

Saccharomyces boulardii in Crohn's disease: biologic plausibility without sufficient support for routine adjunctive use

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Abstract

Background and Aims

Durable remission remains incomplete in Crohn's disease despite standard therapy, and epithelial barrier dysfunction may persist even when overt inflammation improves. That gap has kept *Saccharomyces boulardii* in view as a possible adjunct. The clinically important question, however, is not whether biologic plausibility exists, but whether current evidence supports routine adjunctive use to improve remission outcomes.

Methods

We conducted a protocol-guided, question-centred translational evidence synthesis integrating direct Crohn clinical studies, mechanistic studies, public GEO host-response datasets, organism-side transcriptomic resources, and a public terminal-ileum disease-anchor dataset. Evidence classes were kept separate as direct, derived, adjacent, or cross-dataset contextual evidence to avoid category error. Direct Crohn clinical reports were synthesized by endpoint class. Formal meta-analysis was not pursued because the direct clinical record was sparse and distributed across non-commensurable endpoint classes.

Results

The core analysable evidence base comprised 23 studies and datasets, 5 of which were direct Crohn clinical records. These included 2 remission-maintenance or relapse studies, 1 remission permeability study, 1 symptom-focused randomized pilot in clinically stable disease, and 1 uncontrolled retrospective cohort. One additional brief Crohn clinical letter was logged during screening but excluded from the analysable set because it did not provide enough methodological or outcome detail for appraisal. Barrier rescue and inflammatory attenuation were the strongest retained mechanistic domains, whereas remission durability was the weakest and clinically decisive domain. Organism-side data supported strain-specific plausibility rather than efficacy. Anti-pathobiont support weakened materially under strict admissibility because evidence was stronger in generic pathogenic *Escherichia coli* or enteropathogenic *E. coli* settings than in direct Crohn-relevant AIEC systems. The direct Crohn clinical record remained the deciding limitation, and the larger negative maintenance trial carried more interpretive weight than the earlier maintenance and symptom-focused pilots.

Conclusions

S. boulardii retains a credible Crohn-relevant biologic rationale, particularly around barrier support and inflammatory attenuation. Current evidence supports further direct study, especially in barrier-oriented remission-support or maintenance settings, but does not support routine adjunctive use to improve remission outcomes.

Introduction

Crohn's disease management has improved, but durable remission remains incomplete for many patients. Control of overt inflammatory activity does not reliably restore epithelial integrity or stabilise the host-microbe interface, and residual barrier dysfunction may persist even when luminal or systemic inflammatory markers improve.^{13,23}

For an adjunctive strategy in this setting, the endpoint hierarchy is clinical before it is mechanistic. Durable remission, relapse prevention, and remission maintenance are the burden-bearing outcomes. Symptom movement, permeability shifts, and biomarker trends can be informative, but they are supportive unless they track with remission durability or clearly illuminate a mechanistic pathway relevant to it.^{13,23}

Saccharomyces boulardii remains plausible within that framework. Experimental work has linked it to epithelial restitution, preservation of barrier function under pathogen challenge, attenuation of inflammatory signalling, and organism-specific behaviour not captured by generic *Saccharomyces* biology.³⁻¹¹ Those observations justify continued interest. They do not, by themselves, answer the treatment question.

That distinction is easy to lose. Evidence for probiotics as a class is not evidence for a single organism. Generic *Saccharomyces* biology is not proof of *S. boulardii* efficacy. Findings in generic pathogenic *E. coli* or enteropathogenic *E. coli* systems are not interchangeable with Crohn-relevant evidence for antagonism of adherent-invasive *E. coli* (AIEC). Supernatant or postbiotic effects are likewise not equivalent to live-organism clinical efficacy.^{1-3,7,8,17,18}

We therefore conducted a protocol-guided translational evidence synthesis centred on a predefined clinical question: does current evidence support routine adjunctive *S. boulardii* use during standard Crohn's disease treatment to improve remission outcomes? The analysis was designed to keep direct clinical evidence separate from mechanistic, derived, adjacent, and cross-dataset contextual evidence so that biologic plausibility would not be mistaken for efficacy.

Methods

Study design and analytic frame

This was a protocol-guided, question-centred translational evidence synthesis using literature and public data to answer a narrow clinical question: whether routine adjunctive *S. boulardii* use is supported during standard Crohn's disease treatment to improve remission outcomes. The scope was limited to adjunctive use alongside standard care. It was not designed to evaluate monotherapy, probiotic-class efficacy, or inflammatory bowel disease outcomes without Crohn-specific assessment.

The analytic goal was to preserve evidentiary hierarchy rather than to derive a single summary effect across biologically and clinically non-equivalent records. Direct Crohn clinical evidence was therefore treated as the decisive layer for the primary question, with mechanistic and public-data analyses used to define plausibility, scope, and limits.

Source discovery, selection, and evidence classes

Sources were identified from the logged literature searches, dataset searches, and structured source registry contained within the project. Direct Crohn clinical studies involving *S. boulardii* were prioritized for the primary question. Mechanistic, organism-side, and host-response sources were retained when they informed a defined biologic domain relevant to that question. Generic probiotic reviews, ulcerative-colitis-only efficacy data, and studies that shifted biologic context in ways that would overstate Crohn relevance were not allowed to support the primary claim.^{1,2}

Evidence classes were kept separate to prevent category error. Direct evidence addressed the domain under discussion in the same biologic context. Derived evidence preserved the biologic theme but required contextual inference, such as separate-arm comparison. Adjacent evidence was supportive but non-defining, such as engineered or evolved strain work. Cross-dataset analyses, including disease-anchor alignment and reversal analyses, informed biologic interpretation but were not treated as intervention data.

Organism-side and public host-response data

Organism-side analysis used public transcriptomic resources to assess whether *S. boulardii* should reasonably be treated as an organism-specific question rather than as a proxy for generic *Saccharomyces* biology. The GSE155032 accession and companion publication were retained as organism-side plausibility context, but the bundled raw count files were not used as a standalone auditable differential-expression backbone because the two organisms are represented in different feature namespaces within the deposited bundle.¹⁰ Acid-stress context was taken from the publication by Cascio and colleagues rather than from a reprocessed bundled GEO series.¹¹ Organism-side interpretation was therefore publication-anchored and conservative.

Host-response and disease-anchor analysis used public GEO datasets. GSE63299 provided mono-association transcriptomic arms for *S. boulardii* and AIEC LF82 relative to germ-free controls, allowing replicated host-state comparison but not direct antagonism.¹⁷ GSE31394 provided a single processed epithelial treatment profile for *S. boulardii* exposure plus pathogen comparators, which was used directionally rather than as a replicated differential-expression analysis.¹⁸ GSE75214 provided active terminal-ileum Crohn and control biopsies, which were used as a disease-side anchor for module scoring in the host-response synthesis and supporting tables.²³

Anti-AIEC admissibility rules

Because anti-AIEC claims were especially prone to overreach, microbial-context evidence was partitioned into generic pathogenic *E. coli*, EPEC/EHEC, and AIEC. For a study to contribute to the primary AIEC score, it had to involve true AIEC, direct testing of live *S. boulardii*, and a biologic context relevant to Crohn's disease. Generic pathogenic *E. coli* and EPEC studies were retained as supportive context but excluded from primary AIEC support.^{7,8} Separate-arm AIEC host-response comparisons were treated as derived evidence rather than proof of antagonism.¹⁷

Clinical synthesis and handling of heterogeneous endpoints

Direct Crohn clinical reports were first logged in the source registry and then triaged by endpoint class.^{12-15,22} Four records with extractable quantitative endpoint data were carried into the structured clinical subpanels used for figure display, while 1 additional symptom-focused pilot was retained in the architecture panel and text only. Relapse-prevention, permeability, symptom-focused pilot outcomes, and uncontrolled within-cohort symptom or biomarker outcomes were treated as distinct endpoint classes. Brief clinical letters without enough methodological or outcome detail for appraisal were excluded from the analysable set.

Formal meta-analysis was not pursued. The direct Crohn record was sparse, and the retained studies did not estimate a single clinically coherent endpoint class across the evidence base. Even within remission maintenance, only 2 studies were available, and study-level appraisal was more informative than a pooled estimate would have been for the question at hand. The synthesis therefore reported the direct clinical record study by study rather than forcing pooled inference across non-commensurable outcomes.

Comparative synthesis and sensitivity analyses

Five biologic and clinical domains were evaluated: organism-side plausibility, anti-pathobiont pressure, barrier rescue, inflammatory attenuation, and remission durability under standard therapy. The synthesis considered direct Crohn clinical support, Crohn relevance, host-response support, microbial-context evidence, reproducibility, strain specificity, biologic alignment, and uncertainty penalties. Sensitivity analyses then tested whether the overall interpretation changed under stricter restrictions, including Crohn-only human evidence, human-only evidence, direct live-*S. boulardii* evidence, AIEC-strict admissibility, and broader mechanistic integration.

The comparative scoring framework was used as a structured descriptive synthesis rather than as a validated quantitative measurement instrument. Its purpose was to preserve the ordering and contradiction structure of the retained evidence, not to replace study-level interpretation.

Reproducibility and provenance

Source logs, evidence tables, sensitivity summaries, figure inputs, and provenance metadata are retained within the repository. Figure rendering is scripted from curated tables, whereas the adjudication scores remain curator-authored synthesis artifacts and the organism-side GSE155032 layer is publication-anchored rather than a fully reproducible raw-count comparison. The basis for each section can therefore be audited directly, with the provenance limits stated explicitly.

Results

Evidence profile and endpoint hierarchy

The core analysable evidence base comprised 23 studies and datasets, 5 of which were direct Crohn clinical records. Nineteen records were direct within their analytic domain, 2 were derived, and 2 were adjacent. One additional brief Crohn clinical letter was screened but excluded from the analysable set because it did not permit reproducible appraisal.

Those 5 clinical reports define the endpoint hierarchy of the manuscript. They consisted of 2 remission-maintenance or relapse-prevention studies, 1 remission permeability study, 1 symptom-focused randomized pilot in clinically stable disease, and 1 uncontrolled retrospective cohort.^{12-15,22} Only 4 supplied quantitative endpoint detail suitable for the clinical subpanels. No convincing remission-induction dataset was identified. Durable remission under standard therapy therefore remains the burden-bearing domain for the primary question.

Direct Crohn clinical evidence is the decisive limiting layer

The direct Crohn record does not support routine adjunctive use. Figure 1 shows why. The retained clinical literature contains early positive or supportive signals, but the studies are endpoint-heterogeneous, and the most informative maintenance trial is negative.

The 1993 randomized placebo-controlled pilot by Plein and Hotz was conducted in clinically stable Crohn disease with residual symptoms and suggested improvement in stool frequency and BEST Index over 10 weeks.²² That study remains relevant as a symptom-focused pilot, but it was not a remission-maintenance trial. The later pilot by Guslandi and colleagues is more directly connected to remission maintenance and suggested a lower relapse count with adjunctive *S. boulardii*.¹² In that trial, relapse occurred in 1 of 16 patients receiving mesalamine plus *S. boulardii* and in 6 of 16 patients receiving mesalamine alone over 6 months. The signal is suggestive, but the comparator structure was not dose-symmetric for mesalamine, which limits clean causal interpretation.

The barrier-facing study by Garcia Vilela and colleagues contributes a different kind of information.¹³ In 34 patients with Crohn remission, the lactulose/mannitol ratio changed by -0.008 +/- 0.006 in the *S. boulardii* arm and by +0.004 +/- 0.010 in the placebo arm at 3 months. This is the closest human barrier readout in the manuscript, but it is not a relapse-prevention result.

The most informative direct trial is the 2013 randomized placebo-controlled maintenance study by Bourreille and colleagues.¹⁴ It enrolled 165 patients and directly addressed relapse prevention during remission maintenance. The abstract reported relapse in 38 patients in the *S. boulardii* group (47.5%) and 42 in the placebo group (53.2%), with no significant difference at 52 weeks. The study also did not show benefit for time to relapse, CDAI, ESR, or CRP. Because it is larger, methodologically stronger, and better aligned with the clinical question than the earlier pilot studies, it carries greater interpretive weight.

The remaining direct record does not reverse that conclusion. The 2020 single-center retrospective cohort included 154 patients in clinical remission, of whom 92 who received treatment for more than 6 months were analysed; CDAI decreased from 38.52 to 30.53, but fecal calprotectin and CRP did not change significantly.¹⁵ As a single-arm retrospective cohort, it is supportive at most and cannot establish efficacy.

These studies were not collapsed into a single effect estimate because they do not answer a single clinical question in a single endpoint language. Two addressed relapse prevention or maintenance, one addressed permeability, one was symptom-focused, and one reported uncontrolled within-cohort change.^{12-15,22} Read study by study, the direct Crohn record supports continued investigation but not routine adjunctive use.

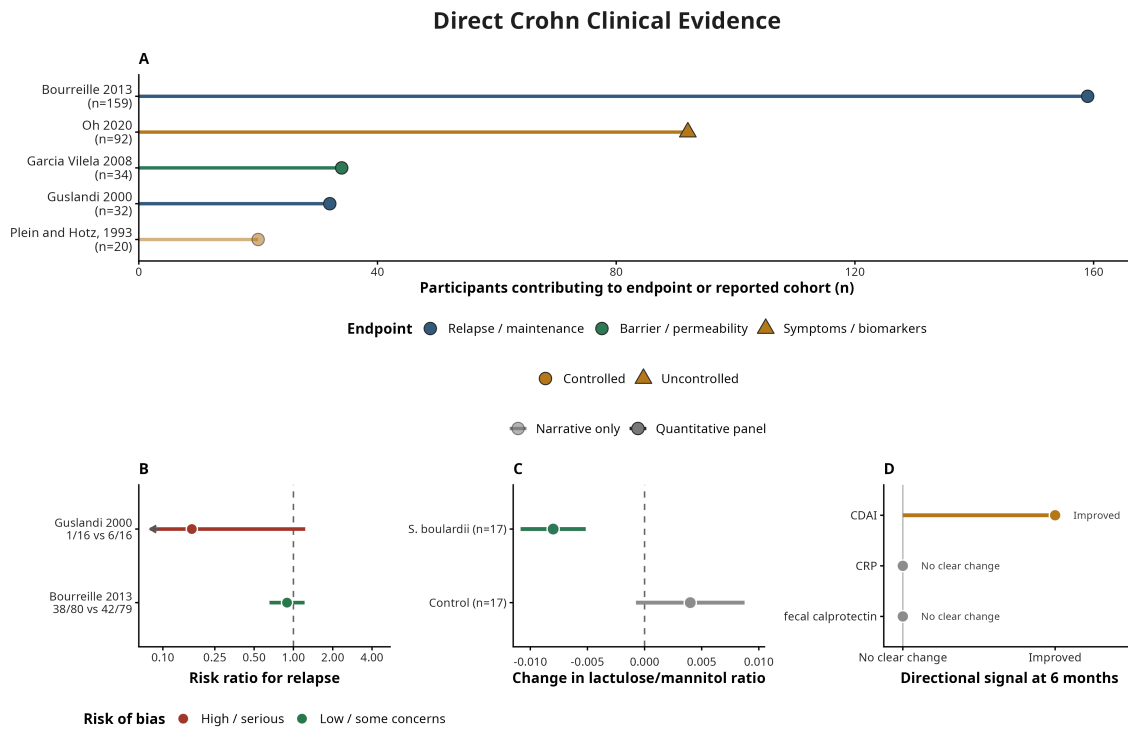


Figure 1. Direct Crohn clinical evidence, interpreted by endpoint class. Panel A shows the five retained appraisable direct Crohn clinical reports in the analysable evidence base, including the 1993 symptom-focused pilot. One additional brief Crohn clinical letter was screened but is not shown because it lacked enough methodological or outcome detail for appraisal. Panels B to D retain study-level display rather than pooled estimates because the direct records address different endpoint classes. Panel B is the key clinical comparison: the larger negative randomized maintenance trial is more informative for relapse prevention than the earlier positive pilot. Panel C shows the barrier-facing permeability study as arm-specific change in lactulose/mannitol ratio, and Panel D shows the uncontrolled cohort directionally, with CDAI improvement but no corresponding clear CRP or fecal calprotectin improvement. The figure shows why direct Crohn evidence remains too limited and too heterogeneous to support routine adjunctive use. CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Barrier rescue and inflammatory attenuation retain the strongest mechanistic support

The mechanistic case that survives this clinical reading is concentrated rather than diffuse. In the comparative summary, barrier rescue was the highest retained domain, with a weighted score of 11.7, followed by inflammatory attenuation at 10.7 and remission durability at 3.4. That ordering reflects the clearest biologic asymmetry in the manuscript.

Barrier rescue draws on epithelial restitution studies, barrier preservation under pathogen challenge, the remission permeability study, and the public host-response analyses.^{5-7,13} The human contribution is limited but meaningful: the permeability study is the most direct barrier-facing result in Crohn remission and is biologically coherent with the broader experimental literature.¹³ It should not, however, be treated as a surrogate for relapse prevention.

Inflammatory attenuation is the next strongest retained domain. Across several systems, *S. boulardii* is associated most clearly with attenuation of NF-kappaB-linked signalling, IL-8-associated responses, and selected cytokine outputs rather than with a broad anti-inflammatory reset.^{3,4,9,16,18} Much of this literature arises from non-Crohn settings, non-human models, or supernatant-based designs, so it strengthens plausibility without changing the clinical answer.

Organism-side evidence supports specificity, not efficacy

The organism-side record supports treating *S. boulardii* as an organism-specific question rather than folding it into generic *Saccharomyces* reasoning. The GSE155032 accession and companion paper describe differentiated *S. boulardii* versus *S. cerevisiae* behaviour under host-related conditions, consistent with organism-specific plausibility rather than simple interchangeability.¹⁰ In the current repository, this layer is therefore retained as publication-anchored plausibility context rather than as a standalone reprocessed differential-expression result. Acid-stress data from Cascio and colleagues qualify that picture

by suggesting conditional competence rather than uniform robustness.¹¹ Engineered and evolved strain studies broaden the plausibility space but were kept separate because they do not define the baseline properties of the native organism.

Public host-response contextualization shows where plausibility concentrates

Figure 2 does not show a uniform rescue signature. It localises the most coherent *S. boulardii*-associated directions to inflammatory attenuation, with a narrower and less consistent barrier-facing pattern. After combining the directional GSE31394 epithelial profile with the replicated GSE63299 mono-association contrasts, the clearest protective directions remained in NF-kappaB and IL-8/neutrophil modules, whereas barrier-facing, permissiveness, and TNF/IL-6/IL-1B modules were mixed or non-protective in the aggregated summary.^{17,18}

The public terminal-ileum Crohn anchor from GSE75214 sharpens that interpretation.²³ Disease-side increases in permissiveness, IL-8/neutrophil, and TNF/IL-6/IL-1B modules occur alongside loss of tight-junction signal. The figure therefore helps distinguish where *S. boulardii*-associated directions do and do not oppose a genuine Crohn tissue state. It provides context for barrier rescue and inflammatory attenuation; it does not imply intervention efficacy.

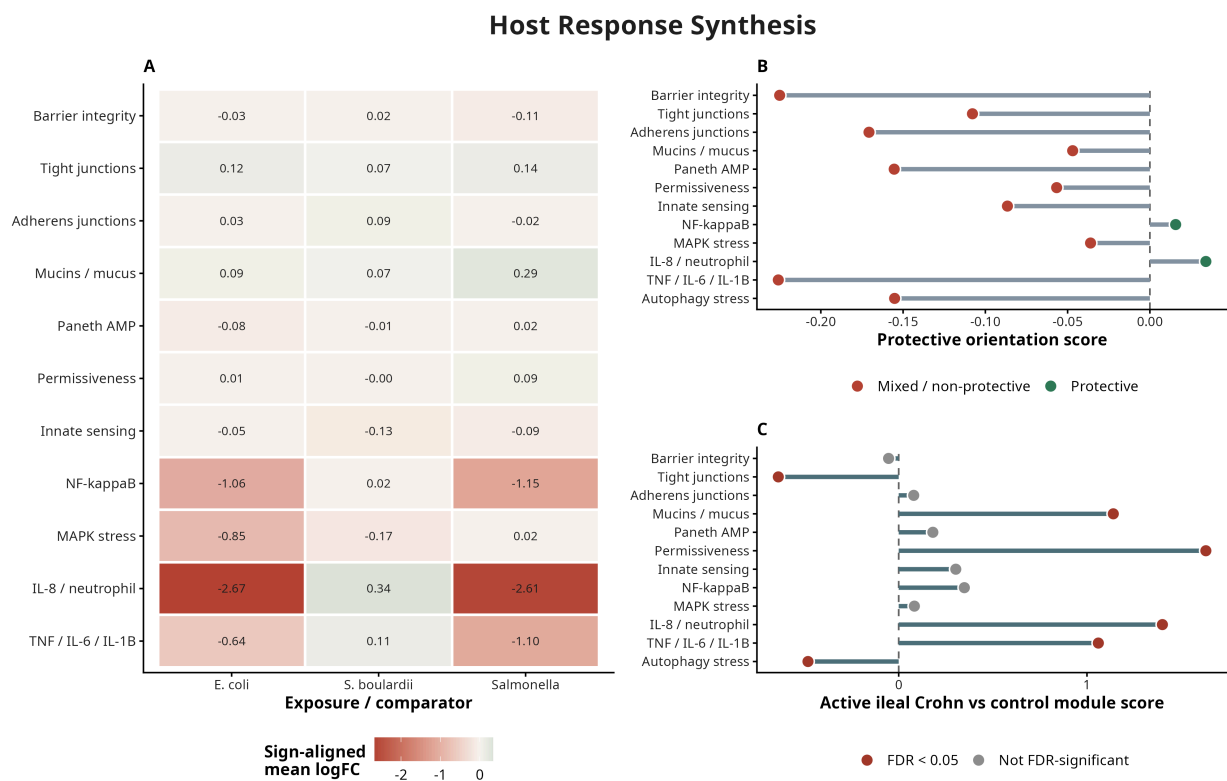


Figure 2. Host-response synthesis with public ileal Crohn anchor. Public host-response datasets were used to localise where *S. boulardii*-associated directions are most coherent, not to infer intervention efficacy. Panel A shows sign-aligned module behaviour across the GSE31394 epithelial comparator profiles for *S. boulardii*, *E. coli*, and *Salmonella*. Panel B shows the aggregated *S. boulardii* summary across retained public host-response datasets, in which NF-kappaB and IL-8/neutrophil modules provide the clearest protective direction while barrier-facing, permissiveness, and TNF/IL-6/IL-1B modules remain mixed. Panel C shows module-level shifts in active terminal-ileum Crohn versus control biopsies from GSE75214, highlighting disease-side increases in permissiveness and inflammatory modules together with reduced tight-junction signal. The figure defines where mechanistic plausibility concentrates and where it does not. GEO, Gene Expression Omnibus.

Anti-pathobiont support weakens under strict AIEC admissibility

The anti-pathobiont story is materially weaker under strict admissibility. Evidence is stronger in generic pathogenic *E. coli* and EPEC contexts than in direct Crohn-relevant AIEC systems. Barrier preservation under EPEC challenge and mannose-sensitive trapping of some pathogenic bacteria on the yeast surface remain biologically interesting.^{7,8} They do not establish that live *S. boulardii* antagonizes AIEC in a Crohn-relevant model.

That distinction matters because anti-AIEC claims are especially vulnerable to translational overreach. Under the admissibility rules used here, generic pathogenic *E. coli*, EPEC, and ETEC studies did not contribute to the primary AIEC score. The most Crohn-relevant public AIEC dataset placed AIEC LF82 and *S. boulardii* in separate mono-association arms, which allowed host-state comparison but not direct live antagonism.¹⁷ This domain therefore cannot carry the clinical argument.

Integrated synthesis separates plausibility from efficacy

Figure 3 makes the domain asymmetry explicit. Support concentrates in barrier rescue and inflammatory attenuation, not in remission durability, and barrier-first interpretations are better supported than anti-AIEC-first interpretations. The integrated picture is asymmetric rather than equivocal.

Sensitivity analyses sharpen the same point. When the evidence was restricted to Crohn-only human studies, the verdict shifted to not supported. The same occurred under human-only restriction and under AIEC-strict admissibility. Broader mechanistic integration preserved biologic plausibility, but the routine-use question remained constrained by the direct Crohn clinical record.



Figure 3. Comparative summary of biologic and clinical support. Panel A shows retained support after uncertainty penalties across the major biologic and clinical domains. Panel B shows the composition of that support and the separation between mechanistic plausibility and remission durability. Panel C displays the evidence components underlying the comparative sequences examined, including directness, Crohn relevance, quantitative support, mechanistic plausibility, contradiction burden, and net score. Panel D compares alternative biologic orderings and shows that barrier-first interpretations are better supported than anti-AIEC-first interpretations. The figure makes the domain asymmetry explicit: support concentrates in barrier rescue and inflammatory attenuation, whereas remission durability remains the weakest and clinically decisive domain. AIEC, adherent-invasive *Escherichia coli*.

Discussion

The manuscript’s answer is decided by endpoint hierarchy. An adjunct intended for Crohn remission care should be judged chiefly on durable remission, relapse prevention, and remission maintenance. That is where the direct evidence is weakest, and it is why the larger negative maintenance trial deserves more interpretive weight than the earlier smaller positive or symptom-focused signals.^{12,14,22}

What remains after that clinical judgment is a bounded but credible translational rationale. Barrier rescue and inflammatory attenuation retain the strongest support across epithelial restitution studies, pathogen-challenge models, the permeability study in Crohn remission, and the public host-response analyses.^{3-7,13,17,18,23} The signal is real, but it is concentrated rather than uniform. That distinction matters: biologic coherence can justify targeted follow-up, but it cannot substitute for evidence that relapse is reduced or durable remission is improved.

The anti-AIEC axis does not currently close that gap. It remains a plausible biologic bridge between epithelial permissiveness, microbial persistence, and inflammatory activity in Crohn’s disease, but the strongest supporting studies sit in generic

pathogenic *E. coli* or EPEC settings rather than in direct Crohn-relevant AIEC systems.^{7,8,17} That domain is best treated as hypothesis-generating context rather than as a pillar of efficacy inference.

The value of the present synthesis lies in keeping those categories separate. A coherent mechanistic story can easily be mistaken for treatment support when sparse direct trials are surrounded by a broader, more favourable experimental literature. Here, the evidence-class separation points to a restrained conclusion: the organism remains worth studying, but the clinical record does not justify recommendation.

The most informative next studies are therefore specific. Experimentally, live *S. boulardii* should be tested directly in Crohn-relevant epithelial or organoid systems with barrier, inflammatory, and AIEC-related readouts measured together. Clinically, the next useful study would be a strain-defined adjunctive remission-maintenance trial conducted alongside standard therapy, with relapse or durable remission as the primary endpoint and barrier-oriented measures prespecified as mechanistic anchors. If benefit exists, the current record suggests it is more likely to emerge in barrier-disrupted or residual-inflammation settings than in unselected cohorts.

Safety should remain proportionate to the efficacy record. The direct Crohn studies did not identify a dominant tolerability signal, but the broader literature documents rare yet consequential fungemia in line-associated, critically ill, or otherwise high-risk settings.¹⁹⁻²¹ In the absence of clear clinical benefit, that profile supports restraint rather than routine use.

Limitations

The direct Crohn clinical base remains thin. Five appraisable clinical reports were retained, but only 2 addressed remission maintenance directly and only 4 provided extractable quantitative endpoint detail suitable for study-level plotting.^{12-15,22} One additional brief Crohn clinical letter was identified during screening but could not be appraised reproducibly.

Much of the mechanistic record is indirect relative to the clinical question. Several domains depend on non-Crohn models, non-human systems, supernatant experiments, separate-arm comparisons, or disease-anchor contextualization rather than direct live-organism testing in Crohn-relevant intervention settings.^{3,4,7,16-18,23} The organism-side GSE155032 layer also remains publication-anchored rather than a fully auditable raw-count comparison within the deposited bundle.¹⁰

The comparative framework should also be read in proportion to its purpose. It is a structured descriptive synthesis intended to preserve directness, contradiction, and evidentiary asymmetry across domains. It is not a validated measurement instrument and should not be interpreted as replacing study-level evidence.

Conclusion

S. boulardii has real biologic plausibility in Crohn's disease, with the strongest retained support in barrier rescue and inflammatory attenuation. The decisive limitation is the direct clinical record, which is sparse, endpoint-heterogeneous, and includes a larger negative maintenance trial that outweighs earlier smaller positive signals. Further direct Crohn-relevant study is justified, but current evidence does not support routine adjunctive use for remission outcomes.

Data Availability

Search documentation is retained in the searches directory, including the literature search log, dataset search log, and source registry. The core tables underlying the manuscript and figures are retained in results/tables, and supporting evidence notes are retained in results/supplementary.

Code Availability

The manuscript figures were rendered from curated source tables using the scripts in analysis/11_r_figures. Public host-response and ileal disease-anchor rebuild scripts are retained in analysis/03_host_signature_analysis.

Association

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References

1. Guslandi, M. Role of probiotics in Crohn's disease and in pouchitis. *Journal of Clinical Gastroenterology* **49** Suppl 1, S46-S49 (2015).
2. Rolfe, V. E., Fortun, P. J., Hawkey, C. J. & Bath-Hextall, F. Probiotics for maintenance of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* CD004826 (2006).
3. Sougioultzis, S. *et al.* *Saccharomyces boulardii* produces a soluble anti-inflammatory factor that inhibits NF-kappaB-mediated IL-8 gene expression. *Biochemical and Biophysical Research Communications* **343**, 69-76 (2006).
4. Lee, S. K., Kim, Y. W., Chi, S. G., Joo, Y. S. & Kim, H. J. The effect of *Saccharomyces boulardii* on human colon cells and inflammation in rats with trinitrobenzene sulfonic acid-induced colitis. *Digestive Diseases and Sciences* **54**, 255-263

- (2009).
5. Canonici, A. *et al.* Saccharomyces boulardii improves intestinal cell restitution through activation of the alpha2beta1 integrin collagen receptor. *PLoS One* **6**, e18427 (2011).
 6. Canonici, A. *et al.* Saccharomyces boulardii improves intestinal epithelial cell restitution by inhibiting alphavbeta5 integrin activation state. *PLoS One* **7**, e45047 (2012).
 7. Czerucka, D., Dahan, S., Mograbi, B., Rossi, B. & Rampal, P. Saccharomyces boulardii preserves the barrier function and modulates the signal transduction pathway induced in enteropathogenic *Escherichia coli*-infected T84 cells. *Infection and Immunity* **68**, 5998-6004 (2000).
 8. Tiago, F. C. P. *et al.* Adhesion to the yeast cell surface as a mechanism for trapping pathogenic bacteria by Saccharomyces probiotics. *Journal of Medical Microbiology* **61**, 1194-1207 (2012).
 9. Justino, P. F. C. *et al.* Modulation of 5-fluorouracil activation of toll-like/MyD88/NF-kappaB/MAPK pathway by Saccharomyces boulardii CNCM I-745 probiotic. *Cytokine* **125**, 154791 (2020).
 10. Pais, P. *et al.* Transcriptome-wide differences between Saccharomyces cerevisiae and Saccharomyces cerevisiae var. boulardii: clues on host survival and probiotic activity based on promoter sequence variability. *Genomics* **113**, 530-539 (2021).
 11. Cascio, V. *et al.* S-Adenosyl-L-methionine protects the probiotic yeast, Saccharomyces boulardii, from acid-induced cell death. *BMC Microbiology* **13**, 35 (2013).
 12. Guslandi, M., Mezzi, G., Sorghi, M. & Testoni, P. A. Saccharomyces boulardii in maintenance treatment of Crohn's disease. *Digestive Diseases and Sciences* **45**, 1462-1464 (2000).
 13. Garcia Vilela, E. *et al.* Influence of Saccharomyces boulardii on the intestinal permeability of patients with Crohn's disease in remission. *Scandinavian Journal of Gastroenterology* **43**, 842-848 (2008).
 14. Bourreille, A. *et al.* Saccharomyces boulardii does not prevent relapse of Crohn's disease. *Clinical Gastroenterology and Hepatology* **11**, 982-987 (2013).
 15. Oh, G. M. *et al.* Changes in the Crohn's Disease Activity Index and safety of administering Saccharomyces boulardii in patients with Crohn's disease in clinical remission: a single hospital-based retrospective cohort study. *The Korean Journal of Gastroenterology* **76**, 314-321 (2020).
 16. Thomas, S., Metzke, D., Schmitz, J., Dorffel, Y. & Baumgart, D. C. Anti-inflammatory effects of Saccharomyces boulardii mediated by myeloid dendritic cells from patients with Crohn's disease and ulcerative colitis. *American Journal of Physiology-Gastrointestinal and Liver Physiology* **301**, G1083-G1092 (2011).
 17. Hoffmann, T. W. *et al.* Microorganisms linked to inflammatory bowel disease-associated dysbiosis differentially impact host physiology in gnotobiotic mice. *The ISME Journal* **10**, 460-477 (2016).
 18. Audy, J., Mathieu, O., Belvis, J. & Tompkins, T. A. Transcriptomic response of immune signalling pathways in intestinal epithelial cells exposed to lipopolysaccharides, Gram-negative bacteria or potentially probiotic microbes. *Beneficial Microbes* **3**, 273-286 (2012).
 19. Vinayagamoorthy, K., Pentapati, K. C. & Prakash, H. Epidemiology of Saccharomyces fungemia: a systematic review. *Medical Mycology* **61**, myad014 (2023).
 20. Poncelet, A., Ruelle, L., Konopnicki, D., Miendje Deyi, V. Y. & Dauby, N. Saccharomyces cerevisiae fungemia: risk factors, outcome and links with S. boulardii-containing probiotic administration. *Infectious Diseases Now* **51**, 293-295 (2021).
 21. Wombwell, E., Bransteitter, B. & Gillen, L. R. Incidence of Saccharomyces cerevisiae fungemia in hospitalised patients administered Saccharomyces boulardii probiotic. *Mycoses* **64**, 1521-1526 (2021).
 22. Plein, K. & Hotz, J. Therapeutic effects of Saccharomyces boulardii on mild residual symptoms in a stable phase of Crohn's disease with special respect to chronic diarrhea: a pilot study. *Zeitschrift fur Gastroenterologie* **31**, 129-134 (1993).
 23. Vancamelbeke, M. *et al.* Genetic and transcriptomic bases of intestinal epithelial barrier dysfunction in inflammatory bowel disease. *Inflammatory Bowel Diseases* **23**, 1718-1729 (2017).