

REVIEW ARTICLE

Characteristics and health benefits of the probiotic yeast *Saccharomyces boulardii*

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Abstract

Saccharomyces boulardii is a well-established probiotic yeast with documented clinical benefits for gastrointestinal health. This review highlights the key biotherapeutic mechanisms underlying its protective effects, with particular emphasis on its bioactive metabolites, including specialized enzymes, polyamines, organic acids, and vitamins. These postbiotic factors contribute to epithelial barrier reinforcement, immune modulation, and pathogen exclusion, thereby promoting intestinal homeostasis. In addition, *S. boulardii* supports microbial equilibrium through colonization resistance and regulation of inflammatory signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells. Clinical evidence demonstrates its efficacy in the prevention and management of antibiotic-associated diarrhea, inflammatory bowel disease, and irritable bowel syndrome. Safety considerations are also addressed, noting its biological distinction from *Saccharomyces cerevisiae*, particularly its inability to undergo hyphal transformation. Owing to its resilience against gastric acidity, bile salts, and concomitant antibiotic therapy, *S. boulardii* represents a valuable adjunct in contemporary gastrointestinal therapeutics and a promising platform for functional and translational applications.

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1. Introduction

Interest in strategically sustaining gut health has grown substantially in recent decades, highlighting the important role of live microorganisms, delivered through nutrition or health supplements, in supporting human health.¹ Probiotics are defined by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.”² In the context of modern biotherapeutics, this definition is increasingly integrated with the concept of microbial sustainability to ensure long-term gut homeostasis.¹ While probiotic research and commercial applications have traditionally been dominated by lactic acid bacteria, increasing attention has recently been directed toward non-bacterial probiotics, particularly yeasts, due to their distinct physiological

and functional attributes.^{3–5} Unlike many bacterial probiotics, *Saccharomyces boulardii* (*S. boulardii*) exhibits intrinsic resistance to antibiotics,⁶ enabling its concomitant use during antimicrobial therapy without compromising viability.⁶ In addition, it demonstrates remarkable tolerance to gastrointestinal stressors, including low gastric pH, digestive proteases, and bile salts, which supports its persistence and activity within the intestinal tract.^{7,8}

S. boulardii was first isolated in the early 1920s by the French microbiologist Henri Boulard, following observations of reduced diarrheal severity among populations consuming fruit peel preparations in Indochina.⁴ Since then, it has been established as the first well-defined probiotic yeast and has shown consistent clinical efficacy in the prevention and management of antibiotic-associated diarrhea (AAD), traveler's diarrhea, and inflammatory bowel disease.^{9,10} Beyond therapeutic applications, *S. boulardii* has also gained relevance in functional food biotechnology, where it enhances nutritional quality and microbial stability of diverse products.¹¹

Mechanistically, the health benefits of *S. boulardii* extend beyond simple competitive exclusion. Experimental and clinical evidence indicate that this yeast reinforces epithelial barrier integrity,¹² modulates immune signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and inhibits enteric pathogens, such as *Clostridioides difficile*, *Salmonella* spp., *Escherichia coli*, as well as opportunistic fungi such as *Candida albicans*.^{13,14} These protective effects are largely mediated through the secretion of bioactive metabolites and cell wall-derived components, often referred to as postbiotic factors.^{15,16}

Despite its overall favorable safety profile, rare cases of fungemia and invasive infections have been reported in severely immunocompromised or critically ill patients, underscoring the importance of appropriate clinical precautions.¹³

Therefore, this review integrates the most recent findings on the bioactive metabolites of *S. boulardii*, including specialized enzymes, polyamines, and organic acids, and critically examines how these components contribute to immune modulation, pathogen suppression, and the maintenance of gut homeostasis. Furthermore, emerging evidence indicates that the health benefits of *S. boulardii* are not solely dependent on the viability of the microorganism itself, but also arise from its postbiotic components—defined as inanimate microbial structures or metabolites that confer physiological benefits to the host.^{1,17} By extending the analytical focus beyond live-cell activity,

this review highlights postbiotic-mediated mechanisms as strategic contributors to gut microbiome resilience, functional diversity, and long-term ecosystem stability,¹ thereby offering a more comprehensive framework for understanding the therapeutic potential of *S. boulardii*.

Despite the extensive knowledge regarding *S. boulardii* and its therapeutic benefits, most studies have primarily focused on its direct effects in clinical or *in vitro* settings, with limited evaluation of its long-term impact on human gut microbiome dynamics.^{3,6} Furthermore, the interactions between live microbial cells and postbiotic components require deeper investigation to determine optimal dosages and the intestinal environmental conditions that maximize therapeutic outcomes.¹⁷ Consequently, there is a significant opportunity for future research to integrate molecular, immunological, and microbiological data to elucidate the precise mechanisms that ensure sustained gut health, while also assessing safety in critically ill or immunocompromised populations.⁸

2. Taxonomic classification and distinctive traits: *Saccharomyces boulardii* versus *Saccharomyces cerevisiae*

Saccharomyces is a genus of yeasts belonging to the family Saccharomycetaceae (phylum Ascomycota, Kingdom Fungi).¹⁸ A hallmark characteristic of the members of this genus is their potent metabolic capacity to enzymatically convert fermentable sugars into carbon dioxide and ethanol. Within this genus, *S. boulardii* stands out as a unique non-pathogenic strain with specialized probiotic properties.¹⁹

The clinical efficacy of *S. boulardii* is well documented, yet its exact taxonomic position remains debated.³ Although closely related to the model yeast *Saccharomyces cerevisiae*, *S. boulardii* exhibits distinctive molecular and physiological characteristics that support its recognition as a specialized probiotic strain.

2.1. Genomic differences between *S. boulardii* and *S. cerevisiae*

Comparative genomics has revealed that *S. boulardii* and *S. cerevisiae* differ in gene copy numbers across several chromosomes, particularly I, VII, and XII. Reduced copy numbers were observed in genes encoding nonessential membrane proteins (*PRM9*, *MST27*, *MST28*, *YAR050W*, *CUP1*, and *ASP3*), lectin-like flocculation proteins, copper metallothioneins, and cell wall L-asparaginase II, respectively.²⁰ These variations may explain unique physiological traits, including increased copper sensitivity in *S. boulardii*.²⁰

2.2. Gene amplification and stress response

Conversely, several genes are present in higher copy numbers, notably those involved in protein synthesis, such as ribosomal proteins (RPL31A, RPL41A, RPL2B, RPS24B, RSA3), and stress response proteins, including heat shock proteins (HSP26, HSP42, HSP78), ATPases (SSA3), and cell wall stress-related genes (*SED1*, *PBS2*).²⁰ These gene amplifications may contribute to enhanced growth, pseudo-hyphal switching, and tolerance to alkaline stress.¹¹

2.3. Pseudo-hyphal switching

Under nitrogen starvation, *S. boulardii* exhibits accelerated pseudo-hyphal switching compared with *S. cerevisiae*. Genes associated with filamentous growth, such as *CDC42*, *DFG16*, *RGS2*, *CYR1*, and *CDC25*, have increased copy numbers, while *STE11*, *SKM1*, and *RAS1* have fewer copies.²⁰ Many of these genes participate in the cyclic adenosine monophosphate signaling pathway, suggesting that hyperactivation may drive rapid filamentous development.²⁰

2.4. Flocculation and adhesion genes

Variations in flocculation genes, particularly *FLO1*, result in additional repeat residues compared with most *S. cerevisiae* strains.¹¹ Mutations in the regulator gene *FLO8* lead to truncated proteins in some strains, impairing adhesion and flocculation.²¹ In contrast, *FLO10* and *FLO11* show conserved repeat numbers. These genomic differences may influence flocculation, adhesion, and stress tolerance in *S. boulardii*.¹¹

2.5. Metabolic adaptations

Despite possessing all genes for galactose uptake and fermentation, *S. boulardii* cannot efficiently metabolize galactose, potentially due to energetic limitations or mutations in phosphoglucomutase (*PGM2*).²² The yeast is also unable to utilize palatinose, likely because of the absence of isomaltase genes (*IMA2*, *IMA3*, *IMA4*).¹¹

The genomic and physiological distinctions between *S. boulardii* and *S. cerevisiae* underscore the adaptive specialization of *S. boulardii* as a probiotic yeast rather than a generalist fermentative organism. Gene amplifications associated with stress response, protein synthesis, and filamentous growth plausibly enhance survival and functional persistence under gastrointestinal conditions. However, these advantages appear to be accompanied by metabolic constraints, particularly in sugar utilization, suggesting evolutionary trade-offs that may shape both its ecological niche in the gut and its suitability for specific industrial applications.^{3,6}

3. Bioactive metabolites (postbiotics) produced by *S. boulardii*

Yeast *S. boulardii* CNCM I-745 is an effective probiotic, although its benefits extend beyond its transient colonization of the gastrointestinal tract.³ Rather than relying solely on physical presence, its positive effects are primarily mediated by biologically active compounds released into the intestinal lumen.²³ These metabolites exhibit antimicrobial activity, support the integrity of the mucosal barrier,²⁴ and regulate host cellular functions.²⁵ These metabolites, as postbiotics, are crucial to *S. boulardii*'s probiotic efficacy, acting to both directly inhibit pathogens and maintain a healthy intestinal environment.¹³

3.1. Enzymatic regulation: The primary mode of *S. boulardii* action

Among *S. boulardii*'s bioactive metabolites, enzymes are the most studied and functionally diverse class.²⁶ These enzymes enhance gut homeostasis through two primary mechanisms: direct neutralization of the pathogen virulence factors (e.g., bacterial toxins) and enhancement of host digestive and protective functions, demonstrating their therapeutic potential.^{26,27,28} This dual mechanism simultaneously targets pathogen virulence factors and influences host epithelial signaling pathways.²⁹ This approach yields a significant mechanistic benefit, elevating the probiotic's therapeutic and protective efficacy within the gut lumen.³⁰

3.1.1. Serine protease of 54-kDa

A key enzymatic mechanism attributed to *S. boulardii* CNCM I-745 is the release of a 54-kDa serine protease,³¹ which has been implicated in protection against toxin-driven intestinal injury. This enzyme can hydrolyze *C. difficile* toxins A and B,^{32,33} thereby limiting epithelial damage and reducing toxin-induced inflammatory signaling. Interestingly, yeast-conditioned medium has also been reported to degrade several ileal brush border proteins, suggesting that the protease may display broader substrate activity beyond bacterial toxins.²⁶ However, whether such effects contribute meaningfully to peptide digestion *in vivo*, particularly in humans, remains unclear and requires further clinical investigation.³⁰

3.1.2. Alkaline phosphatase

A well-documented enzymatic factor secreted by *S. boulardii* CNCM I-745 is alkaline phosphatase, which has been implicated in anti-inflammatory and detoxifying functions within the gut.³⁴ Studies have shown that *S. boulardii* releases a protein phosphatase capable of

dephosphorylating lipopolysaccharide (LPS) from *E. coli*, thereby reducing endotoxin activity and attenuating downstream inflammatory signaling in animal models.³⁵

Additionally, *S. boulardii* has been reported to stimulate the activity of intestinal alkaline phosphatase at the brush border, which enhances the dephosphorylation of proinflammatory bacterial moieties, including LPS, and contributes to mitigated inflammatory responses and maintenance of epithelial integrity.³⁰

Intestinal alkaline phosphatase has been recognized more broadly for its role in detoxifying bacterial components such as phosphorylated LPS and in supporting gut homeostasis, suggesting that yeast-derived alkaline phosphatase-like activity may complement host enzyme functions to neutralize proinflammatory microbial products and help preserve mucosal immune balance.³⁶

3.1.3. Aminopeptidases and trophic effects

Beyond its effects on toxins, *S. boulardii* has also been reported to influence intestinal peptidase activity.³¹ In experimental rat models, supplementation with *S. boulardii* CNCM I-745 increased jejunal and ileal mucosal leucine-aminopeptidase activity, suggesting a potential role in supporting peptide digestion and mucosal recovery.³⁰ Such trophic effects may be particularly relevant under conditions of intestinal injury or resection.²⁶ Nevertheless, whether these enzymatic changes translate into measurable digestive or clinical benefits in humans remains uncertain and warrants further investigation.

3.1.4. Specialized enzymes: Functional and clinical implications

Beyond its proteolytic enzymes, *S. boulardii* CNCM I-745 acts as a metabolic factory, secreting highly active disaccharidases—notably sucrase, maltase, and trehalase.³ The clinical relevance of these enzymes is well-documented, particularly in pediatric cases of congenital sucrase-isomaltase deficiency, where oral yeast administration significantly reduced carbohydrate malabsorption, as evidenced by decreased breath hydrogen production and improved gastrointestinal symptoms.^{37,38} Experimental models further confirm that *S. boulardii* treatment enhances mucosal α , α -trehalase activity and intestinal fluid enzymatic capacity, supporting nutrient digestion under specific pathological or enzyme-deficient conditions.^{6,39,40}

Regarding mineral bioavailability, while certain *Saccharomyces* species possess the genetic capacity to produce phytases that hydrolyze phytate (IP6), their functional efficacy in the gastrointestinal tract remains under investigation. Evidence suggests that phytase activity in wild-type yeast strains is often limited by physiological

factors such as luminal pH and inorganic phosphate concentrations.⁴¹

Although earlier work suggested that IP6 degradation by *S. cerevisiae* may depend on strain characteristics and culture density, more recent studies demonstrate significant practical reductions of phytate under food-relevant conditions. According to Vilanculos *et al.*,⁴² high-phytase yeast strains (e.g., genetically enhanced *S. cerevisiae* YD80 and BY80) have achieved up to ~95–99% IP6 reduction during composite bread fermentation, substantially lowering the IP6: iron and IP6: zinc molar ratios and indicating enhanced mineral bioavailability compared with controls lacking phytase activity.

Collectively, these findings underscore that *S. boulardii* CNCM I-745 exhibits a multifaceted enzymatic profile that complements host digestive functions. Such enzymatic contributions align with broader mechanistic insights into yeast's probiotic efficacy, including the reinforcement of gut barrier function and the modulation of microbial metabolism. This synergy is supported by recent proteomic analyses,⁴³ which suggest that *S. boulardii* sustains metabolic support and nutrient utilization under fluctuating gastrointestinal conditions.⁴³

The diverse enzymatic and postbiotic activities of *S. boulardii* CNCM I-745 reflect a multifaceted strategy through which these probiotics influence host physiology. By concurrently neutralizing pathogenic toxins, supporting epithelial integrity, and enhancing digestive enzyme activity, the yeast occupies a functional interface between microbial activity and host responses. Nevertheless, despite compelling mechanistic and preclinical evidence, the extent to which these enzymatic effects translate into consistent, clinically meaningful benefits in humans remains insufficiently resolved. Addressing this gap will require future studies that integrate quantitative postbiotic profiling with well-controlled human intervention trials, thereby clarifying the relative contribution of individual enzymes and metabolites and enabling more targeted therapeutic applications of *S. boulardii* across diverse gastrointestinal conditions.³

3.2. Polyamines: Essential mediators of trophic effects

Spermine, spermidine, and putrescine are the biogenic polyamines that *S. boulardii* secretes actively,³⁵ which are essential to its significant trophic effects (growth-promoting activity) in the intestine.³⁰ These polyamines are important because of their wide range of cellular regulatory capabilities:

- promote epithelial proliferation,³⁵
- maintain cellular homeostasis,^{30,35}

- enhance digestive enzyme activities,⁴⁴
- alter diamine oxidase levels,^{30,44}
- reduce oxidative stress while promoting autophagy.^{45,46}

This intricate modulatory function underscores the yeast's capacity to actively enhance the host mucosa's structural integrity and function, while also inhibiting pathogenic activity.⁴⁷

The secretion of biogenic polyamines by *S. boulardii* underscores a critical postbiotic mechanism through which the yeast exerts trophic and regulatory effects in the gut. By promoting epithelial proliferation, enhancing digestive enzyme activity, and modulating oxidative stress and autophagy, polyamines act as essential mediators of mucosal resilience and functional homeostasis. Importantly, these activities complement the enzymatic actions discussed earlier, suggesting a synergistic network of bioactive factors that collectively optimize intestinal structure and host metabolism. While mechanistic studies in animal models provide robust support, the extent to which polyamine-mediated effects translate into consistent clinical outcomes in humans remains an area for further investigation, highlighting the need for integrated postbiotic profiling in translational research.²⁸

3.3. Organic acids

The production of organic acids by *S. boulardii*,⁴⁸ particularly acetic acid, directly supports competitive exclusion within the gut lumen.⁴⁹ By generating these acidic metabolites, the yeast significantly lowers the local gut pH,⁵⁰ effectively creating an immediate and hostile microenvironment that impairs the growth and proliferation of most invading enteric pathogens.⁵¹ The relatively rapid therapeutic effect of *S. boulardii* in some acute diarrheal settings may be attributable to this straightforward but effective mechanism.^{3,8}

The production of organic acids by *S. boulardii* represents a rapid and largely non-specific postbiotic strategy for maintaining intestinal homeostasis. Through luminal acidification, these metabolites generate an unfavorable microenvironment for pathogenic microorganisms, acting in concert with the enzymatic and polyamine-mediated mechanisms discussed earlier. Beyond immediate antimicrobial effects, organic acid production may also shape gut microbial community structure and metabolic signaling, thereby reinforcing competitive exclusion and epithelial barrier integrity. Although *in vitro* and clinical evidence support the relevance of this mechanism in acute diarrheal settings, its long-term contribution to microbiome stability and host resilience remains insufficiently quantified and warrants further investigation.³⁴

3.4. Folates and B-vitamins: A nutritional contribution

S. boulardii has been reported to contribute to folate enrichment in fermented matrices,⁵²⁻⁵⁴ supplying a nutrient indispensable for crucial host functions, including one-carbon metabolism,⁵⁵ nucleotide biosynthesis, and critical methylation reactions.^{55,56} The magnitude of folate production is highly dependent on factors like strain specificity,⁵⁷ growth medium composition,⁵⁴ and fermentation conditions.⁵⁸ These folates enhance the nutritional value of fermented foods⁵² and make *S. boulardii* a natural dietary source of folate.⁵³ Consequently, this biosynthesis not only enhances the nutritional value of foods fermented using *S. boulardii*^{53,54} but also positions the yeast as a highly valuable, natural dietary source for meeting human folate requirements.^{3,55}

The production of folate and B vitamins by *S. boulardii* represents an often-underappreciated dimension of its probiotic functionality, positioning the yeast not only as a modulator of gut microbiota and immune responses but also as an active contributor to host micronutrient status. This role may be particularly relevant in populations vulnerable to folate insufficiency. The pronounced variability in folate biosynthesis across strains and fermentation conditions underscores the need for targeted strain selection and rational optimization of food matrices to achieve consistent nutritional benefits. Also, these observations support the incorporation of *S. boulardii* into functional food strategies aimed at natural micronutrient fortification, while also highlighting the need for *in vivo* studies to elucidate its metabolic interactions with the host and resident gut microbiota.⁵⁵

4. Mechanisms of action of *S. boulardii*

The gut microbiome plays a central role in maintaining human health⁵⁹ by protecting against pathogen colonization,⁶⁰ modulating immune responses,⁶¹ and preserving epithelial barrier integrity.⁶² The therapeutic potential of probiotics arises from their ability to shape the gut environment,⁶¹ strengthen mucosal defenses,²⁶ and reduce inflammatory signaling.⁵⁹

Among these probiotics, *S. boulardii* contributes to gut health through multiple interconnected mechanisms,⁶³ including antitoxin effects,⁶⁰ metabolic regulation, immune modulation,^{61,62} pathogen competition, and trophic support.³ Critically, the enzymes and polyamines secreted by *S. boulardii* (Sections 3.1 and 3.2) coordinate these effects, enhancing nutrient absorption³⁰ and promoting intestinal mucosal growth.³⁵ The following sections critically examine these mechanisms and their integrated impact on host physiology.

4.1. Modulation of the gut microbiome: Transient yet potent influence

Probiotics modulate the gut microbiome both directly, via antimicrobial compound production, and indirectly, by enhancing gut barrier integrity⁸ and stimulating immune function.⁶² *S. boulardii* offers a distinct advantage; it largely transits the digestive system, exerting potent modulatory effects without permanent colonization.⁶⁴ Evidence shows that *S. boulardii* restores the intestinal microbiome following antibiotic-induced or infectious dysbiosis.⁶⁵ Its positive effects are also documented in inflammatory bowel conditions,⁵⁹ where it stabilizes microbial communities and improves clinical outcomes.⁶⁴ Unlike some bacterial probiotics that may persist in the gut,⁶⁴ the transient yet multifaceted action of *S. boulardii* effectively supports microbiome resilience,⁸ restores intestinal homeostasis, and enhances overall host function.^{3,47} Crucially, it acts as a functional surrogate during the post-antibiotic susceptibility period, protecting the host until the indigenous microflora is fully re-established.³⁰

The transient nature of *S. boulardii* colonization offers a distinctive advantage for gut modulation, enabling rapid yet reversible shifts in microbial dynamics. Such ephemerality reduces the risks associated with permanent colonization while preserving key functional benefits, including reinforcement of epithelial barrier integrity and suppression of opportunistic pathogens. Importantly, the yeast's capacity to function as a temporary surrogate during post-antibiotic vulnerability highlights its strategic role in sustaining microbial ecosystem stability. From a mechanistic standpoint, the convergence of enzymatic activity, polyamine secretion, and immune modulation reflects a multi-layered mode of action, underscoring that the efficacy of *S. boulardii* arises not from persistence alone, but from a coordinated orchestration of host-microbe interactions.³⁰

4.2. Multifaceted pathogen suppression by antimicrobial activity

S. boulardii exhibits a broad spectrum of antimicrobial activities⁴⁷ through complementary, compound-specific mechanisms. These include limiting pathogen access to nutrients⁶⁶ and releasing inhibitory proteins and metabolites (such as acetic acid). Notably, acetic acid production is enhanced near the oxygen-rich epithelial surface, effectively lowering the local pH and creating a targeted unfavorable environment for pathogen growth.^{20,47} Collectively, these actions reduce pathogen adhesion and interfere with toxin activity through the secretion of specialized proteins. Specifically, *S. boulardii* secretes a 54-kDa serine protease that cleaves toxins A

and B from *C. difficile* and a 63-kDa alkaline phosphatase that dephosphorylates *E. coli* endotoxins (LPS), thereby reducing proinflammatory responses such as tumor necrosis factor- α .^{23,47} Furthermore, a 120-kDa protein diminishes cholera toxin-induced chloride secretion by reducing intracellular cyclic adenosine monophosphate levels. Despite these potent activities, genomic sequencing has not yet definitively identified the genes encoding these specific proteins, suggesting complex metabolic regulation.^{20,47} Additionally, *S. boulardii* counteracts *Bacillus anthracis* lethal toxin by releasing specific proteases that preserve epithelial monolayer integrity and prevent stress-fiber formation *in vitro*. This multifaceted antimicrobial profile contributes not only to direct pathogen suppression but also to maintaining microbial balance and limiting the progression of enteric infections.⁴⁹⁻⁵¹

4.2.1. Pathogenic mechanisms of enteric microbes and counteracting effects of *S. boulardii*

Enteric pathogens—including enterohemorrhagic *E. coli* (EHEC), *Salmonella*, *C. difficile*, and rotavirus—induce pathology through complex mechanisms, including disruption of epithelial integrity,⁶⁶ induction of apoptosis, and triggering excessive proinflammatory responses.^{29,31} The protective mechanisms of *S. boulardii* complement these pathogenic effects by inhibiting apoptosis,⁶⁶ preserving tight junction integrity, reducing proinflammatory cytokine secretion,³⁴ and detoxifying microbial toxins.³⁴

Furthermore, the clinical utility of *S. boulardii* extends to the management of *Helicobacter pylori* (*H. pylori*) infections. Recent meta-analyses confirm that it acts as a crucial adjunct to triple therapy, not only by enhancing eradication rates but also by mitigating antibiotic-associated side effects and restoring microbial diversity.⁶⁷

A fundamental distinction between *S. boulardii* and its bacterial counterparts lies in its unique physical and biological properties. Unlike bacterial probiotics, *S. boulardii* has a significantly larger cell surface area, which facilitates the entrapment and clearance of pathogens such as *E. coli* and *Salmonella typhimurium* (*S. typhimurium*) through a process known as “microbial decoy.”^{3,6} Furthermore, while many bacterial probiotics are susceptible to antibiotic-induced depletion, *S. boulardii* maintains its functional integrity and antimicrobial activity during concurrent antibiotic therapy.⁴³ Recent proteomic analyses have further elucidated that the yeast's stress-tolerance networks enable it to consistently secrete inhibitory proteases and organic acids, providing a stable antagonistic environment that exceeds the competitive exclusion capabilities of many common lactic acid bacteria.⁴³

The antimicrobial profile of *S. boulardii* reflects a highly integrated defense strategy that extends beyond direct pathogen inhibition. Through the coordinated secretion of targeted enzymes, organic acids, and inhibitory proteins, the yeast establishes a multi-layered barrier that restricts pathogen adhesion, neutralizes toxins, and preserves epithelial integrity. Its functional resilience during antibiotic therapy further distinguishes it from bacterial probiotics, allowing sustained activity within disrupted microbial ecosystems. Mechanistically, the convergence of physical pathogen interactions, enzymatic detoxification, and localized pH modulation generates a dynamic protective milieu that supports both immediate pathogen control and longer-term microbial homeostasis. In concert, these observations underscore that the efficacy of *S. boulardii* arises from synergistic rather than additive interactions among secreted metabolites, host tissues, and transient microbial networks.²⁰

4.3. Adhesion to gut mucosa and competitive exclusion

Probiotic efficacy relies on the ability of microorganisms to adhere to the gut mucosa⁶⁸ and to competitively exclude pathogens from binding sites.⁶⁰ *S. boulardii* expresses various cell-surface adhesins²⁸ and cell wall proteins that facilitate attachment to intestinal mucins and epithelial cells,⁶⁹ including those encoded by the *CIS3*, *CWP2*, *FKS3*, *PIR3*, and *SCW4* genes, which mediate the yeast cell binding to pathogens such as *S. typhimurium*. A key mechanism involves the mannose-rich components of the yeast cell wall, which act as a “molecular decoy.” Pathogens that would typically bind to intestinal mannose receptors are instead trapped on the yeast surface.⁷⁰ Bile salts may influence these yeast pathogen interactions.⁷¹ This occurs by altering bacterial adhesion and virulence,⁷² which consequently enhances pathogen exclusion.²⁸ These mechanisms together allow *S. boulardii* to protect the intestinal mucosa,⁷³ maintain gut microbial balance, and limit the progression of enteric infections.⁷⁴ Beyond enteric bacteria, *S. boulardii* has also shown a remarkable biotherapeutic potential against fungal pathogens. It specifically interferes with the formation and stability of *Candida albicans* biofilms, thereby significantly reducing fungal virulence and preventing its overgrowth in the gut.⁷⁵

The adhesion and competitive exclusion mechanisms of *S. boulardii* reveal a sophisticated interface between the probiotic and the host environment. By presenting mannose-rich cell wall components and a suite of surface adhesins, the yeast effectively acts as a molecular decoy, intercepting pathogenic bacteria and fungi before they can colonize the gut epithelium.⁷⁰ This strategy not

only prevents pathogen attachment but also indirectly modulates microbial community dynamics, supporting intestinal homeostasis. The interplay with bile salts and the ability to disrupt fungal biofilms further illustrate that *S. boulardii*'s protective effects are context-dependent and multifactorial.⁷¹ In combination, these findings suggest that adhesion is not merely a static binding phenomenon but a dynamic, adaptive process that underpins both immediate defense against pathogens and the long-term resilience of the gut microbiome.

4.4. Anti-inflammatory and immunomodulatory properties

S. boulardii significantly reduces inflammation and modulates the immune system.²⁸ One of its main mechanisms is the inhibition of the NF- κ B signaling pathway⁷⁶ and modulating mitogen-activated protein kinases (MAPK), such as p38, which attenuates inflammatory responses²⁶ and protects epithelial cells from damage caused by toxins.²⁹ Simultaneously, the yeast reduces endotoxin-driven inflammation through a specific enzymatic action: dephosphorylation of bacterial lipopolysaccharide (LPS).⁴⁷ This neutralization of LPS toxicity effectively controls the subsequent cascade of proinflammatory cytokines.³⁴ Beyond simply suppressing inflammation, it exhibits a unique differential immunomodulatory effect; for instance, during *Salmonella* infection, it may enhance proinflammatory interferon- γ in the small intestine for early pathogen clearance while increasing anti-inflammatory interleukin-10 in the cecum to prevent tissue damage. A distinctive cellular mechanism involves the “imprisonment” of T-helper cells within mesenteric lymph nodes, effectively limiting their recruitment to the inflammatory site and protecting the epithelial lining.⁷⁷

S. boulardii improves host immune defenses through a variety of immunomodulatory pathways in addition to these direct anti-inflammatory effects.²⁸ Secretory immunoglobulin A (sIgA) production is stimulated by the yeast,⁷⁸ which enhances mucosal immunity and neutralizes pathogens.⁸ Furthermore, it supports both innate and adaptive immune functions by enhancing the activation and functional maturation of dendritic cells and macrophages. A new probiotic blend composed of effective strains (*S. boulardii*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, and *Bifidobacterium breve*) has been reported to significantly reduce intestinal dysbiosis caused by *E. coli*, *Serratia marcescens*, and *Candida tropicalis* in patients with Crohn's disease. This amelioration is achieved by increasing short-chain fatty acid (SCFA) production and modulating essential adaptive immune pathways.⁷⁹

Furthermore, *S. boulardii* supports both innate and adaptive immune responses by promoting the activation and functional maturation of dendritic cells and macrophages. Recent studies have also suggested that engineered *S. boulardii* strains may be designed to modulate key inflammatory pathways, thereby reducing inflammation-associated tumorigenesis and offering a potential preventive strategy against colorectal cancer.⁸⁰ In addition, emerging evidence indicates that the yeast can alleviate cellular stress responses and improve resilience under adverse conditions, further reinforcing its role in maintaining intestinal homeostasis.⁸¹

The anti-inflammatory and immunomodulatory activities of *S. boulardii* demonstrate a highly nuanced and context-dependent orchestration of host defenses. By targeting key signaling pathways such as NF- κ B and MAPKs, the yeast simultaneously attenuates excessive inflammation while preserving essential pathogen-clearing responses, exemplifying a balanced immune modulation. Its ability to differentially regulate cytokine profiles in distinct intestinal compartments, coupled with the retention of T-helper cells in mesenteric lymph nodes, indicates that *S. boulardii* exerts spatially selective control over immune recruitment. Furthermore, its influence on both innate and adaptive immunity—including sIgA secretion and dendritic cell maturation—positions the yeast not merely as an anti-inflammatory agent but as a strategic modulator of mucosal immune homeostasis.⁸² These mechanisms synergistically underscore that *S. boulardii*'s therapeutic effects are integrative, linking direct anti-pathogenic activity to long-term regulation of intestinal immunity and tissue protection.

4.5. Trophic effects and intestinal regeneration

Beyond its antimicrobial roles, *S. boulardii* acts as a potent modulator of enzyme activity to maintain gastrointestinal health. It exerts significant trophic effects by stimulating brush border membrane digestive enzymes, such as sucrase, lactase, and maltase.^{23,48} This enzymatic enhancement is largely due to the yeast's ability to secrete polyamines, specifically spermine and spermidine, which promote RNA binding and stabilize protein synthesis within enterocytes.³⁰ Consequently, the induction of host lactase activity provides a strategic biotherapeutic approach to alleviate lactose intolerance and improve carbohydrate degradation.^{23,83}

Furthermore, the yeast facilitates the restoration of SCFA levels, which are typically depleted during enteric disease.²⁵ Among these, acetate and butyrate play a fundamental role in maintaining the intestinal barrier and fueling colonocytes.⁶⁴ Notably, the production of

acetic acid by *S. boulardii* serves a dual purpose: it acts as an antimicrobial agent and functions as a substrate for the microbiome to produce butyrate.⁸⁴ These SCFAs also stimulate T-regulatory cells and induce the expression of mucus-secreting genes, further reinforcing mucosal defense.⁸⁵

At the molecular level, *S. boulardii* activates essential signal transduction pathways, including the extracellular signal-regulated kinases 1 and 2 and phosphoinositide 3-kinase, which govern enterocyte maturation.^{30,86} By influencing the GRB2-SHC-Ras-Raf-GAP cascade, the yeast accelerates the regeneration of the damaged brush border membrane and enhances the activity of nutrient transporters, such as the sodium-glucose cotransporter 1.^{25,30,87} Collectively, these metabolic activations ensure the rapid recovery of intestinal absorptive functions following injury or infection.³⁰

The therapeutic efficacy of *S. boulardii* is attributed to its multifaceted mechanisms of action within the gastrointestinal tract, which can be categorized into direct trophic effects and indirect immunomodulatory responses. As illustrated in [Figure 1](#), these pathways involve a synergistic interplay between the live yeast (probiotic effect) and its secreted bioactive metabolites, such as enzymes and organic acids (postbiotic effect). These mechanisms collectively work to reinforce the intestinal barrier, suppress proinflammatory signaling, and facilitate the competitive exclusion of enteric pathogens.

5. Applications of *S. boulardii*

5.1. Clinical and therapeutic applications

The clinical effectiveness of *S. boulardii* CNCM I-745 in gastrointestinal disorders has been widely investigated.⁸ Clinical evidence supports its use in preventing and treating several diarrheal conditions, including pediatric diarrhea,⁸⁸ AAD,⁸⁸ acute infectious diarrhea,⁸⁸ traveler's diarrhea,⁸⁹ and diarrhea related to enteral nutrition.⁶⁰ Across studies, treatment with *S. boulardii* has been associated with reduced disease severity, shorter symptom duration, and lower relapse rates.⁶⁰

Notably, it has been demonstrated that *S. boulardii* serves as a useful adjuvant in *H. pylori* eradication regimens.⁹⁰ Its co-administration improves treatment tolerability by reducing therapy-related side effects, especially AAD-related side effects, but it does not replace traditional antimicrobial therapy.⁹¹ Comparable benefits are also provided in cases of *Clostridium difficile* infection (CDI),⁹¹ where it lessens the severity of symptoms,⁹² decreases recurrence rates, and mitigates antibiotic-associated side effects.⁹³

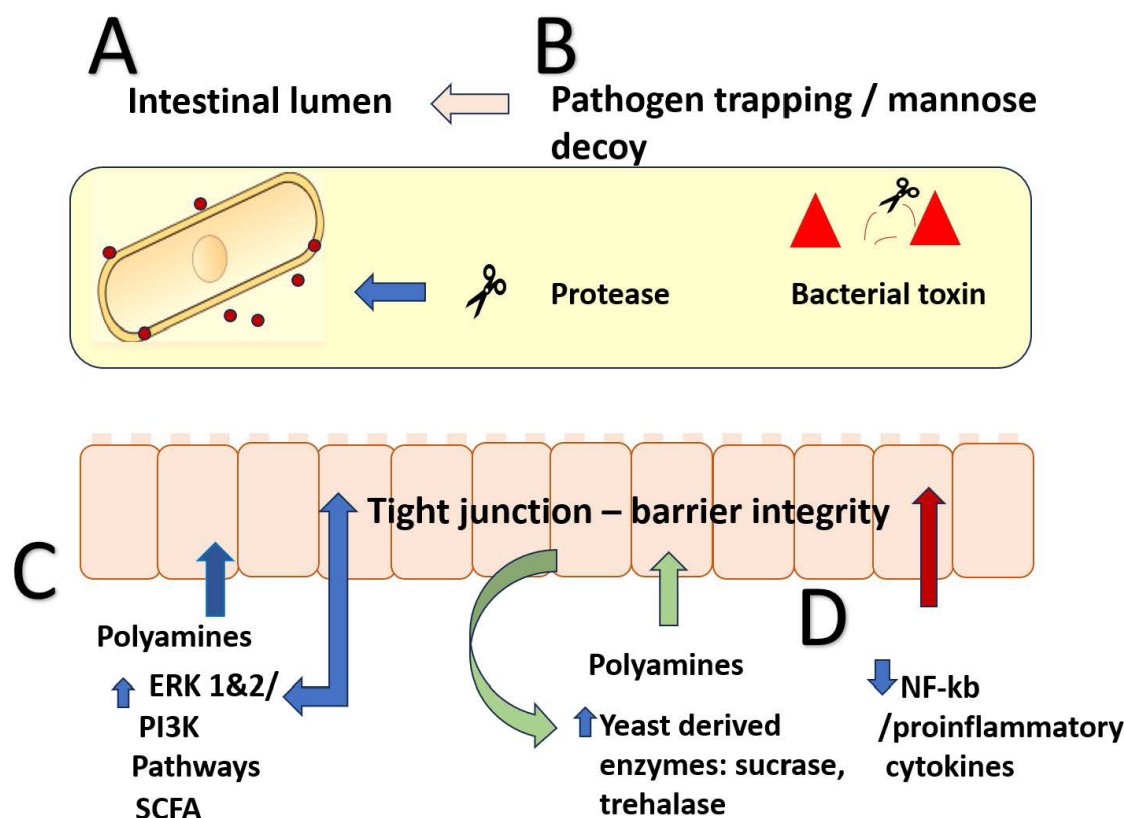


Figure 1. Multifactorial mechanisms of *S. boulardii* in promoting gut health. The schematic provides a comprehensive overview of the yeast's biotherapeutic roles, highlighting both its probiotic actions and postbiotic-mediated pathways. Key mechanisms include: (A) Enhancement of epithelial barrier integrity through the secretion of polyamines and short-chain fatty acids; (B) modulation of inflammatory pathways, specifically the inhibition of NF-κB and activation of ERK1 and 2 and PI3K signaling; (C) direct pathogen control via mannose-mediated trapping and the secretion of toxin-degrading proteases; and (D) stimulation of the mucosal immune response, notably through increased secretory immunoglobulin A levels.

Abbreviations: NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; ERK 1 and 2: Extracellular signal-regulated kinases 1 and 2; PI3K: Phosphoinositide 3-kinase; SCFA: Short-chain fatty acid. Image created by the authors (icons from Bioicons).

Probiotic yeasts may help with functional bowel disorders other than infectious diarrhea, according to new research.⁹⁴ Probiotic yeast strains have been shown in randomized controlled trials to improve overall symptom scores and abdominal pain in patients with irritable bowel syndrome. *S. cerevisiae* CNCM I-3856 supplementation, in particular, significantly reduced symptoms when compared to a placebo,¹⁰ underscoring the therapeutic potential of yeast-based probiotics in the treatment of irritable bowel syndrome.⁹⁴

5.2. Functional and nutritional benefits

S. boulardii enhances nutrition and metabolic function,⁹⁵ in addition to its therapeutic benefits.⁴⁸ In order to increase the bioavailability of vital minerals,⁹⁶ like iron, zinc, calcium, and magnesium,^{97,98} yeast produces phytases that

support the hydrolysis of dietary phytates.^{25,58} Because high IP6 content can restrict mineral absorption,⁹⁹ this effect is especially advantageous for populations following plant-based diets.¹⁰⁰ Increased mineral uptake⁹⁶ promotes hematopoiesis,⁹⁹ bone health,¹⁰¹ metabolic processes, and the byproducts of IP6 degradation, inositol phosphates,⁹⁶ may offer further protective benefits, such as possible cancer prevention.¹⁰²⁻¹⁰⁴

S. boulardii also produces folate,^{25,105} a water-soluble B-vitamin essential for DNA synthesis, repair, and methylation, and critical for preventing neural tube defects during pregnancy.¹⁰⁶ Folate-producing probiotics and bioactive molecules have been associated with multiple health benefits, including improved homocysteine metabolism and cardiovascular health, maintenance

of DNA stability, and potential cancer-preventive effects^{107,108} and cognitive support, such as a reduced risk of neurodegenerative diseases, including Alzheimer's.^{105,109} These findings highlight the yeast's ability to produce bioavailable folate, subsequently complementing dietary intake and addressing folate deficiencies in at-risk populations.¹¹⁰

S. boulardii CNCM I-745 supplementation in animal nutrition improved intestinal architecture (villus height and width, goblet cell numbers), stimulated mucosal immunity, and increased digestive enzyme activities,¹¹¹ indicating its potential as a safe substitute for antibiotic growth promoters in poultry production.³⁰

5.3. Barrier protection and immunomodulatory effects

S. boulardii strengthens intestinal barrier integrity¹¹² by supporting the tight junction structure,¹¹³ reducing pathogen-induced permeability,¹¹⁴ and modulating inflammatory responses.⁶⁶ It also detoxifies luminal toxins,³² contributing to the protection of epithelial cells.¹¹³ These actions are reflected in clinical recommendations endorsing the use of probiotics for maintaining gut health.¹¹⁵

At the immunological level, *S. boulardii* modulates inflammatory pathways,²⁷ including inhibition of NF-κB and p38 MAPK signaling,^{116,117} while stimulating the secretion of immunoglobulin A⁸³ and modulating T-cell, dendritic cell,^{118,119} and macrophage activity.¹²⁰ β-glucans in the yeast cell wall interact with dectin-1,¹²¹ complement receptor 3,¹²² and toll-like receptors,¹²² triggering cytokine production and enhancing pathogen clearance.¹²³ Non-clinical studies also show improved tissue regeneration,¹²⁴ reduced inflammation,²⁵ and beneficial modulation of the microbiome and metabolism.¹⁰⁹

5.4. Industrial and food applications of *S. boulardii*

Owing to its probiotic functionality and notable metabolic versatility, *S. boulardii*, alongside other non-conventional yeasts, has gained increasing attention in industrial and food applications.^{48,125} In particular, the dairy sector has leveraged probiotic-driven biotransformation to develop functional products with enhanced antioxidant capacity and sensory appeal.¹²⁶

Sarwar *et al.*¹²⁷ demonstrated that functional yogurt formulations containing *S. boulardii* in combination with inulin showed sustained increases in antioxidant activity during chilled storage. In parallel, probiotic and synbiotic yogurts—defined as a synergistic combination of probiotics and prebiotics that confers a health benefit⁵—showed a progressive enrichment in volatile compounds

during storage. Notably, elevated ethanol levels (S3–Syn1 = 306.81 ± 22.08 mg/100 g; S4–Syn1.5 = 304.44 ± 18.20 mg/100 g) indicate that *S. boulardii* actively fermented available carbohydrates, thereby promoting the formation of diverse volatile metabolites, including alcohols, organic acids, esters, and terpenoid-related compounds such as limonene.¹²⁷

Importantly, these metabolites were absent or detected only at trace levels in the control yogurt, suggesting that their generation was directly driven by synbiotic fermentation rather than by baseline dairy metabolism. Beyond compositional changes, the simultaneous enhancement of antioxidant capacity and volatile complexity highlights a functional interaction between *S. boulardii* and the inulin matrix, exceeding a simple additive effect. From a formulation standpoint, such interactions support the development of synbiotic dairy systems with improved sensory attributes and technological stability, while conceptually aligning with broader strategies aimed at restoring gut microbiome diversity and promoting microbial sustainability through functional food design.¹²⁷

Beyond dairy matrices, *S. boulardii* has also been applied in breadmaking, sourdough, and cereal-based fermentations, where its phytase activity substantially improves nutritional quality. By hydrolyzing phytic acid,¹²⁸ *S. boulardii* enhances the release of bioavailable minerals such as iron, zinc, calcium, and magnesium.¹²⁹ Increased mineral availability during sourdough fermentation has been consistently reported,¹³⁰ with comparable effects observed in wheat bread systems.^{125,131} Such enzymatic activity supports mineral absorption and underpins natural food fortification strategies.^{132,133} In parallel, the formation of lower inositol phosphates has been associated with antioxidant and anticancer properties, further extending the functional relevance of these fermentations.^{133,134}

Additionally, *S. boulardii* serves as a natural source of folates in fermented foods,⁵² contributing to increased folate levels in bread, sourdough, and other cereal-based products.⁵⁴ Folate-enriched fermentations have been linked to improved one-carbon metabolism, DNA synthesis,¹³⁵ methylation processes,¹³⁶ and cardiovascular health. Collectively, these attributes position *S. boulardii* as a versatile and sustainable biotechnological tool for the development of nutritionally enhanced foods, offering a promising alternative to synthetic fortification approaches in industrial food systems.^{137,138}

6. Safety profile, contraindications, and clinical efficacy

According to clinical evidence, *S. boulardii* is generally safe for both healthy people and critically ill patients.⁸⁸

The majority of studies report either no adverse events¹³⁹ or only mild side effects.^{89,140} Its overall safety profile in a variety of populations is further supported by clinical guidelines and systematic reviews.¹⁴¹

Although probiotics, including commensal microorganisms, theoretically carry a risk of epithelial translocation and systemic infection,²⁴ the condition of fungemia associated with *S. boulardii* is exceedingly rare, estimated at one case per 5.6 million users.¹⁴² When it does occur, such infections are generally confined to severely ill, immunocompromised patients or those with central venous catheters¹⁴³⁻¹⁴⁵ and respond well to antifungal therapy with fluconazole or amphotericin B.^{145,146} By contrast, fungemia due to *S. cerevisiae* is associated with worse outcomes.^{147,148}

Despite this, certain contraindications must be considered. *S. boulardii* is not recommended for severely immunocompromised individuals, such as those with human immunodeficiency virus/acquired immunodeficiency syndrome, active malignancies, or multiple sclerosis, due to the increased risk of systemic dissemination.⁴³ Furthermore, clinical caution is warranted when administering this probiotic to premature infants and the elderly. A key biological distinction contributing to its safety is that *S. boulardii* has a significantly reduced capacity for invasive hyphal growth compared to other pathogenic fungi, which limits its tissue-invasive potential.¹⁴⁹ Nonetheless, rare instances of deep mycoses, including urinary tract infections, have been reported in critically ill patients, necessitating careful clinical monitoring.

Moreover, *S. boulardii* CNCM I-745 has been shown to mitigate antibiotic-induced functional alterations in the gut microbiome independently of the host, further reinforcing its role in clinical recovery.⁶ It also avoids common probiotic safety issues, such as the transfer of antibiotic resistance genes. Clinical surveillance confirms that it does not acquire these genes,¹⁵⁰ in contrast to many bacterial probiotics.^{150,151} Recent proteomic and functional analyses have further revealed complex stress tolerance networks that enable *S. boulardii* to survive gastrointestinal challenges without compromising host safety (Table 1).⁴³

According to pharmacokinetic data, the yeast is eliminated from the intestine three to five days after stopping treatment.⁷² There are only sporadic mild side effects, such as constipation in patients with *Clostridium difficile* infection, according to data from more than 90 clinical trials.⁹¹

When combined, *S. boulardii* demonstrates a strong safety profile and clinically significant efficacy in a variety of gastrointestinal disorders, bolstering its potential as a useful probiotic therapeutic agent.^{91,92} Long-term clinical experience and thorough safety assessments provide additional support.

6.1. Summary

An overview of the main mechanisms, targets, effects, and key molecular pathways by which *S. boulardii* exerts its probiotic effects is summarized in Table 2. This table also highlights the key molecular mediators involved.

Table 1. Enteric pathogens, pathogenic mechanisms, and counteracting effects of *S. boulardii*

Pathogen	Key pathogenic mechanisms (references)	Counteracting effects of <i>S. boulardii</i> (references)
EHEC	(i) Shiga toxin production (ii) Hemolysin secretion (iii) Tight junction disruption (iv) Induction of apoptosis (152,153)	(i) Preservation of tight junction integrity (ii) Inhibition of caspase-mediated apoptosis (iii) Reduction of TNF- α and IL-8 secretion (152,154)
EPEC	(i) Pore formation (ii) Tight junction disruption (iii) Apoptosis induction (31,155)	(i) Stabilization of tight junctions (ii) Inhibition of apoptosis via MAPK signaling (31,155)
ETEC	(i) Enterotoxin-mediated diarrhea (ii) Intestinal inflammation (156)	(i) Reduction of proinflammatory cytokines and chemokines (ii) Decreased bacterial adhesion (156,157)
<i>Salmonella</i> spp.	(i) Mucosal inflammation (ii) Epithelial necrosis (iii) Diarrhea induction (158,159)	(i) Reduced epithelial adhesion (ii) Inhibition of Rac1 activation (iii) Preservation of cytoskeletal integrity (158,159)

(cont'd...)

Table 1. (Continued)

Pathogen	Key pathogenic mechanisms (references)	Counteracting effects of <i>S. boulardii</i> (references)
<i>Shigella flexneri</i>	(i) Tight junction disruption (ii) IL-8-mediated neutrophil recruitment (160,161)	(i) Restoration of tight junction integrity (ii) Inhibition of ERK1 and 2 and IκB phosphorylation (160,161)
<i>Clostridioides difficile</i>	(i) Toxins A and B (ii) Apoptosis induction. (iii) Inflammatory signaling (24,59)	(i) Degradation of toxins A and B by a 54-kDa serine protease (ii) Protection of the intestinal epithelium (24,59)
Rotavirus	(i) Chloride secretion (ii) Oxidative stress induction (162,163)	(i) Limitation of ROS formation (ii) Restoration of antioxidant balance (162,163)
<i>Candida albicans</i>	Induction of IFN-γ, IL-1β, and TNF-α (164)	(i) Reduction of proinflammatory cytokines (ii) Enhancement of IL-4 and IL-10 production (165,166)

Abbreviations: EHEC: Enterohemorrhagic *Escherichia coli*; EPEC: Enteropathogenic *E. coli*; ERK1 and 2: Extracellular signal-regulated kinases 1 and 2; ETEC: Enterotoxigenic *E. coli*; IFN-γ: Interferon-gamma; IκB: Inhibitor of κB; IL: Interleukin; MAPK: Mitogen-activated protein kinase; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor alpha.

Table 2. Mechanisms of probiotic action of *S. boulardii*

Mechanism	Target/effect	Key molecules/pathways
Gut microbiome modulation	(i) Restores microbiota after antibiotic- or disease-induced dysbiosis ⁶² (ii) Stabilizes microbial communities ⁶⁴ (iii) Improves clinical outcomes ⁶²	(i) Transient intestinal colonization (ii) Metabolic byproducts (iii) Immune-mediated effects (64)
Antimicrobial activity	(i) Inhibits the growth of <i>Clostridioides difficile</i> ³¹ (ii) Suppresses <i>Citrobacter rodentium</i> ¹¹⁶ (iii) Limits the growth of <i>Candida albicans</i> and <i>Bacillus anthracis</i> ¹⁶⁷ (iv) Reduces toxin activity ¹⁶⁸ (v) Limits the adhesion of pathogens ^{116,169}	(i) Secreted proteins, ^{31,32} including a 54-kDa serine protease, a 63-kDa phosphatase, and a 120-kDa antitoxin-associated factor (ii) Acidic metabolites (e.g., acetic acid) ^{49,51}
Adhesion and competitive exclusion	(i) Adheres to the intestinal mucosa ⁶⁹ (ii) Prevents invasion by <i>E. coli</i> and <i>Salmonella</i> spp. ^{167,170} (iii) Reduces colonization of <i>C. difficile</i> ¹⁷¹ (iv) Limits <i>Entamoeba histolytica</i> attachment ¹⁷²	(i) Cell surface adhesins (ii) Yeast cell wall proteins (CWP2, SCW4, CIS3, FKS3, PIR3) ⁶⁵ (iii) Mannose residues ⁷⁰ (iv) Bile salt-mediated pathogen capture ^{119,173}
Anti-inflammatory and immunomodulatory Effects	(i) Inhibits NF-κB signaling ^{26,29} (ii) Suppresses p38 MAPK activation ^{84,85} (iii) Regulates cytokine production (IL-1β, IL-6, TNF-α, IL-10) ^{34,66} (iv) Protects epithelial cells from toxin-induced damage. ²⁹ (v) Enhances mucosal immunity via sIgA ^{83,116}	(i) Protein phosphatases ^{20,28} (ii) β-glucans ^{94,95} (iii) Secretory IgA ⁸³ (iv) Costimulatory molecules (CD80/CD86) ²⁹ (v) T-cell and dendritic cell modulation ^{117,174}
Trophic effects & regeneration	(i) Stimulates digestive enzymes (sucrase, lactase, maltase) (ii) Enhances nutrient transport and cellular adaptation ^{78,84} (iii) Accelerates healing of the intestinal brush border ^{33,81}	Signaling cascades (ERK1 and 2 and PI3K pathways) ^{28,33}

Abbreviations: CD: Cluster of differentiation; ERK1 and 2: Extracellular signal-regulated kinases 1 and 2; IL: Interleukin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK: Mitogen-activated protein kinase; PI3K: Phosphoinositide 3-kinase; sIgA: Secretory immunoglobulin A; TNF-α: Tumor necrosis factor alpha.

7. Conclusion

S. boulardii has been shown to play a significant role in gut health. Its advantages include temporary persistence in the gastrointestinal tract and a wide range of bioactive metabolites, including vitamins, organic acids, polyamines, and enzymes, which work together to affect microbial balance, maintain epithelial integrity, and reduce pathogen-associated damage. These mechanistic insights are supported by clinical findings, especially in conditions such as inflammatory bowel disease, irritable bowel syndrome, and AAD. The potential of yeast beyond clinical use, such as its use in fermented foods and functional products, is also highlighted by the growing interest in food biotechnology.

However, despite its robust safety profile, clinical caution is warranted. *S. boulardii* administration is not recommended for severely immunocompromised individuals, such as those with human immunodeficiency virus/acquired immunodeficiency syndrome or active malignancies, due to the rare but serious risk of fungemia. Its use in premature infants and the elderly should also be carefully monitored, acknowledging that while it lacks the invasive hyphal growth of *S. cerevisiae*, it remains an occasional opportunistic risk in critically ill patients.

Although there is sufficient evidence to support its probiotic potential, additional research is needed to clarify the individual contribution of certain metabolites, define strain-specific effects, and optimize large-scale industrial formulations. Considering all characteristics, *S. boulardii* is both a potent probiotic for human health and a promising biological resource for food industry innovation. However, important gaps remain. Most current evidence derives from whole-organism studies, which limit conclusions about the individual contributions of specific metabolites. Future research should therefore place greater emphasis on postbiotic-focused approaches and on the understanding of how environmental conditions in the gastrointestinal tract influence metabolite production.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

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