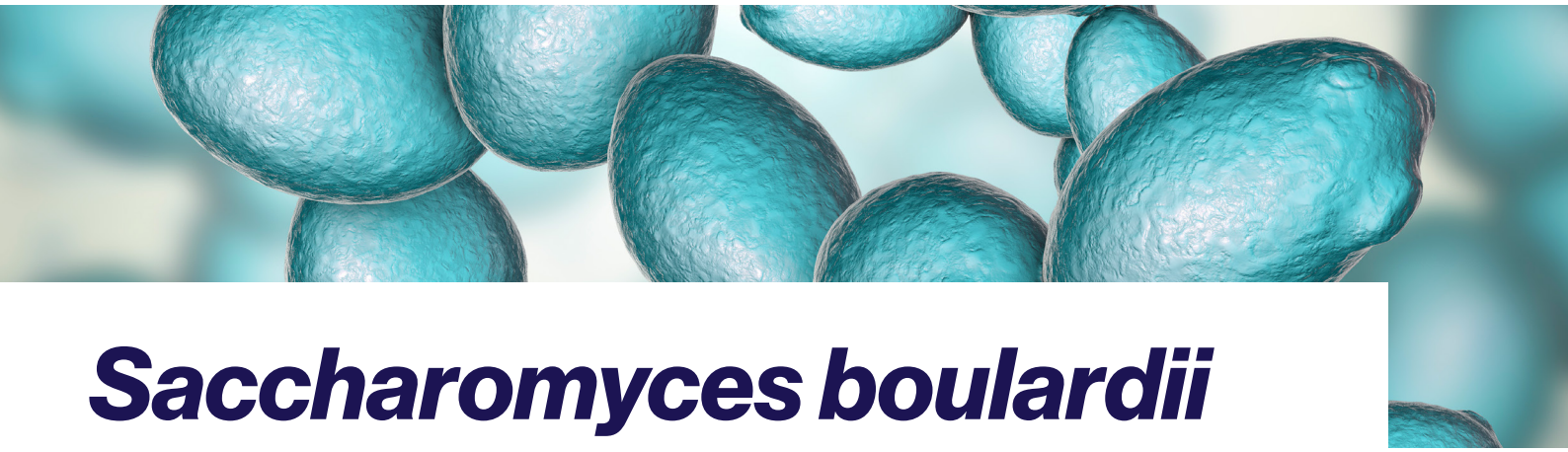

Saccharomyces boulardii and Nutrients to Support Gastrointestinal Health

BACKGROUND

The gastrointestinal tract (GIT) has the largest surface area exposed to the external environment of all the organs in the body. This barrier is critical for protecting the tissues external to the intestinal tract from pathogens and antigens. However, it also acts as a regulated exchange surface for nutrients and metabolites produced by the intestinal tissue and microbiota. Disruption of this barrier can lead to increased intestinal permeability and translocation of intestinal contents. This is often termed 'leaky gut' and is linked to intestinal and systemic diseases.[1]

The GIT is also home to millions of microorganisms, called the microbiome. This contains around 1000 bacterial species, but also yeasts and fungi which make up around 0.1%.[2,3] The microbiome has crucial roles including protection against pathogens, epithelial barrier maintenance and immune modulation.[4] Additionally, 70-80% of the bodies immune cells reside in the intestinal environment.[5]

KEY ACTIONS AND BENEFITS

- Modulate and restore normal microbiota balance[1,3,4]
- Interact with gut microbiota and intestinal mucosa[7,8]
- Increase beneficial microbiota numbers and diversity[3,9]
- Reduce intestinal inflammation and permeability[1,3]
- Regulate, maintain and restore intestinal epithelial barrier integrity[8]
- Antagonise pathogens and their toxins[7]
- Protect intestinal barrier against pathogen-related colitis and intestinal injury[8,10]
- Improve the digestive capacity, nutritional and antioxidant status of the intestinal environment[1,3,4]
- Assist in re-establishing short chain fatty acid (SCFA) levels[7]
- Regulate, enhance and modulate immune function[2,7]
- Modulate inflammatory cytokine secretion and production[1-2]

KEY ACTIONS AND BENEFITS

Bacteria-based probiotics are well-known for their benefits in GIT health. However, one species of yeast has been researched and shown to have beneficial probiotic effects. *Saccharomyces cerevisiae* (boulardii), or SB, is genetically close but physiologically and metabolically distinct from baker's yeast (*S. cerevisiae*).[4]
SB also differs in its probiotic traits to bacterial probiotics, as it:[4,6-7]

- has optimal growth at human body temperature (37°C)
- has greater viability at higher temperatures and naturally stable at room temperature
- is resistant to gastric acid and remains viable at low pH levels
- is resistant to digestive enzymes and bile acids
- does not colonise the gut, so its actions are due to its transient nature
- is resistant to antibiotics and other antibacterial agents.

SB also has a wide variety of intestinal health benefits to protect against pathogenic assault, modulate immune system function, support the nutritional health of the GIT, and restore and maintain the microbiome and integrity of the intestinal barrier, especially after infection or illness.

Various nutrients, including vitamins A and D and minerals zinc and selenium, also play complex and important roles in intestinal and systemic immune function, intestinal barrier health and integrity, and microbiota support.

CLINICAL APPLICATIONS

- Microbiota, intestinal function and integrity support
- Support beneficial intestinal microbiota during and after antibiotic use
- Dysbiosis[4]
- Clinical dysbiosis post antibiotic therapy[11]
- Antibiotic associated diarrhoea (AAD)[12]
- Prevention of travellers' diarrhoea[13]
- Infectious and acute diarrhoea[1,7]
- Candidiasis[3]
- *Clostridium difficile* infection (CDI) treatment and recurrence prevention[7,14]
- Giardiasis[7]
- *Helicobacter pylori* eradication adjunct therapy and reduction in antibiotic side-effects, including symptoms of:[9,15,16]
  - nausea
  - diarrhoea
  - abdominal discomfort and pain
  - bloating
- Other GIT infections caused by pathogenic organisms, including:[1,7]
  - *Escherichia coli*
  - *Shigella*
  - *Salmonella*
  - *Vibrio cholerae*
  - Rotavirus
- Enteral nutrition-related diarrhoea and intestinal permeability[4]
- Colitis and mucositis[7,8]
- Inflammatory bowel disease (IBD)[6]
  - Ulcerative colitis
  - Chron's disease
- Irritable bowel syndrome (IBS)[7]
- Small intestinal bacterial overgrowth (SIBO) in patients with systemic sclerosis[17]
- Support in lactose intolerance alleviation[4]
- HIV-related diarrhoea, inflammation, intestinal integrity and microbiota modulation[7,18]
- Other conditions related to intestinal permeability or compromised barrier function, including:[19]
  - food allergies
  - malabsorption syndromes
  - coeliac disease

DOSAGE RANGES

	Interventions	Dose and duration	Ref
Saccharomyces cerevisiae (boulardii)	General digestive function and microbiota support	500-1000 mg (10-20 billion)	7
	Clinical dysbiosis post antibiotic therapy	750 mg (15 billion)	11
	Traveller's diarrhoea prevention	250-1000 mg (5-20 billion)	13
	Acute diarrhoea in adults	500-750 mg (10-15 billion)	7
	Antibiotic associated diarrhoea	250- 1000 mg (5-20 billion)	12
	Clostridium difficile infection (CDI) recurrence prevention	500-1000 mg (10-20 billion)	14
	Clostridium difficile infection (CDI) treatment	1000 mg (20 billion)	7
	Giardiasis	500 mg (10 billion)	7
	Enteral nutrition-related diarrhea prevention	2000 mg (40 billion)	7
	Helicobacter pylori eradication and antibiotic side-effect reduction	250-1000 mg (5-20 billion)	7,16
	Ulcerative colitis (adjunct to mesalazine therapy)	750 mg (15 billion)	6
	Chron's disease	500-1000 mg (10-20 billion)	6
	Irritable bowel syndrome	750-1000+ mg (10-20 billion+)	3,10
	HIV-related diarrhoea	3000 mg (60 billion)	7
	HIV-related intestinal integrity and microbiota modulation	339 mg (approx.. 7 billion)	18
	SIBO in systemic sclerosis	400 mg (8 billion)	17
Zinc	Zinc-deficiency related disorders, including diarrhoea, Chron's disease and coeliac disease	Up to 40 mg to restore zinc levels and reverse deficiency	19,26
Vitamin D	Vitamin D deficiency is associated with a wide range of conditions, including IBD	To prevent deficiency: 600-800 IU per day (15-20 mcg) Optimal serum 25(OH)D levels are considered between 75-150 nmol/L	31,34,35
Vitamin A	Vitamin A deficiency is associated with several conditions, including IBD	700-900 mcg RE* from all sources	31,36
Selenium	Selenium deficiency is associated with several conditions, including IBD	60-70 mcg from all sources	32,37

**Retinol equivalents*

Saccharomyces boulardii (SB)

SB plays multifactorial roles as a probiotic to support GIT health, integrity and function, and counteract numerous pathogenic organisms and their toxic effects[1,4] Research has revealed numerous mechanisms of action; however, the underlying mechanics of many of its actions are yet to be fully defined.[4]

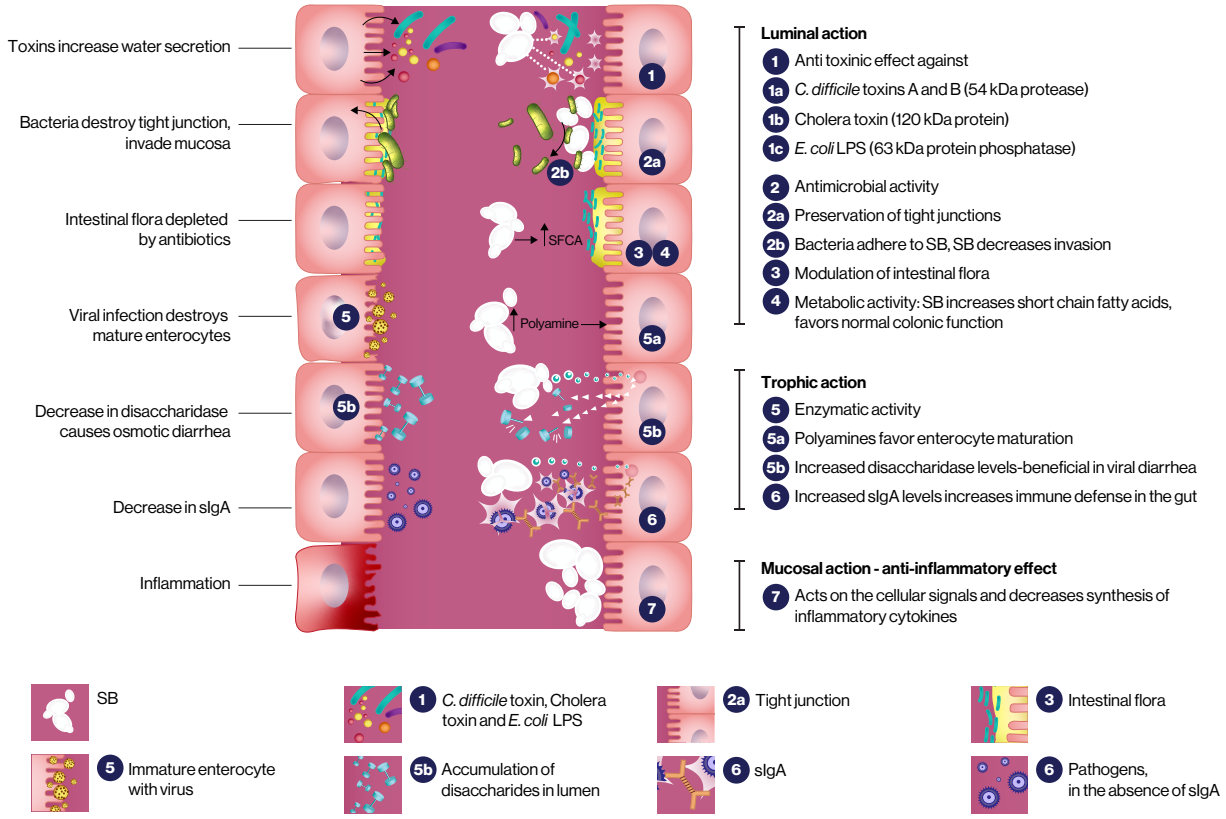

Figure 1. Some of the potential mechanisms of action of SB, showing the effects of pathogenic organisms on the left-hand side and the seven protective effects of SB on the right-hand side.[7] (AMOX)-resistant strains.[14]

The following (Table 1) outlines the complexities and potential actions by which SB supports intestinal and systemic health.

Table 1. Mechanisms of action of SB

Action	Mechanism

Restores and improves gut barrier function and integrity, and reduces intestinal permeability	• Via actions on tight junctions (TJs) and adherens:[1,3,8]
	  • Inhibits MLC phosphorylation to preserve the cell membrane TJ.
	  • Restores claudin-1 expression (claudin-1 reduction disrupts TJs).
	  • Enhances delivery of E-cadherin to the epithelial cell surface and maintaining its expression to restore enterocyte adherens junctions.
	  • Protects the expression of zona-occludens-1 (peripheral membrane protein) and occludin (transmembrane protein) in the intercellular TJ.
	• Reduces inflammatory effects on intestinal epithelial integrity by:[1,20]
	  • restoring glutathione to inhibit reactive oxygen species (ROS) production,
	  • increasing production of superoxide dismutase, catalase and glutathione peroxidase
	  • inhibiting pro-inflammatory (NF-kB and IL-8) and upregulating anti- inflammatory cytokines (IL-10 and TGF-alpha).
	• Anti-diarrhoeal effect by:[1,4,7]
	  • restoring barrier integrity and reducing intestinal permeability
	  • secreting 120 kDa protein, which decreases cyclic AMP (cAMP) resulting in reduced chloride secretion
	  • increasing SCFA levels, particularly butyrate
	  • increasing disaccharidase levels.

MECHANISMS OF ACTION

Action	Mechanism

Modulates gut inflammation and systemic immune functions	• Modulates host cell signalling pathways, including NF-kB and MAPK activation to:[1,3,4,7,20,21]
	  • decrease TNF-alpha and INFy levels
	  • reduce pro-inflammatory cytokines IL-8, IL-6 and IL-1 ß
	  • upregulate anti-inflammatory cytokines IL-10 and IL-4 and TGF-ß .
	• Interacting with gut-associated lymphoid tissue (GALT) to stimulate the immune response of the intestinal epithelial cells, increasing the secretion of IgA and IgG.[4,22]
	• Producing Saccharomyces anti-inflammatory factor (SAIF).[20]
	• Production of SCFAs with immunomodulatory actions (acetate, propionate, butyrate).[2]
	  • Influencing T helper cell (Th1/Th2) balance through the production of IFN-y .[21]

Inhibits pathogens and their toxins, and modulates gut microbiota	• Competitive adhesion and limits pathogen colonisation by binding to pathogens for elimination in faeces.[1,4,7]
	• Modulates pathogenic bacteria enterocyte attachment through alkaline phosphatase secretion.[1]
	• Produces SCFAs, including acetic, butyrate and capric acid, to lower the intestinal pH and antagonise pathogens.[2,4,20]
	• Produces anti-inflammatory factors.[3,20]
	• Stimulates secretory IgA against microbial toxins and pathogen colonisation.[1,22]
	• Blocks pathogen toxin receptors or acts as a receptor decoy.[4]
	• Adheres to cholera toxin wall to inhibit its effects.[4]
	• Other antitoxin effects through the production of proteins that cleave microbial toxins or reduce cAMP levels:[1,4,7-8]
	  • 54 kDa protease induces proteolysis of *C. difficile* toxins A and B and destroys its colonic receptor site
	  • 120 kDa protein is antagonistic to cholera toxin
	  • 63 kDa protein phosphatase is antagonistic to *E. coli* lipopolysaccharide (LPS) and decreases TNF-alpha levels.
	• Inhibits *C. difficile* growth and adhesion.[4]
	• Blocks epithelial attachment of *H. pylori* through the expression of neuraminidase activity, which inhibits binding of *H. pylori* to sialic acid receptors.[3,23]
	• Inhibits *Candida albicans* virulence and pathogenicity by:[20]
	  • producing the SCFA capric acid that inhibits *C. albicans* filamentation and has antifungal activity
	  • reducing biofilm formation and cellular adhesion
	  • producing small bioactive anti-candida molecules
	  • preventing translocation in the GIT
	  • reducing inflammatory TNF um.[20]
	• Preserves cellular physiology and interacts with gut microbiota.[7]

Improves intestinal mucosa nutrition and function	• Trophic effects to maintain a healthy gastrointestinal tract by:[3-4,7]
	  • secreting polyamines (spermine and spermidine) that improve nutritional status and digestive capacity of the GIT, but also regenerate brush border damage and assist with enterocyte maturation, by stimulating the production of:
	  • brush border membrane digestive enzymes (lactase, maltase, sucrase)
	  • nutrient transporters (sodium-glucose transport proteins).
	  • increasing glucose intestinal absorption and mediating lactose breakdown
	  • producing SCFAs for their antimicrobial, anti-inflammatory, immune modulation and barrier function activities
	  • stimulating protein and energy production.

MECHANISMS OF ACTION

Zinc

Zinc is essential for innate and adaptive immunity. It functions to maintain immune health through catalytic, structural and regulatory functions, with involvement in highly complex cell signalling pathways. Zinc affects overall immune function by many actions, including:[24-26]

- directly binding to regulatory cell signalling proteins
- indirectly influencing kinase and phosphatase enzyme
- regulating proinflammatory cytokines through transcription modulation of NF-kB
- immune cell maturation, differentiation and cell cycle progression
- antioxidant activities, neutralising ROS and reactive nitrogen species (RNS).

Additionally, as pathogenic organisms also require zinc, the immune system sequesters zinc through the expression of pro-inflammatory mediators, such as IL-6, which increases zinc binding, thereby having an antimicrobial effect. With adequate zinc, the immune system can also use zinc to intoxicate pathogens engulfed within macrophages.[24]

In the GIT, zinc is also necessary for dendritic cell function and the intestinal epithelial barrier.[19,25] Zinc deficiency can increase apoptosis, compromising TJs and epithelial integrity, leading to increased intestinal permeability. Along with its antimicrobial effects, zinc also reduces cAMP-regulated chloride secretion, with a beneficial effect on diarrhoea.[19]

Vitamin D

Vitamin D is important for multiple roles in the immune and GIT. Once converted in the body to its active calcitriol form (1,25-dihydroxycholecalciferol), vitamin D interacts with vitamin D receptors (VDRs). VDRs are highly expressed in the large intestine and act as transcription factors for hundreds of genes to regulate defensins, cathelicidin, claudins, TLR2, zonulin occludens and NOD269 function, which are involved in:[27,28]

- intestinal homeostasis
- inflammation modulation
- TJs
- pathogen invasion
- commensal bacterial colonisation
- mucosal defence.

Research has also shown that there is bidirectional cross-talk between VDRs and the gut microbiota, with vitamin D supplementation increasing akkermansia and bifidobacterium taxa and the bacteroidetes to firmicutes ratio. Although the mechanism is unknown, it may be through the same actions noted above.[27]

In the immune system, vitamin D has a signalling and modulating role with VDRs expressed in the innate and adaptive systems, including in B and T lymphocytes, neutrophils, monocytes and dendritic cells (DC).[28]

Vitamin D also has antimicrobial effects by enhancing chemotaxis, autophagy, phagolysosomal fusion of immune cells and inducing antimicrobial peptides ß2 ß4, such as defensins and cathelicidin antimicrobial peptide. In the intestines these processes also strengthen the epithelial barrier function.[28]

As an inflammation modulator, vitamin D blocks NF-kB to downregulate pro-inflammatory cytokines (IL-12, IL-6, IFN-y , IL-8, TNF-a, IL-9) and upregulate the anti-inflammatory cytokines (IL-4, IL-5, IL-10). It also induces T regulatory (Treg) cells, modulates Th1/Th2 balance and promotes self-tolerance through the inhibition of DC differentiation.[28]

MECHANISMS OF ACTION

Vitamin A

Vitamin A is a potent regulator of numerous biological processes, including in the innate and adaptive immune systems and the GIT.[29] It increases immune competence, facilitates mucosal tolerance and maintains intestinal epithelial surfaces.[29,30]

Vitamin A is hydrolysed to retinoic acid when in the body.[30] This active form regulates gene expression and impacts immune function by:[29,31]

- controlling leukocyte homing and Treg function
- assists in the development of T-helper, Treg and B cells
- modulating Th1/Th2 balance through cytokine production
- enhancing neutrophil, macrophage and NK cell function
- promoting IgA response and phagocytic functions.

A deficiency in vitamin A has been shown to increase intestinal permeability. Retinoic acid supports intestinal health and regeneration of mucosal barriers by promoting the secretion of IL-22, known to:[30]

- promote epithelial cell proliferation and healing
- restore TJs
- increase goblet cell mucus production.

Vitamin A also regulates intestinal T cell homing, which modify the gut inflammation risk.[30]

Selenium

Selenium is an essential nutrient, that through its incorporation into selenoproteins in the body, is necessary for immune and intestinal function and health.[32,33] Selenium has antioxidant, anti- inflammatory and cell signalling roles. It is involved in immunoregulation and cell activation, proliferation, and differentiation within innate and adaptive immune systems.[33]

Among many other functions selenium, as selenoproteins, acts by: [32,33]

- influencing various leukocytic effector functions including adherence, migration, phagocytosis and cytokine secretion
- maintaining balanced reduced/oxidised cellular molecule levels
- regulating immune cell effector functions, including T-helper cells affecting B cell function and antibody production
- modulating eicosanoid synthesis and function
- impacting the expression of NF-kB and peroxisome proliferator activated receptor (PPAR) influencing the expression of nuclear factor erythroid factor 2-related factor 2 (Nrf2), important for redox homeostasis.

Selenium also plays crucial roles in the gut with intestinal microbiota using selenium to make their own selenoproteins. The interaction with commensal bacteria appears to be synergistic with adequate selenium required for beneficial modulation of gut microbiota. Selenium deficiency can also affect gut barrier function, as it is necessary for cellular and paracellular permeability, redox balance and inflammatory cell infiltration.[32]

CLINICAL EVIDENCE

	Study	Participants	Interventions	Outcomes	Ref
SB, probiotics and prebiotics	Effect of probiotics and prebiotics on preventing travellers' diarrhoea. *Systematic review and meta-analysis*	Systematic review and meta-analysis of RCTs and blinded interventions published in peer-reviewed journals between 1977 to June 2018.	Probiotics and prebiotics, including SB.	From 12 RCTs, a total of 10 different probiotics and three prebiotic formulations were analysed. The pooled data showed an overall protective effect from the probiotics. However, after reviewing strain specific information only, SB was the only type to show a statistically significant risk reduction (p< 0.001; CI 0.72-0.87) of travellers' diarrhoea.	13
Saccharomyces boulardii	Reduction of H.pyolri treatment-associated-side effects and improvements on microbial profile with SB *Single-blinded RCT*	74 patients aged 18-55 years, with typical dyspepsia symptoms.	*H. pylori* positive participants randomly assigned to two groups: conventional therapy and antibiotic therapy plus 750 mg (15 billion) of SB for two weeks.	Participants who received SB had significantly less abdominal pain occurrence with trends towards a lower occurrence of other GIT side-effects. Additionally, at treatment completion and one month follow-up, they had greater microbiota diversity with a lower abundance of bacteroides and clostridia and a higher abundance of enterobacteria.	9
	Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea *Systematic review and meta-analysis*	21 RCTs (4780 participants). Fifteen trials were performed in adults and six in children, all who had received antibiotics.	SB at any dose.	Overall, SB reduced the risk of AAD in patients post antibiotics from 18.7% to 8.5% (Risk ratio RR 0.47; CI 0.38-0.57), confirming the effectiveness of SB in reducing the risk of AAD. The risk of Clostridium difficile infection in children was also significantly reduced.	12

CAUTIONS AND CONTRAINDICATIONS

- Fungaemia with SB is rare. However, to reduce the risk, SB is not recommended in those with indwelling catheters, who are critically ill or are immunosuppressed.[7,38,39]
- Theoretically, antifungal medications may interfere with SB effectiveness. It is suggested to separate doses by at least 4 hours.[7,39]
- Theoretically, patients with true yeast allergy can be allergic to SB; use with caution.[39]

Pregnancy and lactation: Avoid using SB in pregnancy and lactation. There is insufficient reliable information available. [39]

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