CIBTech Journal of Biotechnology ISSN: 2319-3859 (Online)
An Online International Journal Available at http://www.cibtech.org/cjb.htm
2013 Vol. 2 (2) April-June, pp.1-6/Prajapati et al.
Review Article

SACCHAROMYCES BOULARDII - A PROBIOTIC OF CHOICE

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ABSTRACT
The term "probiotic" was first used in 1965 by Lilly and Stillwell, to describe substances secreted by one organism which stimulate the growth of another probiotics as "live micro-organisms", which, when administered in adequate amounts confer a health benefit on the host .The use of probiotics for the prevention of antibiotic associated diarrhea (AAD) and the treatment of Clostridium difficile infections (CDI) has been tested in randomized controlled clinical trials. Probiotics have demonstrated an ability to prevent and treat some infections. The advantages of probiotic therapy include multiple mechanisms of action against pathogens, the ability to interact with the host's natural defense systems, survival to the target organ and a good risk to benefit ratio. *Saccharomyces boulardii* is non-pathogenic yeast which has been used as both a preventive and therapeutic agent for the treatment of a variety of diarrheal diseases. The mechanisms of action of *Saccharomyces boulardii* depend mainly on the inhibition of some bacterial toxins, anti-inflammatory effects mechanisms of action of probiotics include production of pathogen-inhibitory substances, inhibition of pathogen attachment, inhibition of the action of microbial toxins, Probiotics have demonstrated an ability to prevent and treat some infections. Effective use of probiotics could decrease patients' exposure to antimicrobials. Additional controlled studies are needed to clearly define the safety and efficacy of these agents.

Key Words: *Probiotic, Saccharomyces Boulardii, Biotherapeutic Agent, Diarrhoea, Acute Diarrhea, Mechanism of Action.*

INTRODUCTION
Saccharomyces boulardii was discovered by a French microbiologist, Henri Boulard in 1920 when he was in IndoChina searching for new strains of yeast that could be used in fermenting processes. *Saccharomyces boulardii (S. boulardii*) is a yeast isolated from the skin of Lychees grown in Indochina and belongs to the same species as *Saccharomyces cerevisiae (S. cerevisiae)*, although it definitively has different taxonomy, physiological, metabolic and genetic characteristics (Rajkowska *et al.*,2012). The term probiotics was derived from the Greek word, meaning for life (Grover *et al.*, 2011). The name used most commonly, including on commercial labels, is probiotics. A probiotic is generally defined as a live microorganism or microbial mixture administered to beneficially affect the host animal by improving its microbial balance (Gary, 2002).

Saccharomyces boulardii (Sb) is a non-pathogenic yeast used for many years as a probiotic agent to prevent or treat a variety of human gastrointestinal disorders, including antibiotic associated diarrhea and recurrent Clostridium Difficile disease (Sougioultzis *et al.*, 2006). Probiotics are viable, non-pathogenic microorganisms (bacteria or yeast) which when administered in adequate amounts, confer a Health benefit on the host (Cananil *et al.*, 2011). Probiotic yeast cultures have been used as both a preventive and a therapeutic agent for the treatment of a variety of diarrhoeal diseases Rajkowska *et al.*, 2012). Probiotics are generally recommended to help strengthen host systems and assist in recovery from certain diseases (Lynne, 2010). Probiotic is derived from Greek and means for life. Probiotics are defined as living microorganism (bacteria and yeast) resistant to digestion and reaching the colon alive and, when ingested in adequate amounts, have a health benefit for the host (Vandenplas *et al.*, 2008) .Commonly used bacterial probiotics include *Lactobacillus* species, *Bifidobacterium* species,

Escherichia (E.) coli, *Streptococcus* species, and the yeast *Saccharomyces boulardii* (*Sb*) (Cananil *et al*, 2011).

A probiotic is defined as a live microbial feed supplement which beneficially affects the host by improving its microbial balance which is assumed to provide protection against various diseases (Juliana *et al.,* 2004) .*S. boulardii* is thermotolerant yeast that grows optimally at 37°C (Rajkowska *et al* ,2012) **.** Lyophilized preparations of the yeast *Saccharomyces boulardii* have been used for the treatment of antibiotic induced gastrointestinal disorders (Juliana *et al.*,2004). *S. boulardii* has been used internationally and extensively as a probiotic (Marcia *et al.*, 2009). *S. boulardii* is live yeast that has been lyophilized and is available in 250- mg capsules for adults (Jeanne *et al.,* 2003).A probiotic is defined as a viable microbial dietary supplement that beneficially affects the host through its effects in the intestinal tract. The most commonlyused probiotics mainly come from two genera, *Lactobacillus* and *Bifidobacterium*. Their ability to relieve gastrointestinal disorders and bacterial and viral infections is well documented (Kaur *et al.,* 2009**).**

Saccharomyces boulardii, which has been used as an adjunctive therapy, was shown to be a separate species from *Saccharomyces cerevisiae* on the basis of metabolic and molecular parameters (Juliana *et al*, 2004).Several studies indicate that Sb may exert its beneficial effects by multiple mechanisms including competition with pathogens for nutrients, inhibition of pathogen adhesion, strengthening of enterocyte tight junctions, neutralization of bacterial virulence factors and toxins, and enhancement of the mucosal immune response (Sougioultzis *et al*, 2006) *S. boulardii*, nonpathogenic yeast that grows optimally at body temperature, has been tested for efficacy in the prevention of antimicrobial-associated diarrhea in a community setting and an institutional setting. This yeast is commercially available as lyophilized cells in capsule form in many countries (Gary, 2002).Beneficial effects of *S. cerevisiae* var. *boulardii* against enteric pathogens involve different mechanisms, such as prevention of bacterial adherence and translocation in the intestinal epithelial cells, production of factors that neutralize bacterial toxins and modulation of the host signaling pathway with proinflammatory response during bacterial infection Preclinical and experimental studies of *S. boulardii* have demonstrated an anti-inflammatory, antimicrobial, enzymatic, metabolic and antitoxinic activity (Billoo *et al.,* 2006).A powerful evolution of this definition was coined by Parker in 1974 who proposed that probiotics are 'organisms and substances which contribute to intestinal microbial balance'. In more modern definitions, the concept of an action on the gut microflora, and even that of live microorganisms disappeared. Salminen *et al*. defined probiotics as the 'food which contains live bacteria beneficial to health', whereas Marteau *et al*., defined them as 'microbial cell preparations or components of microbial cells that have a beneficial effect on the health (Soccol1et *et al.,* 2010). Probiotics can also modify toxin receptors and block toxin-mediated pathology. *Saccharomyces boulardii* degrades *Clostridium difficile* toxin receptors in the rabbit ileum26 and blocks cholera-induced secretion in rat jejunum by the production of polyamines (Kaur *et al.,* 2009).

Properties of S. boulardii

It must survive passage to its target organ (most commonly the colon). Organisms need to survive at body temperature, be resistant to stomach acids and bile acids, and exist in the competitive milieu of the intestinal tract. Probiotic strains of *Saccharomyces* have been shown to have these abilities. Although the optimal temperature for most strains of *Saccharomyces* range from 22-30 c, *S. boulardii* survives best at 37 c, giving it a unique advantage of being one of the few yeasts that do best at human body temperatures (Lynne, 2010). These studies indicate that *S. boulardii* is a safe and effective biotherapeutic agent for the treatment of gastrointestinal disease (Mcfarland *et al.,* 1993). The use of probiotics must be carefully considered when these living drugs are used therapeutically in patients at high risk for opportunistic infections or when the gastrointestinal tract is badly damaged (Gary, 2002).

Stability

Probiotic product manufacturing may affect its shelf-life. Probiotics may be available as lyophilized or heat-dried preparations (Cananil *et al.,* 2011). Lyophilized preparations of *Sb* are stable over one year at room temperature, as long as it is protected from moisture (Cananil *et al.,* 2011). Daily administration of

lyophilized *S. boulardii* at standard doses results in detectable levels of live yeast throughout the GI tract. *S. boulardii* does not attach to the mucosa of the intestine (Marcia *et al.,* 2009).

Mechanism of Action

Probiotics are live non-pathogenic microorganisms that are taken orally to aid in the maintenance and/or restoration of healthy gastrointestinal (GI) microflora (Marcia *et al.,* 2009). Most probiotics are bacteria; *S. boulardii* is a noncolonizing, non-systemic yeast. It was first isolated in 1923 from lychee fruit in Indonesia by French scientist Henri Boulard who noted that natives of the area used the skin of the fruit to treat symptoms of cholera (Marcia *et al.,* 2009). A very active research in this field has provided interesting data on several mechanisms of action of *Sb* (Cananil *et al.,* 2011).

Anti-Microbial Action

Direct anti-toxin effects The anti-toxin action elicited by *Sb* is mainly due to small peptides produced by the yeast. A 54kDa 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 (Cananil *et al.,* 2011). The rationale for using probiotics is based on the assumption that they modify the composition of colonic microflora and counteract enteric pathogens ***(***Alfredo Guarino *et al.,* 2008).

A common belief about how probiotics work (and one used in marketing these products) is that ingestion improves the balance of the intestinal and vaginal microflora so that pathogen growth is restricted (Gary Elmer, 2002) . More specific mechanisms of action have been identified for individual probiotics. The ability of a probiotic to inhibit pathogen adhesion or to stimulate a local immunoglobulin A-mediated immune response would be highly desirable, because these properties would provide a broad spectrum of antipathogen activity (Gary, 2002).

S. *boulardii* has several different types of mechanisms of action. which may be classified into three main areas: luminal action, trophic action and mucosal-anti-inflammatory signaling effects (Lynne, 2010) *S. boulardii* may interfere with pathogenic toxins, preserve cellular physiology, interfere with pathogen attachment, interact with normal microbiota or assist in reestablishing short chain fatty acid levels (Lynne, 2010).

Inhibition of growth and invasion of pathogens

In vitro, *Sb* directly inhibits the growth of several pathogens (*Candida albicans, E. coli, Shigella, Pseudomonas aeruginosa, Staphylococcus aureus, Entamoeba hystolitica),* and cell invasion by *Salmonella typhimurium* (Cananil *et al.*, 2011). This mode of action is most likely important for the prevention and therapy of infectious diseases but also for the treatment of (chronic) inflammation of the digestive tract or parts thereof. In addition, this probiotic action could be important for the eradication of neoplastic host cells; (*ii*) Probiotics can also have a direct effect on other microorganisms, commensal and/or pathogenic ones (Soccol1 *et al.*, 2010).

Mechanisms of action of probiotics (Gary, 2002).

1. Inhibition of action of microbial toxins
2. Inhibition of pathogen attachment
3. Stimulation of immunoglobulin A

Saccharomyces boulardii as Biotherapeutic Agent

Biotherapeutic agents, sometimes referred to as probiotics, are living microorganisms that have important therapeutic applications. Bacteria associated with probiotic activity are most commonly lactobacilli and bifidobacteria, but other non-pathogenic organisms, such as certain strains of *Escherichia coli* and non-bacterial organisms such as *Saccharomyces boulardii*, have been used (Periti, 2001). Biotherapeutic agent has been used to describe a microbe having specific therapeutic activity against a specific disease. An example of effective use of a biotherapeutic agent is the oral administration of *Saccharomyces boulardii* to treat recurrent Clostridium difficile-associated disease. Another name used is prebiotic this refers to the use of chemicals or nutrients that modify the environment of the gastrointestinal tract to favor proliferation of the beneficial components of the intestinal microflora (Gary, 2002). All biotherapeutic agents are derived from biological sources and are intended to promote health and prevent illness.

Examples of these agents include the lactobacilli, bifidobacteria, and *Streptococcus faecium* bacteria and the *S. boulardii* yeast (Periti, 2001) *Saccharomyces boulardii* is commercially available yeast in many countries 8. It is generally administered in lyophilized powder, corresponding to approx 3×10 /g of colony forming units (CFU) (Periti, 2001).The terms "probiotic" and ″biotherapeutic agent" have been used to describe these products: probiotic is a relatively vague term referring to microorganisms having general beneficial effects on the health of animals or humans. Biotherapeutic agents is a term used more suitably for microorganisms having therapeutic effects in humans. There are increasing experimental and clinical data to support their use in the prevention and treatment of many gastrointestinal disorders, including inflammatory bowel disease, infectious and antibiotic-related diarrheas (Periti, 2001). There are relatively few pharmaceuticals classified as living microorganisms that have proven therapeutic effects when administered to humans; of those biotherapeutics which have been used in therapy (Periti, 2001).

Clinical applications of S. boulardii

An increasing number of potential health benefits are being attributed to probiotic treatments **(**Vandenplas *et al.,* 2008).

Acute diarrhea

S. boulardii for the treatment of acute diarrhea One meta-analysis aimed at evaluating the effectiveness of *S. boulardii* in treating acute infectious diarrhea in children (Vandenplas *et al.,* 2008). *S. boulardii* has been used in the treatment of several types of diarrhea, either as a preventive agent for antibiotic associated diarrhea or in nasogastric tube-associated diarrhea, or as a treatment for diarrhea in adults or children associated with *C. difficile*, in chronic diarrhea in HIV-infected patients or in acute diarrhea in children and adults (Mcfarland *et al.,* 1993).

Diarrhea is defined as a change in bowel movements in an individual with an increase in the water content, volume, and—usually—frequency of stools. In the vast majority of cases, acute diarrhea is the result of a gut infection—mostly viral in the developed countries. The mainstay of therapy for dehydrating gastroenteritis is oral rehydration (Vandenplas *et al.,* 2008).

Since the mid-1980s, several case series, open prospective studies, and randomized controlled trials have evaluated the efficacy of *S. boulardii* in the treatment of acute diarrhea associated with gastroenteritis in children (Marcia *et al.,* 2009). Several probiotic preparations have been shown to be of significant benefit as an adjunct to oral rehydration for acute diarrhea (Gary, 2002) The patients were treated with *S. boulardii* 250 mg given two to four times per day for 15 days (Marcia *et al.,* 2009).

Antibiotic-Associated Diarrhoea

Recent meta-analysis evaluating the available evidence on probiotics for the prevention andtreatment of antibiotic-associated diarrhoea concluded that probiotic administration- (namely, *L. rhamnosus, L. casei*, and the yeast *S. boulardii*, as these are the probiotics predominantly included in the majority of trials) is associated with a reduced risk of the condition (Kechagia *et al.,* 2013).

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 (Mercenier *et al.,* 2002). 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 (Mercenier *et al.,* 2002).

The efficacy of *S. boulardii* in the prevention of antibiotic-associated diarrhea has been demonstrated in several clinical trials (Periti *et al.,* 2001) Antimicrobial-associated diarrhea is the most common adverse effect of antimicrobial therapy. While common, this diarrhea can be serious and is associated with an increase in hospital stay, a higher risk for other infections, and a threefold increase in mortality (Gary, 2002).

S. boulardii, nonpathogenic yeast that grows optimally at body temperature, has been tested for efficacy in the prevention of antimicrobial-associated diarrhea in a community setting and an institutional setting. This yeast is commercially available as lyophilized cells in capsule form in many countries (Gary, 2002) There have been ten randomized controlled trials in adults using *S. boulardii* for the prevention of AAD

(Lynne, 2010) The patients required discontinuation of antibiotics or hospitalization, and no adverse events were reported. The results of these two studies are similar to a number of clinical trials in adults demonstrating the utility of *S. boulardii* in preventing antibiotic-associated diarrhea (Marcia *et al.*, 2009) .Several studies that have been carried out suggest that probiotic use is associated with a reduced risk of antibiotic-associated diarrhea (Kechagia *et al.*, 2013).

CONCLUSION

The use of *S. boulardii* as a therapeutic probiotic is supported by its mechanisms of action, pharmacokinetics, and efficacy from animal models and clinical trials. The overall safety profile for *S. boulardii* is beneficial. *S. boulardii* can be recommended for several diseases. *S. boulardii* is a useful and welcome addition to the treatment of acute diarrhoea in children. *S. boulardii* reduces the frequency of stool, and duration of illness. Probiotic agents are living microorganisms belonging to the normal flora, with low or no pathogenicity and a positive effect on the health and well-being of the host. Probiotic therapy uses bacterial interference and immunomodulation in the control of several infectious, inflammatory, and immunologic conditions.

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