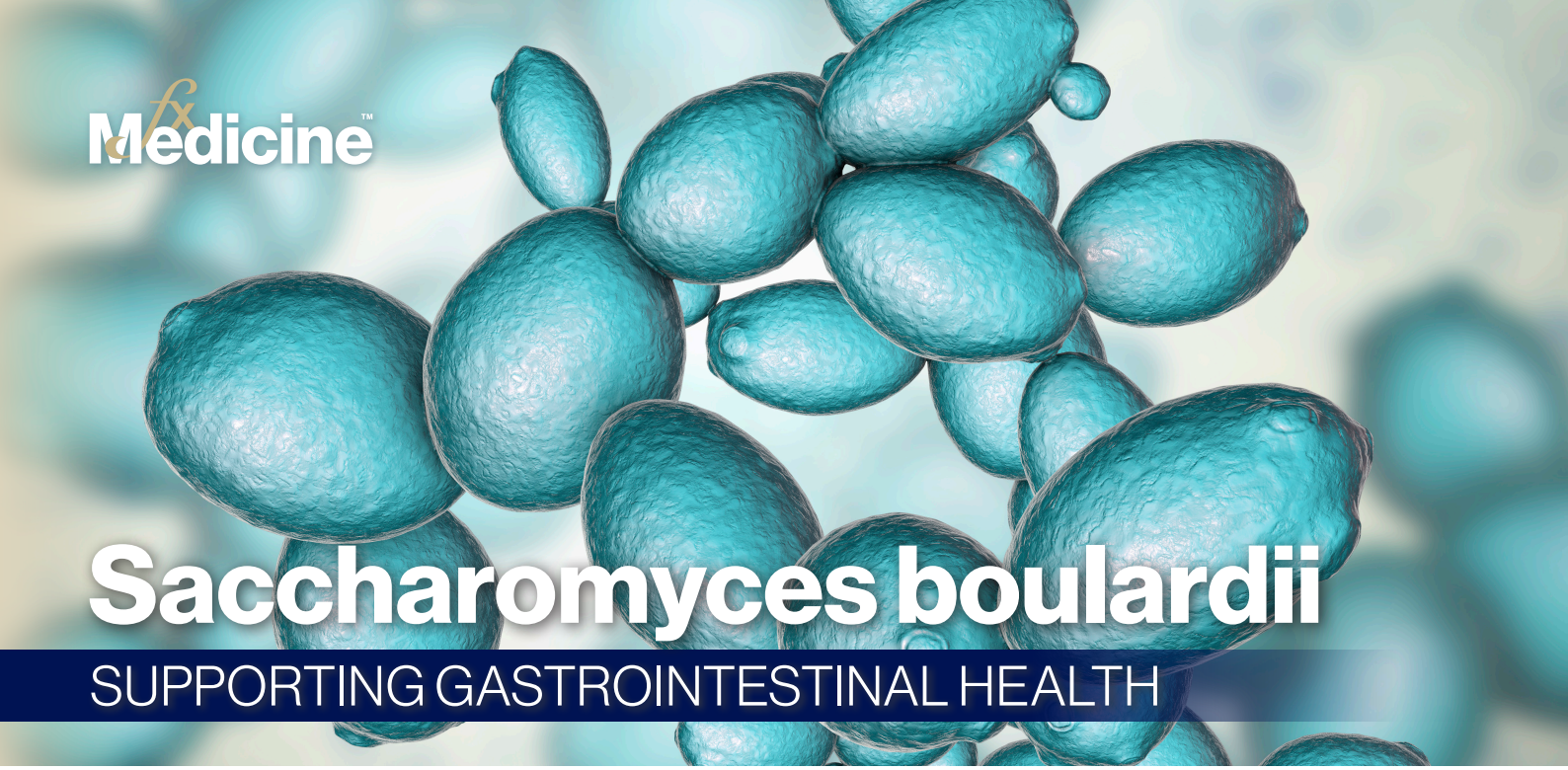


Saccharomyces boulardii

SUPPORTING GASTROINTESTINAL HEALTH

ARTICLE BY
FX MEDICINE

As we continue to learn more about the implications of gastrointestinal inflammation on the immune response, digestive health and longer-term health risks, the need to expand our natural medicine toolkit to support a reduction of inflammation, or inflammation causing pathologies, is critical.

In 1920 during a cholera outbreak[1], microbiologist, Henri Boulard, first documented the benefit of *Saccharomyces boulardii* (*S. boulardii*) in Indonesia after observing the use of a tea made of lychee skins and mangosteen fruits for the prevention of diarrhoea.[2] One hundred years later, *S. boulardii*, continues to be a mainstay in the prevention and treatment of diarrhoea.[1]

Commonly associated with gut inflammation, diarrhoea continues to be one of the leading causes of morbidity and hospitalisation worldwide alongside meaningful economic burden.[2] This continued prevalence emphasises the demand for alternative therapies from the standard protocol of hydration and electrolyte therapy, both ineffective at reducing stool volume, frequency and duration of diarrhoea.[2]

In this article, we put the spotlight on *S. boulardii*, a probiotic lauded for its benefits in reducing gut inflammation, and for the treatment and prevention of diarrhoea-associated conditions including traveller's diarrhoea.

WHAT IS *SACCHAROMYCES BOULARDII*?

Categorised as a probiotic within the World Health Organisation's definition of a 'live microorganism that confers a health benefit on the host',[1] *S. boulardii* differs from bacteria probiotics as a eukaryote probiotic yeast.[2] While similar to *Saccharomyces cerevisiae* or baker's yeast,[3] *S. boulardii* has "different taxonomic, physiological, metabolic and genetic" properties.[2]

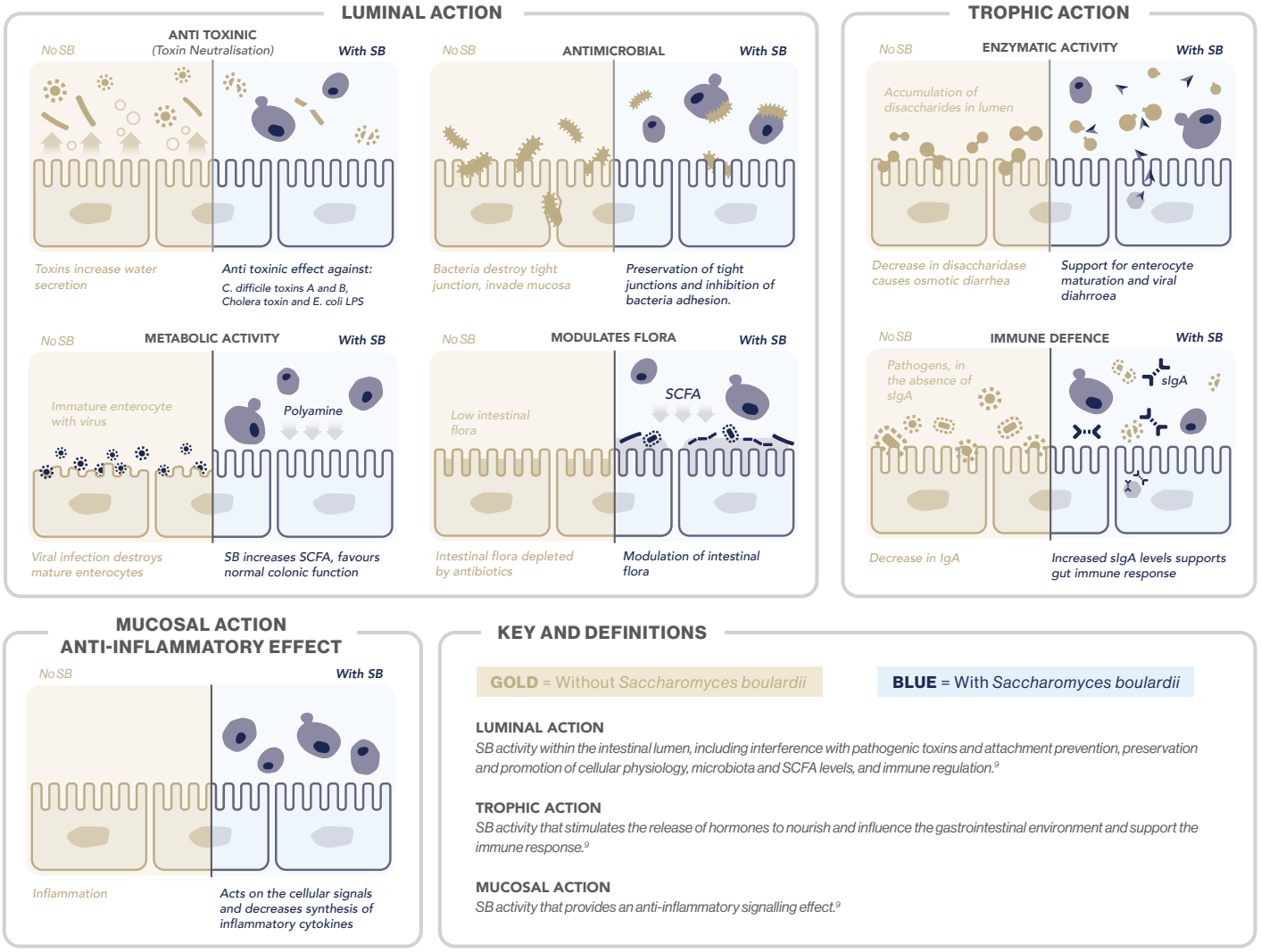
S. boulardii has an optimum growth temperature of 37 degrees celsius,[1] consistent with human body temperature.[2] The yeast can maintain 65% viability up to 52 degrees celsius[3] allowing for a shelf-stable product.

While other treatments may be challenged by the gastrointestinal environment, *S. boulardii* is resistant to low and high pH and bile acids, allowing it to survive the gastrointestinal tract[1] for up to 3 hours.[3] To support supplementation, encapsulation in sodium alginate or gelatin allows *S. boulardii* to remain viable in the presence of bile salts for longer.[3]

With a half-life of six hours, consistent administration of *S. boulardii* results in steady-state concentration from three days of administration, taking a further 2-5 days to clear the body from the point of discontinuation.[1]

Transient and unable to effectively colonise the intestine long term due to its inability to adhere to the epithelium, *S. boulardii* can influence the microbial profile of the individual to an extent, based on the pre-existing gastrointestinal microbial composition.[3] This selective action of *S. boulardii* on the microbiota differentiates it from the actions of other probiotics.[9]

Figure 1: A visual depiction of the functions of *Saccharomyces boulardii*[9]



An impressive safety profile

S. boulardii has an excellent safety profile with minimal adverse reactions.[3] The presence of translocated fungus or yeasts within the blood from the gut, is known as fungemia.[4] A retrospective study identified the use of *S. boulardii* as a risk factor for the development of fungemia and recommends extreme caution when administering *S. boulardii* to the elderly patient more susceptible to translocation due to altered gut permeability.[4] Furthermore, *S. boulardii* is contraindicated in intensive care, those hospitalised with a central venous catheter, immunocompromised or critically ill patients.[4]

A means to reduce gastrointestinal inflammation

Intestinal permeability controls the transport of substances across the gastrointestinal epithelium and into circulation.[5] Altered intestinal permeability results in increased inflammation, pathogen translocation, and potential disease progression, including Crohn's disease.[5] Translocation of lipopolysaccharides promotes inflammation through the release of IL-6 and TNF-α, a process counteracted by *S. boulardii* through the enhancement of IL-10 levels, a known anti-inflammatory.[6]

S. boulardii limits inflammation by production of the protein phosphatase 63 kDa, capable of reducing the toxicity of lipopolysaccharides, and reducing inflammation.[6] Within the cell, *S. boulardii* functions to inhibit the production of the proinflammatory cytokine IL-8 by inhibiting the NF-kB and MAPK signalling pathways.[6] Further studies have demonstrated that a preexposure to *S. boulardii* reduces inflammation by stimulating the production of immuno-globulins and cytokines, to support the immune response to future infection.[6]

THE BEST USE OF *S. BOULARDII*

Due to its favourable role in gastrointestinal health, the therapeutic benefits of *S. boulardii* focus on the reduction of diarrhoea and inflammation and microbiome restoration.

Diarrhoea treatment

Well-regarded for its role in reducing diarrhoea, *S. boulardii* influences short chain fatty acid (SCFA) production, involved in water and electrolyte absorption.[7]

One of the most researched functions of *S. boulardii* is its ability to reduce hospitalisation and diarrhoea duration[7] with the mean reduced by 24 hours.[2]

Acute paediatric diarrhoea

Of 24 randomised control trials looking at the efficacy of *S. boulardii* to treat paediatric diarrhoea, 83% also found *S. boulardii* beneficial in reducing acute diarrhoea by up to one day, with no adverse events identified.[1] Typically, the treatment period for these trials was seven days with doses ranging from 1 x 1010 CFU/day to 500 mg/day.[1] A meta-analysis found a reduction in the stool frequency from day 2 of treatment with *S. boulardii*[2] suggesting benefits to recovery also.

Antibiotics and *S. boulardii* – the perfect match

Often prescribed alongside the use of antibiotics for the reduction and prevention of antibiotic-associated diarrhoea (AAD), studies looking at AAD in the treatment of *Clostridium difficile* demonstrated both a preventative and curative effect of *S. boulardii*.[7] Studies involving the use of antibiotics known to reduce SCFA levels in conjunction with *S. boulardii* have demonstrated *S. boulardii's* ability to maintain SCFA levels during antibiotic therapy.[7] Early administration of *S. boulardii* at the commencement of antibiotic therapy has been shown to offer greatest benefit.[7]

Unlike most probiotics, *S. boulardii* is resistant to antibiotics[2] and does not contribute to antibiotic resistance due to its fungal nature[2] supporting its concomitant use with antibiotic therapy.

Helicobacter pylori infection

Involving 1-2 antibiotics and a proton pump inhibitor for the treatment of *Helicobacter pylori* infection, studies have identified that the additional treatment of *S. boulardii* reduced the incidence of antibiotic associated diarrhoea in 93% of the treatment groups.[1]

Saccharomyces boulardii for the treatment of traveller's diarrhoea (TD)

Affecting more than 20 million tourists annually, TD impacts 38-79% of travellers travelling to developing countries.[8] Predominantly associated with pathogenic bacteria including *Escherichia coli*, *Campylobacter jejuni*, *Shigella*, *Salmonella*, and *Yersinia enterocolitica*,[7] the average TD bout lasts for 1-4 days, with 3% of sufferers requiring hospitalisation.[8] Long term implications of TD include symptoms extending beyond 90 days post-infection and the development of post-infectious complications including irritable bowel syndrome.

An Australian study demonstrated a 10% decline in TD with the administration of 1 g/day to study participants when administered five days prior to travelling and continued throughout the travel period[2] (approximately 3 weeks in duration).[1]

DOSAGE

Guidelines for the use of *S. boulardii* recommend daily doses of >109 per day for a period of 1 week to 6 months, used either alone or as an adjunctive treatment.[1] See Table 1 for condition specific dosage recommendations.

Table 1: Recommended doses of *Saccharomyces boulardii*.

CONDITION	ADULT DOSAGE RANGE (PER DAY)
General digestive function and microbiota support	500-1000 mg (10-20 billion)[9]
Clinical dysbiosis post antibiotic therapy	750 mg (15 billion)[10]
Traveller's diarrhoea prevention	250-1000 mg (5-20 billion)[11]
Acute diarrhoea in adults	500-750 mg (10-15 billion)[9]
Antibiotic associated diarrhoea	250-1000 mg (5-20 billion)12
***Clostridium difficile* infection recurrence prevention**	500-1000 mg (10-20 billion)[13]
***Clostridium difficile* infection treatment**	1000 mg (20 billion)[9]
Giardiasis	500 mg (10 billion)[9]
Enteral nutrition-related diarrhoea treatment	2000 mg (40 billion)[9]
***Helicobacter pylori* eradication and antibiotic side-effect reduction**	250-1000 mg (5-20 billion)[9]
Adjunctive ulcerative colitis therapy	750 mg (15 billion)[14]
Crohn's disease	500-1000 mg (10-20 billion)[16]
Irritable Bowel Syndrome	750-1000+ mg (10-20 billion)[15]
HIV-related diarrhoea	3000 mg (60 billion)[9]
HIV-related intestinal integrity and microbiota modulation	339 mg (approx. 7 billion)[16]
SIBO in systemic sclerosis	400 mg (8 billion)[17]

MECHANISM OF ACTION

S. boulardii has multiple mechanisms of action (see Table 2).

Table 2: The mechanisms of action of *Saccharomyces boulardii*.

MECHANISM	DESCRIPTION
Antitoxin/antimicrobial effect	• *S. boulardii* operates as a decoy receptor, blocking receptor sites from pathogenic toxins and directly destroys pathogens including *Clostridium difficile*.[1] • Production of acetic acid from *S. boulardii* inhibits the survival of *Esherichia coli* while operating to lower the pH allowing for the antimicrobial activity of SCFAs.[3] • Stimulates the secretion of proteins to cleave microbial toxins and reduce cAMP levels.[3]
Physiological protection	• Preservation of enterocyte tight junctions and intestinal permeability, subsequently preventing fluid loss[1] and bacterial translocation.
Microbiota modulation	• *S. boulardii* has little impact on the healthy microbiome, however, in the presence of antibiotic use, *S. boulardii* may support the colonisation of *Enterobacteriaceae and Bacteriodes* populations while decreasing the *Clostridium coccoides* and *Eubacterium rectale* populations in the days following antibiotic use as observed in animal studies.[7] • Provision of surrogate microflora following the disruption to the microbiota due to antibiotics, illness, or surgery.[1,3] • Inhibition of the proliferation of opportunistic bacteria within the gastrointestinal tract, known as 'colonisation resistance'.[1]
Metabolic regulation	• Capable of regulating the production of SCFAs, particularly following illness, preventing adverse changes to colonic fermentation.[1]
Nutritional and trophic effect (endocrine gland stimulation)	• Reduction of mucositis - the inflammatory state of the gastrointestinal tract including the mouth, often associated with chemotherapy.[1] • Enhanced protein (lactase, maltase, sucrase)[3] and energy production[1] supporting a reduction in lactose intolerance.[3] • Support for enterocyte maturation via the release of polyamines, spermine and spermidine[1] involved in cell proliferation. • Beneficial for the expression of intestinal digestive enzymes and nutrient uptake transporters.[9] Support for intestinal glucose absorption.[3]
Immune modulation	• Operating to reduce pathogen penetration across the intestinal epithelium, *S. boulardii* promotes immune exclusion by modulating the immune response, supporting the structure of gastrointestinal epithelial tight junctions and increasing secretory IgA and mucus concentration in both the intestinal fluid and cryptic cells to quarantine microorganisms.[7] • Stimulates the secretion of intestinal secretory IgA as a first line defence by preventing pathogen adhesion,[6] including C. difficile toxins.[1] • Modulation of the immune response, including the stimulation and suppression of the inflammatory response[1] by influencing the levels of pro-inflammatory cytokines including interleukin-8 and mitogen activated protein kinases.[3] • Increases in anti-inflammatory cytokines including interleukin-4 and interleukin-10.[3] • Beta-glucan contained within the cell wall of *S. boulardii* is known for its immune modulating capacity.[6] • Inhibition of pathogen growth including *Candida albicans*, *S. typhimurum*, *Yersenia enterocolitium*, and *Aeromonas hemolysin*.[1] • Increases the production of IgM and Kupffer cells (liver macrophages).[6] • Interception of Nuclear Factor-kB-mediated signal transduction pathways involved in cytokine production and inflammation.[1] • Reversal of lipopolysaccharide pro-inflammatory cytokine action by bacteria, reducing IL-6 and TNF-a.[6] • Secretion of proteins to minimise adhesion of Citrobacter rodentium to epithelial cells.[3]

With research into the therapeutic benefits of yeasts centring around the *S. boulardii* strain, further investigation into other yeasts may be beneficial. Strong evidence supports the use of *S. boulardii* for the prevention and treatment of acute diarrhoea, whether it be from travel, antibiotic use or other aetiology. *S. boulardii* also supports the reduction of inflammation produced as a result of gastrointestinal injury or infection, making *S. boulardii* an essential supplement for all first aid kits.

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