organization's Global Guideline and American Gastroenterology association all state on administration of specific probiotics in risky patients upon initiation of antibiotics thus prevent ADD and *Clostridium difficili* infection (65,66).

The yeast *Saccharomyces boulardii* is not normally part of the intestinal microbiota and, unusually, is a eukaryote;

therefore, it is resistant to the effects of antibiotics, making it a more suitable probiotic for administration to patients with an elevated risk of developing ADD (65).

Recent studies and Szajewska and Kołodziej's (67) meta-analysis suggest that *Saccharomyces boulardii* treatment reduced the risk of developing ADD by 18% and significantly reduced the risk of developing *Clostridium difficile* infections.

Role of *Saccharomyces boulardii* in Traveler's Diarrhea

One of the frequent and common GI illnesses is traveler's diarrhea (TD), that affected both sexes equally with rate of up to 70% depending on term and residence, where there were 10-40 million people who had TD yearly (68). TD is usually resolved within 2 days but 10% need medical intervention and 3% need hospital admission (69,70).

Avoiding contaminated food and beverages through effective education about the risk of TD is the best preventive method; prophylactic antibiotics may disrupt the intestinal microbiome and are therefore strongly not recommended (71).

Using prophylactic probiotics nowadays have special attention, Alharbi et al. (71) in her metanalysis study in 2024 suggest that using of *Saccharomyces boulardii* is an effective method in preventing and\or treating of TD depending on dose and strain of *Saccharomyces boulardii*.

Role of *Saccharomyces boulardii* in Persistent Diarrhea

Persistent diarrhea is defined by WHO as "an episode which start acutely but persist for 14 days or longer." Recent studies from clinical trials improve the effectiveness of using *Saccharomyces boulardii* in treatments of persistent diarrhea in children with significant rate of 50% in comparison with placebo (72,73).

Role of *Saccharomyces boulardii* in Enteral Nutrition-Related Diarrhea

Diarrhea is considered most common complications in patients with total enteral nutrition (TEN) that involve change in intestinal short chain fatty acids (SCFAs), recent studies of Schneider et al. (73) and Abid et al. (21) showed there was increased in SCFAs concentrations in patients with *Saccharomyces boulardii* treatment that explained the preventive role of this yeast on TEN patients in comparison to normal control patients.

Role of *Saccharomyces boulardii* in Eradication of Pylori Infection

Multiple studies evaluate the effectiveness of *Saccharomyces boulardii* supplementation in *Helicobacter pylori* eradication; these studies improve that the *Saccharomyces boulardii* can improve eradications rate and reduce the side effects related to triple eradication module of *Helicobacter pylori* like diarrhea also it found to induce morphological changes and decrease the colonization rate of *Helicobacter pylori* in children (74).

CONCLUSION

Extensive research, including clinical trials and meta-analyses, has demonstrated that *Saccharomyces boulardii* therapeutic potential for the prevention and treatment of colorectal cancer, as well as for a number of acute and chronic gastrointestinal illnesses.

Although fungemia remains a recognized clinical concern, no notable side effects have been documented in the literature to date. However, small sample sizes frequently limit the strength of current evidence for illnesses such as TD. Large-scale clinical trials are therefore required to confirm the effectiveness of this yeast in larger populations. To optimize treatment outcomes for various intestinal diseases, further experimental research is needed to evaluate the synergistic benefits of combining *Saccharomyces boulardii* with other probiotics.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: A.F.H., S.S.A., Concept: A.F.H., K.I.N., S.S.A., Design: A.F.H., K.I.N., S.S.A., Data Collection or Processing: A.F.H., K.I.N., Analysis or Interpretation: A.F.H., Literature Search: K.I.N., Writing: A.F.H., S.S.A.

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