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# SYNERGISTIC EFFECTS OF DIETARY POLYPHENOLS AND PHYSICAL ACTIVITY ON IRRITABLE BOWEL SYNDROME: A REVIEW OF GUT BARRIER FUNCTION, INFLAMMATION AND MICROBIOTA MODULATION

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**ABSTRACT**

Irritable bowel syndrome (IBS) is a common disorder of gut/brain interaction characterised by abdominal pain and altered bowel habits with a substantial burden on quality of life. Increasing evidence implicates disrupted gut barrier function, low-grade mucosal inflammation and microbiota shifts as key pathophysiological mechanisms. Dietary polyphenols possess anti inflammatory, antioxidant and prebiotic activity. A growing number of randomised controlled trials demonstrate that polyphenol based nutraceuticals improve IBS symptoms and quality of life. Similarly, increasing physical activity appears to reduce global IBS symptoms, even though the certainty of the evidence is very low. However, mechanistic validation remains limited. Most trials prioritise patient reported outcomes over integrated multi domain biomarker phenotyping and no IBS study has directly tested whether combined polyphenol and physical activity interventions produce synergistic effects. This review integrates evidence on polyphenols and physical activity in IBS, focusing on gut barrier function, inflammation and microbiota modulation. The findings show that inflammatory modulation (CRP, IL-6, TNF-α, GM-CSF) is the most consistently supported mechanistic domain, while barrier proxies (zonulin, I-FABP) often remain unchanged despite clinical benefit. Convergent pathways from mechanistic exercise studies and animal models suggest biological plausibility for synergy, but evidence based testing in IBS is lacking. To determine whether combining lifestyle strategies produces synergistic, clinically meaningful benefits in IBS, future factorial trials must include interaction testing. They should also integrate coordinated measurements of clinical, barrier, inflammatory and microbiome endpoints.

**KEYWORDS**

Irritable Bowel Syndrome, Polyphenols, Physical Activity, Gut Barrier, Inflammation, Microbiota, Synergy

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## Introduction

Irritable bowel syndrome (IBS) is one of the most prevalent functional gastrointestinal disorders, affecting an estimated 10–15% of the global population. It is characterised by recurrent abdominal pain associated with altered bowel habits (diarrhoea, constipation or a mix of both). It imposes a substantial burden on quality of life, healthcare utilisation and work productivity [1,2]. Despite its high prevalence, the pathophysiology of IBS is incompletely understood and is now recognised as a complex, multifactorial disorder of gut/brain interaction. Contributing mechanisms include visceral hypersensitivity, altered motility, low-grade mucosal immune activation, intestinal barrier dysfunction and perturbations of the gut microbiota and its metabolic outputs. The heterogeneity of clinical presentation and underlying biology has obstructed the development of universally effective therapies and many patients continue to experience persistent symptoms despite conventional pharmacological and dietary management [3,4]. Over the past decade, research has increasingly focused on the interaction between the gut barrier, the microbiota and the immune system as central to IBS pathogenesis. Compelling evidence indicates that a subset of IBS patients exhibit increased intestinal permeability, which may allow antigens to trigger mucosal immune responses [4,5]. Concurrently, alterations in the composition and function of the gut microbiota, including changes in short chain fatty acids (SCFAs) and phenolic derived metabolites, have been documented in IBS and are thought to influence intestinal barrier integrity and immune tone [6,7]. Low grade mucosal inflammation, reflected by elevated pro inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), has also been reported. Although findings are inconsistent across studies l. These observations have led to the hypothesis that interventions with the capacity to simultaneously improve barrier function, modulating the microbiota and reducing inflammation could offer synergistic benefits in IBS. Among the lifestyle strategies proposed for IBS, dietary polyphenols and physical activity have gained attention for their potential to target these interconnected pathways. Polyphenols are a large class of bioactive compounds found in fruits, vegetables, cocoa, tea and

other plant-based foods. They are known to possess anti inflammatory, antioxidant and prebiotic like properties. A growing number of randomised controlled trials have examined their efficacy in IBS, with encouraging results for symptom reduction and quality of life improvement [9,10,11]. However, the mechanistic evidence linking polyphenol intake to changes in gut barrier integrity, immune status or microbial metabolism in IBS remains fragmented, largely because most trials prioritise patient reported outcomes over integrated multi-domain biomarker assessment. Similarly, physical activity has been recommended as an adjunctive therapy for IBS. Systematic reviews suggest that increasing activity may improve global symptoms, yet the certainty of evidence is very low and studies seldom include endpoints that directly evaluate barrier function, inflammatory markers or the microbiota [12,13]. Moreover, the potential synergistic effect of combining polyphenol consumption with physical activity, an interaction that could theoretically amplify benefits through overlapping mechanisms, has not been systematically explored in IBS populations. To address this gap, the present review reviews the available evidence on dietary polyphenols and physical activity in IBS, with a specific focus on their effects on gut barrier function, inflammation, and microbiota modulation. We first summarise clinical and mechanistic findings from polyphenol related RCTs, followed by an analysis of physical activity interventions. We then analyse studies that have measured barrier, inflammatory and microbial endpoints in exercise polyphenol contexts, including mechanistic human trials and animal models, to establish the biological likelihood of synergy. Finally, we identify critical knowledge gaps and propose a framework for future factorial trials that could definitively test whether combined polyphenol and physical activity strategies produce synergistic, clinically meaningful benefits in IBS.

## Methodology

This narrative review was conducted to synthesise available evidence on dietary polyphenols and physical activity in relation to gut barrier function, inflammation, and microbiota modulation in IBS. A systematic search of PubMed (including MEDLINE) was performed up to March 2026 using the following keywords and their combinations: “irritable bowel syndrome”, “IBS”, “polyphenols”, “flavonoids”, “tannins”, “curcumin”, “ellagic acid”, “synbiotic”, “physical activity”, “exercise”, “gut barrier”, “intestinal permeability”, “zonulin”, “I-FABP”, “inflammation”, “cytokines”, “microbiota”, “short-chain fatty acids”, and “SCFAs”. Additional records were identified through reference lists of included articles and relevant systematic reviews. Eligible studies were randomised controlled trials (RCTs), systematic reviews, meta-analyses, mechanistic human trials and animal studies that assessed at least one outcome related to symptom severity, quality of life, gut barrier function, inflammatory markers, or microbiota composition/function in IBS or in exercise-polyphenol contexts relevant to IBS pathophysiology. Only English-language articles with available full-text or detailed abstracts were considered. Studies were excluded if they focused exclusively on inflammatory bowel disease without an IBS component or if they reported only preclinical findings without relevance to human IBS. Data extraction and synthesis were performed narratively, focusing on clinical efficacy, mechanistic endpoints and the potential for synergy between polyphenols and physical activity.

## Results

### Polyphenols and IBS

Across IBS-focused studies, polyphenol related interventions show clinically relevant improvements in symptom severity and disease specific quality of life (QoL). At the same time, mechanistic evidence linking these benefits to a unified pathway such as microbiota modulation, barrier reinforcement and reduced inflammation, remains uneven. It is largely because most trials prioritise patient-reported outcomes over multidomain biomarker phenotyping. Recent syntheses demonstrate high heterogeneity in examined composition, duration and endpoints, which complicates inference about the most effective polyphenol classes and their mechanisms of action [3,4]. A systematic review and meta-analysis of biophenol rich nutraceuticals in inflammatory gastrointestinal conditions and IBS reported improved gastrointestinal symptom scores compared with placebo or usual care with no increase in adverse events. However, biomarker improvements such as C-reactive protein (CRP) and malondialdehyde were primarily seen in ulcerative colitis/Crohn’s disease subgroups and IBS-specific mechanistic readouts were not a central focus of this study [2]. Several IBS-specific randomised controlled trials (RCTs) demonstrate symptom or QoL benefits over short timeframes. A double-blind RCT of a curcumin fennel essential oil combination in 121 adults with mild-to-moderate IBS (IBS-Severity Scoring System, IBS-SSS 100–300) reported a significantly larger

relative reduction in IBS-SSS after 30 days compared with placebo, along with a higher proportion of symptom-free participants and improvements across IBS-QoL domains. The intervention consisted of two capsules twice daily, each containing a fixed combination of curcumin and fennel essential oil. [9]. A larger randomised, double blind, placebo controlled trial tested a quebracho + chestnut tannin complex (480 mg/day) for 56 days in 156 IBS patients (79 female, 77 male, 18–70 years), stratified by subtype (IBS-C, IBS-D, IBS-M). The active arm showed a clinically meaningful reduction in IBS-SSS, whereas the placebo group showed no comparable improvement. Parallel improvements were observed for IBS-QoL and the Gastrointestinal Quality of Life Index (GIQLI). Baseline imbalances in IBS-QoL between groups suggest that adjusted analyses would be valuable in future trials [10]. Smaller RCTs add biochemical engagement signals, particularly for inflammation related endpoints. Ellagic acid (180 mg/day for 8 weeks) reduced CRP and interleukin-6 (IL-6), improved oxidative stress indices (decreased malondialdehyde, increased total antioxidant capacity) and enhanced IBS-QoL [8]. A randomised trial in women with IBS tested soy isoflavones (40 mg/day) and cholecalciferol (50,000 IU every 15 days), alone and in combination, for six weeks. Treatment groups showed reductions in plasma inflammatory markers (a panel that included several cytokines) and fecal protease activity (a permeability-related readout) compared with placebo, with no significant effect on antioxidant status. The trial also reported improved gastrointestinal symptoms. [5]. The mechanistically richest IBS RCT is a three-arm, double-blind, placebo-controlled synbiotic/polyphenol trial over 2 months. The complete formulation combined partially hydrolysed guar gum (PHGG, 5 g/day), a defined probiotic blend (Bifidobacterium animalis subsp. lactis BLC1, B. lactis UABla, B. animalis subsp. lactis BS01 and Saccharomyces boulardii), a polyphenol-rich extract from Aronia melanocarpa and Sambucus nigra. Outcomes included IBS-QoL, serum cytokines (IL-6, IL-8, TNF-α, GM-CSF), barrier adjacent markers (serum intestinal fatty acid-binding protein, I-FABP, stool zonulin) and stool short chain fatty acids (SCFAs). QoL improved most consistently in the complete formulation arm, with the largest improvement in the dysphoria area. TNF-α and GM-CSF decreased significantly in the supplemented arms, while stool zonulin and serum I-FABP did not show significant change. This pattern supports a model in which a multicomponent synbiotic/polyphenol strategy can engage immune tone and fermentation outputs (SCFAs) in IBS, even when common permeability proxies remain unchanged [11]. Overall, IBS polyphenol trials indicate that multiple nutraceutical strategies can improve symptoms and QoL over short time frames. The most consistently supported mechanistic domain is inflammatory modulation (CRP/IL-6, TNF-α, GM-CSF, with more limited but suggestive evidence for functional microbiota outputs (SCFAs) and inconsistent support for barrier restoration as measured by zonulin or I-FABP type markers.

**Physical Activity and IBS**

Evidence suggests that increasing physical activity can reduce IBS symptom burden, but diversity in exercise interventions and the limited inclusion of endpoints that directly assess barrier, immune, or microbiota function restrict conclusions about mediation. A Cochrane review synthesising 11 RCTs (622 participants) concluded that physical activity may improve global IBS symptoms compared with usual care, but with very low certainty due to risk of bias, inconsistency and imprecision [12]. Within this evidence base, the largest IBS RCT randomised 102 participants to an intervention supporting a moderate increase in physical activity versus usual care. The intervention was an unsupervised home based programme incorporating exercise counselling, regular telephone contact and a cycle test at six weeks. The trial reported improved IBS-SSS with physical activity, with directionally consistent improvement in the analysis of all randomised subjects and a lower proportion of clinically significant symptom worsening in the intervention group compared with controls (8% vs 23%). Measures of stool form (Bristol Stool Scale), stool frequency and oroanal transit time did not show clear differences, underscoring that symptom improvement can occur without measurable changes in these bowel habit metrics [13]. A second RCT evaluating an exercise consultation intervention for 12 weeks (Rome II IBS) provided a constipation-oriented signal. The trial reported no differences in IBS-QoL between groups at follow up, but improved constipation symptoms in the exercise group versus usual care and higher exercise participation at follow up. Recruitment feasibility was demonstrated, but uptake was low, likely constraining power and representativeness [14]. A long term follow up study of a prior physical activity intervention reported durable improvements at a median of 5.2 years in IBS-SSS and psychological symptom dimensions, alongside increased self-reported physical activity from baseline to follow up (3.2 to 5.2 hours/week) [15]. Across trials, physical activity appears potentially beneficial for IBS symptoms, but mechanistic co-measurement is sparse. IBS activity trials support a clinical signal for movement, but they do not directly test whether the clinical change is mediated by barrier, inflammation or microbiota pathways that polyphenols may also influence.

**Gut Barrier Function**

Objective gut barrier evaluation is most comprehensive in mechanistic exercise settings and in many IBS synbiotic/polyphenol RCT. Within IBS, the synbiotic/polyphenol trial used stool zonulin and serum I-FABP, but found no significant changes across groups or over time, despite improved QoL and reductions in TNF-α and GM-CSF. The authors highlight individual variability and assay limitations for faecal zonulin, supporting cautious interpretation of null barrier-marker findings in IBS RCTs [11]. In the isoflavone/cholecalciferol IBS trial, fecal protease activity decreased in active groups relative to placebo, presented as an improvement in a marker of gut barrier function, though classical permeability tests were not reported [5]. In non IBS exercise/polyphenol trials, barrier endpoints are operationalised using functional permeability tests and injury markers. In a crossover trial with 12 recreational cyclists, participants consumed high-flavonoid (490 mg/day) or low-flavonoid (5 mg/day) dairy-based beverages for 15 days per condition, then performed a 45-min cycling session at 70% $VO_2$max plus a 15-min maximal effort time trial. Plasma I-FABP assessed injury and urinary sugar excretion (lactulose/mannitol ratio) assessed permeability. No between-condition differences were detected for permeability or injury, suggesting that short term flavonoid dosing in this matrix did not buffer exercise induced gastrointestinal barrier stress at this intensity/duration [16]. In contrast, a study in elite football athletes supplemented with dark chocolate (40 g/day, >85% cocoa) over 30 days of training showed that the control arm had increases in lipopolysaccharide (LPS), zonulin, and occludin, whereas dark chocolate prevented these changes and yielded lower endline values relative to controls. In vitro experiments in the same paper showed polyphenol extracts improving occludin expression and reducing zonulin under LPS challenge, supporting barrier protective effects under endotoxin and TLR4-mediated stress [17]. A further human mechanistic trial using a polyphenol and sugar rich diluted cloudy apple juice matrix reported that, after ultra endurance running, the sugar-only drink was associated with less favourable endotoxin recovery compared with the polyphenol containing drink, suggesting an effects on barrier function [18]. Animal models allow more comprehensive barrier phenotyping. In mice, high intensity exercise training induced increased gut permeability (assessed by FITC-dextran), elevated plasma I-FABP, and reduced tight junction protein expression (ZO-1, occludin, claudin-1). Resveratrol (15 mg/kg/day for 28 days) attenuated these exercise-induced changes [19]. In rats, a cocoa enriched diet (10% cocoa powder) partially attenuated alterations induced by a single session of intensive exercise, affecting barrier associated gene expression including occludin, claudins and ZO proteins [20]. Overall, gut barrier evidence indicates that IBS-specific polyphenol trials can show QoL and cytokine benefits without changes in commonly used barrier proxies, whereas exercise/polyphenol studies show both null and protective patterns depending on population, matrix, dose and stress context.

**Inflammation**

Inflammation related outcomes are more commonly reported than direct permeability tests across IBS and exercise/polyphenol studies, but often remain limited to small cytokine panels and various sampling windows. In IBS, ellagic acid reduced CRP and IL-6 while improving QoL over eight weeks [8]. In the synbiotic/polyphenol RCT, TNF-α and GM-CSF decreased significantly in supplemented arms over two months, while stool zonulin and I-FABP did not shift significantly, illustrating a dissociation between cytokine modulation and these barrier markers [11]. In the soy isoflavone/vitamin D trial, plasma inflammatory markers (including IL-6 and TNF-α) and fecal protease activity decreased in treatment groups compared with placebo, without effects on antioxidant status. This positions fecal protease activity as a permeability-related functional readout that may be more responsive than zonulin/I-FABP measures in some IBS contexts [5]. Beyond cytokines, mucosal immune activation was profiled in a pilot multicentre RCT of palmitoylethanolamide/polydatin. The trial did not significantly change mast cell counts in IBS biopsies, but improved abdominal pain severity, suggesting that symptom improvements may occur without measurable shifts in selected immune endpoints [1]. In exercise mechanistic contexts, inflammatory readouts are central and often correlate with barrier biomarkers. In the mouse resveratrol model, exercise induced increases in TNF-α, IFN-γ, and IL-6 with decreases in IL-10, and resveratrol attenuated this pro inflammatory shift [19]. In recreational cyclists, IL-6, IL-10, and TNF-α exhibited time effects after exercise, but flavonoid supplementation did not modify these cytokine responses [16]. In the endurance/ultra marathon study, IL-6 and CD14 were measured with CD14 levels influenced by the drink composition and endotoxin recovery influenced by the context, which was related to immune activation [18]. In rats, a cocoa diet decreased production of pro inflammatory cytokines (IL-1β, IL-6, TNF-α) and attenuated exercise induced mucosal immune alterations [20]. Meta analytic synthesis across IBS and other inflammatory gastrointestinal conditions reported symptom improvements under biophenol rich nutraceuticals and highlighted CRP improvements in

ulcerative colitis/Crohn's disease subgroups. However, IBS specific inflammatory biomarker conclusions remain limited by heterogeneity and reporting gaps [2]. A broader review emphasises inconsistency in inflammation biomarker results and limited mechanistic endpoint coverage for permeability and oxidative stress in IBS polyphenol interventions [4].

**Microbiota Modulation**

Microbiota modulation evidence relevant to IBS, physical activity and polyphenols appears in two main forms: direct microbiota profiling and metabolomics in IBS dietary provocations and shifts in microbiota composition and function in animal models that combine dietary polyphenols with exercise related stressors. Within IBS, a double blind randomised crossover intervention testing FODMAP and gluten provocations reported that FODMAPs altered faecal microbiota (including enrichment of saccharolytic taxa such as Bifidobacterium and Lactobacillus), increased faecal and plasma SCFAs and increased plasma phenolic-derived metabolites and 3-indolepropionate. Correlations between molecular features and IBS symptoms were generally weak [6]. A related IBS crossover metabolomics analysis similarly reported that FODMAP exposure increased bile-acid and phenolic/tryptophan-related metabolite signatures, including 3-indolepropionic acid, with weak associations to abdominal pain and QoL [7]. These IBS provocation studies establish that dietary fermentable substrates can shift phenolic derived metabolite exposure and microbiota linked metabolic outputs in IBS, reinforcing the concept that host exposure to phenolic metabolites depends on microbial metabolism. Among IBS polyphenol interventions, the strongest functional microbiota readout is the synbiotic/polyphenol RCT, which reported higher stool SCFAs in the polyphenol containing arm relative to placebo, aligning with improved QoL and reduced TNF-α/GM-CSF. Although microbiota sequencing was not performed, SCFAs provide functional evidence consistent with altered fermentation ecology under combined fibre/probiotic/polyphenol exposure [11]. In animal models, exercise and polyphenols demonstrate convergent and sometimes distinct effects on microbiota composition and function. In high fat diet mice, exercise training (50 km/week) and resveratrol supplementation (4 g/kg food) altered microbiota composition through different abundance strata, with changes observed independent of a systemic inflammatory marker (serum amyloid A) [21]. In mice on high fat/high sugar diet, exercise increased microbial richness and exercise plus genistein (600 mg/kg diet) altered community structure, including genus level differences such as Ruminococcus abundance, while preventing IL-6 elevation [22]. In Wistar rats, cocoa diet exposure (10% cocoa powder) increased SCFA production and partially attenuated exercise induced alterations in microbiota and mucosal immunity after an intensive exercise session [20]. Taken together, the microbiota evidence suggests that IBS diets can rapidly shift microbiota linked metabolites including phenolic derived compounds. Exercise and polyphenol exposures can modify microbiota composition and function in animal models and in IBS functional readouts (SCFAs). However, IBS trials rarely measure microbiota composition directly.

## Discussion

### Integration of findings

The evidence base supports a clinically relevant signal for both polyphenol related nutraceuticals and increased physical activity as additional strategies in IBS symptom management, but it also highlights a persistent gap between clinical efficacy reporting and mechanistic validation. Polyphenol related RCTs frequently demonstrate improvements in IBS-SSS and IBS-QoL (e.g. curcumin-fennel, tannin complex, ellagic acid), yet most avoid coordinated measurement across barrier, immune and microbiota areas. This gap matters, because IBS is a multifactorial disorder of gut brain interaction. Low grade mucosal immune activation, modified permeability in subgroups and microbiota metabolite shifts plausibly contribute to symptoms. However, the relative contributions vary by phenotype and may require stratified models rather than single mechanism explanations [3,4]. Within IBS, the 2-month synbiotic/polyphenol RCT is particularly informative, because it implements an integrated approach and measures cytokines, SCFAs and barrier adjacent proxies alongside QoL. This pattern suggests that QoL improvements and immunomodulation (TNF-α, GM-CSF reductions) can be measured in relatively small IBS samples and that functional microbial metabolites (SCFAs) may shift in parallel. At the same time, the absence of changes in stool zonulin and serum I-FABP indicates that commonly used barrier proxies may be less sensitive to detect treatment related barrier changes in IBS, at least over 2 months and at the tested doses [11]. For physical activity, evidence indicates that modest increases in activity may improve IBS symptom severity compared with usual care. The overall certainty of the evidence is very low and studies generally lack endpoints, that assess underlying biological pathways [12]. In the largest RCT, symptom improvements appear to occur despite limited change in stool form, frequency and transit time measures. This suggests mediation through gut–brain pathways (stress physiology, central pain processing,

autonomic tone), inflammatory tone or microbiota related mechanisms that were not directly measured [13]. The IBS dietary provocation literature adds an important nuance, molecular shifts in microbiota and metabolite can be solid and systematic, yet they are weakly coupled to short-term symptom variation. FODMAP-based provocations increase phenolic derived metabolites, while shifting faecal microbiota and SCFA patterns, but correlations to symptoms are generally weak [6,7]. These findings suggest that mechanistic changes may be necessary but not sufficient for symptom improvement or that short provocation windows are too brief to observe symptom patterns that depend on longer term mucosal adaptation, immune modulation, or neurosensory recalibration. This disconnection also warns against overinterpreting biomarker changes as clinical benefit in isolation.

**Synergy between polyphenols and physical activity**

Direct evidence for synergy, defined as an interaction where combined polyphenol exposure and physical activity yields effects beyond additivity, has not yet been established in IBS populations. IBS polyphenol trials generally do not prescribe or quantify physical activity change in a way that enables effect modification analyses. IBS physical activity trials rarely quantify background polyphenol intake or include standardised polyphenol supplementation. Therefore, claims of synergy remain speculative from a biological standpoint but have not been empirically validated in IBS RCTs. Nevertheless, the potential for synergy is supported by convergent pathways across the datasets. Both interventions likely affect microbial metabolism. In IBS, the synbiotic/polyphenol RCT reports higher stool SCFAs in supplemented arms, indicating that combined fibre/probiotic/polyphenol exposure can shift fermentation outputs. In animal models, exercise can reshape microbial richness and community structure [21, 22]. These microbial changes can influence epithelial energy balance, mucosal immune tone, and neuroactive metabolite signalling. All of these factors represent plausible mediators of IBS symptoms. Synergy is also potentially at the level of immune tone. Several IBS polyphenol patterns align with inflammation downshifts: ellagic acid reduced CRP/IL-6, the synbiotic/polyphenol formulation reduced TNF-α and GM-CSF and the soy isoflavone/vitamin D trial reported reductions in inflammatory markers and fecal protease activity compared with placebo [5,8,11]. Physical activity is widely associated with improved inflammatory profiles in other contexts, but IBS-specific evidence remains low certainty and is missing biomarker co-measurement, which is a key design gap that future trials should address. Barrier resilience under stress represents another plausible synergy node. However, the evidence demonstrates strong context dependence. In elite athletes, dark chocolate prevented training associated increases in LPS, zonulin, and occludin. In vitro data also support barrier protection under LPS challenge. This suggests that polyphenol rich products can buffer barrier and innate activation signals under certain conditions [17]. In contrast, in recreational cyclists, a 15 day high flavonoid beverage did not reduce exercise induced injury or permeability measured by urinary sugars and I-FABP [16]. This divergence implies that polyphenol effects may depend on matrix, dose, exposure duration, baseline phenotype, and the magnitude and type of stressor. It also suggests that synergy with exercise is not guaranteed and should be tested, not assumed.

**Limitations**

Several limitations constrain inference. First, many studies do not report key methodological details required for mechanistic synthesis and detailed barrier marker results in the synbiotic/polyphenol IBS RCT [11]. These missing items limit cross-trial comparability and prevent quantitative mapping of response relationships. Second, mechanistic outcomes are more common in non IBS exercise stress studies and animal models, than in IBS clinical trials, creating a translational gap. Biomarkers, such as zonulin, occludin, LPS, and I-FABP are informative for barrier physiology, but their predictive value for IBS symptom improvement and their baseline distribution across IBS subtypes are not well established in the trials included here. Third, polyphenol interventions in IBS are varied (tannins, curcumin-containing combinations, ellagic acid, isoflavones, synbiotic blends), often multi-component and therefore difficult to attribute to specific polyphenol classes or to compare directly across compounds and formulations [9,10,11]. Fourth, microbiota data are strongest in IBS provocation studies and animal models [6,7,20,21,22], but are weakly linked to symptom changes and are seldom integrated with permeability and cytokine panels within the same IBS RCT. Finally, evidence for synergy is indirect. The reviewed IBS trials do not test combined polyphenol and physical activity interventions. As a result, synergy conclusions must remain hypothetical and framed as testable propositions rather than established clinical recommendations.

**Implications and future research**

Clinically, the evidence supports two conservative implications. First, selected polyphenol containing nutraceuticals can meaningfully improve IBS-SSS and IBS-QoL over short time frames and some interventions involve readouts related to inflammation or fermentation (CRP/IL-6, TNF-α/GM-CSF, SCFAs). Second, increasing physical activity may improve global IBS symptoms, but evidence remains uncertain and intervention dose should be personalised, with careful attention to IBS subtype and patient tolerability [12]. To move from probability to demonstrated synergy, the field needs factorial IBS trials with interaction testing and aligned measurement across clinical, barrier, inflammatory, and microbiome/metabolome domains. Mechanistic endpoints should include: functional permeability testing (e.g., urinary sugar excretion),a multi-marker barrier panel rather than zonulin alone, inflammatory panels timed to capture both basal tone and post stressor responses and microbiome sequencing plus targeted metabolomics, (including SCFAs and phenolic metabolites), to connect exposure to function. The synbiotic/polyphenol IBS trial demonstrates the practicality of measuring zonulin, I-FABP, cytokines and SCFAs in IBS [11]. While the IBS provocation studies demonstrate feasibility of deep microbiota profiling [6,7]. Exercise stress studies and animal models define candidate mechanistic biomarkers and plausible timing windows to inform sampling schedules and mechanistic hypotheses [17,18,19]. Finally, future trials should incorporate IBS subtype stratification (IBS-C/IBS-D/IBS-M), baseline barrier phenotype (if measurable) and dietary control to reduce confounding by fermentable carbohydrates, that can independently shift microbiota metabolites and symptoms. Such designs would allow the field to move from plausible mechanistic convergence to demonstrated, clinically meaningful synergy.

**Conclusions**

This review synthesises the available evidence on dietary polyphenols and physical activity as potential adjunctive strategies in IBS with a particular focus on gut barrier function, inflammation and microbiota modulation. The findings support a clinically relevant signal for both interventions, yet they also reveal a substantial gap between documented symptom improvements and validated mechanistic pathways. In summary, several key conclusions can be highlighted. First, polyphenol based nutraceuticals consistently improve IBS symptom severity and quality of life over short time frames. These include curcumin-fennel, tannins, ellagic acid and synbiotic formulations. The most reproducible mechanistic evidence points to modulation of inflammatory markers. These include C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and GM-CSF. Second, increasing physical activity also appears to reduce global IBS symptoms, but the evidence is of very low certainty and lacks integration with barrier, immune or microbiota outcomes. Third, the most mechanistically informative IBS study (synbiotic/polyphenol RCT), demonstrates that QoL gains and cytokine reductions can occur without measurable changes in commonly used barrier proxies like zonulin and I-FABP, while increases in stool SCFAs suggest functional shifts in microbial fermentation. Fourth, despite the biological plausibility of synergy between polyphenols and exercise, no IBS trial has directly tested this interaction and findings from exercise/polyphenol studies in athletes and recreational cyclists indicate that such synergy cannot be assumed. The key message is that while both dietary polyphenols and physical activity offer promising avenues for IBS management, the field must move beyond symptom only designs toward integrated mechanistic frameworks. Achieving this will require factorial trials that combine standardised polyphenol interventions with structured physical activity, incorporating aligned measurements across clinical, barrier, inflammatory and microbiome areas.

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