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SAFETY AND TOLERABILITY OF PROBIOTIC AND SYNBIOTIC SUPPLEMENTATION DURING CHEMOTHERAPY

Pooja Shelat[1], Rakesh M Rawal[*2]

[1]Department of Life Science, Food Science and Nutrition, Gujarat University, Ahmedabad-380009, Gujarat, India
Ph.D. Research Scholar
Pdshelat91@gmail.com
+91 9714785148

[2] Department of Medical Biotechnology, Gujarat Biotechnology University, Gandhinagar -382355, Gujarat, India
Head & Professor
*Corresponding author: rakeshrawal.gu@gmail.com
+91 9925244855

Abstract

Chemotherapy, while essential in cancer treatment, often causes gastrointestinal (GI) toxicity due to its damaging effects on the gut epithelium and disruption of the microbiota. Probiotic and synbiotic supplementation has emerged as a promising adjunct to alleviate these side effects by modulating gut microbiota, enhancing mucosal integrity, and reducing inflammation. This review synthesizes current evidence on the safety and tolerability of probiotics and synbiotics during chemotherapy. Clinical trials have demonstrated reductions in chemotherapy-induced diarrhea, mucositis, and abdominal discomfort, particularly with strains like Lactobacillus *and* Bifidobacterium*. Synbiotics offer additional benefits by enhancing probiotic survival and activity through prebiotic synergy. However, safety concerns remain, especially in immunocompromised patients, with rare reports of probiotic-associated infections. Most adverse effects are mild and transient, such as bloating or flatulence. Guidelines recommend cautious use, emphasizing strain specificity, product quality, and individualized risk assessment. Despite encouraging outcomes, challenges such as study heterogeneity, lack of standardized protocols, and product variability persist. Future directions include large-scale trials, personalized supplementation based on microbiome profiling, mechanistic studies, and development of regulatory standards. With appropriate clinical oversight, probiotics and synbiotics hold potential as safe, effective, and patient-friendly interventions to support cancer therapy.*

Keywords: *Probiotics, Synbiotics, Chemotherapy, GI toxicity, Gut microbiota, Safety, Tolerability*

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, with chemotherapy serving as a cornerstone in the treatment of numerous malignancies (Sung et al., 2021). While chemotherapy is effective in targeting rapidly dividing cancer cells, its non-specific cytotoxic effects often extend to healthy tissues, particularly those of the gastrointestinal (GI) tract. The resulting damage to the gut epithelium and disruption of the intestinal microbiota can lead to a spectrum of adverse effects, including nausea, vomiting, diarrhea, abdominal pain, and mucositis (Sonis, 2009). Approximately 40-100% of cancer patients undergoing chemotherapy experience GI toxicities that significantly impair quality of life and may necessitate treatment delays or dose reductions, ultimately affecting therapeutic outcomes (Dahlgren et al., 2021).

The human gut microbiota, comprising trillions of microorganisms, plays a pivotal role in maintaining intestinal homeostasis, modulating immune responses, and protecting against pathogenic colonization (Thursby & Juge, 2017). Chemotherapy-induced changes in the gut microbiome, such as reductions in beneficial bacterial species and increases in opportunistic pathogens, can exacerbate GI toxicity and increase the risk of infection (Zwielehner et al., 2011). Consequently, strategies aimed at preserving or restoring a healthy gut microbiota have garnered increasing attention as adjunctive therapies in oncology.

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts (Hill et al., 2014), and prebiotics, non-digestible food ingredients that selectively stimulate the growth and activity

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of beneficial gut bacteria (Gibson et al., 2017), have been widely studied for their potential to mitigate chemotherapy-associated GI toxicity. Synbiotics, which combine probiotics and prebiotics, are designed to synergistically enhance the survival and colonization of beneficial bacteria within the gut (Markowiak & Śliżewska, 2017). These interventions are thought to exert their beneficial effects through multiple mechanisms, including reinforcement of the intestinal barrier, modulation of local and systemic immune responses, and competitive exclusion of pathogenic microorganisms (Wieërs et al., 2020).

Despite the growing body of evidence supporting the use of probiotics and synbiotics in various clinical settings, concerns persist regarding their safety and tolerability, particularly in immunocompromised patients such as those receiving chemotherapy. The risk of probiotic-associated infections, although rare, has been documented in case reports involving vulnerable populations (Sanders et al., 2016). Furthermore, the tolerability of these supplements—including the incidence of mild GI symptoms such as bloating, flatulence, and abdominal discomfort—must be carefully considered, as these side effects may compound the existing burden of chemotherapy-induced toxicity (Redman et al., 2014).

Given the increasing use of probiotics and synbiotics in supportive cancer care, a comprehensive evaluation of their safety and tolerability during chemotherapy is warranted. This review aims to synthesize current evidence on the safety profile and tolerability of probiotic and synbiotic supplementation in patients undergoing chemotherapy, with a focus on clinical outcomes, adverse events, and practical considerations for use in oncology practice.

MECHANISM OF PROBIOTIC AND SYNBIOTIC ACTION

Probiotics and synbiotics have emerged as promising adjuncts in mitigating chemotherapy-induced gut inflammation, largely due to their multifaceted mechanisms of action. Probiotics are live microorganisms that confer health benefits when administered in adequate amounts, while synbiotics combine probiotics and prebiotics, which are non-digestible dietary components that selectively stimulate the growth or activity of beneficial gut bacteria (Gibson et al., 2017; Hill et al., 2014).

The primary mechanisms by which probiotics exert their beneficial effects include competitive exclusion of pathogens, enhancement of intestinal barrier function, host immunomodulation, and neurotransmitter production. Competitive exclusion refers to the ability of probiotics to compete with pathogenic bacteria for nutrients and receptor-binding sites on the intestinal epithelium, thereby inhibiting the colonization and survival of harmful microorganisms in the gut (Plaza-Diaz et al., 2019). Probiotics also produce antimicrobial substances such as short-chain fatty acids (SCFAs), organic acids, hydrogen peroxide, and bacteriocins, which further suppress the growth of pathogenic bacteria (Markowiak-Kopeć & Śliżewska, 2020).

Enhancement of intestinal barrier function is another critical mechanism. Probiotics stimulate the synthesis of mucin proteins, which form a protective mucus layer over the gut epithelium, and regulate the expression of tight junction proteins such as occludin and claudin-1. These actions strengthen the gut barrier, preventing the translocation of pathogens and toxins from the intestinal lumen into the bloodstream—a process that is often compromised during chemotherapy (Plaza-Diaz et al., 2019).

Probiotics also modulate the host immune system by interacting with intestinal epithelial cells and immune cells such as dendritic cells, macrophages, and lymphocytes. This interaction leads to the production of anti-inflammatory cytokines (IL-10, TGF-β) and suppression of pro-inflammatory cytokines such as IL-6 and TNF-α, thereby maintaining immune homeostasis and reducing gut inflammation (Wieërs et al., 2020). Additionally, certain probiotic strains can influence the gut-brain axis by producing neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), which may affect mood, gut motility, and stress responses (Plaza-Diaz et al., 2019).

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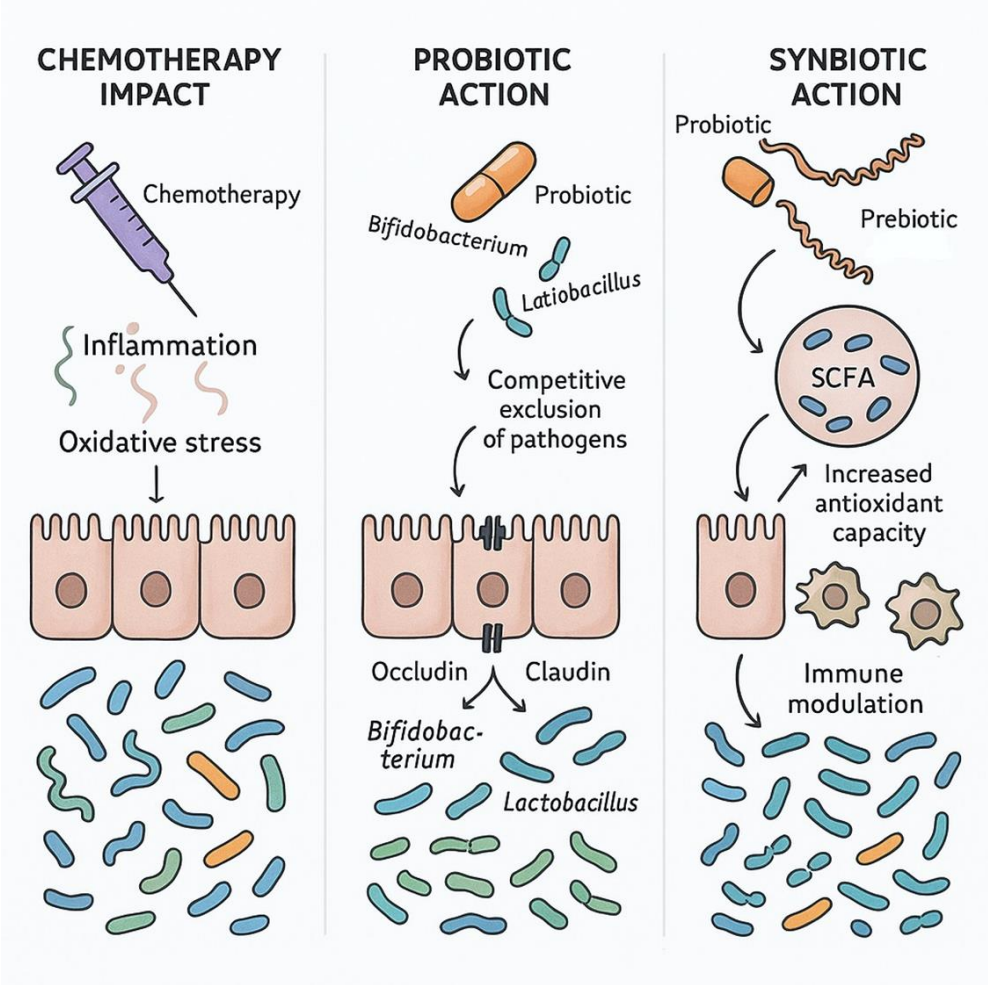

Figure 1: Mechanism of Probiotic and Synbiotic action

Synbiotics are designed to synergistically enhance the survival and activity of beneficial bacteria in the gut. The prebiotic component, which is typically a non-digestible carbohydrate like inulin or fructooligosaccharides (FOS), serves as a selective substrate for probiotic microorganisms, promoting their growth and metabolic activity (Davani-Davari et al., 2019). In the colon, prebiotics are fermented by gut bacteria, resulting in the production of SCFAs such as acetate, propionate, and butyrate. These metabolites serve as energy sources for colonocytes and exert anti-inflammatory, anti-carcinogenic, and barrier-strengthening effects (Markowiak-Kopeć & Śliżewska, 2020).

Synbiotics can act through complementary or synergistic mechanisms. In complementary synbiotics, probiotics and prebiotics independently contribute to health benefits, while in synergistic synbiotics, prebiotics enhance the viability and functionality of probiotics, resulting in greater overall effects than either component alone (Swanson et al., 2020). For example, prebiotics can increase the tolerance of probiotic bacteria to environmental stressors, thereby improving their survival and colonization in the gut (Davani-Davari et al., 2019).

Moreover, synbiotics have been shown to possess antioxidant properties. They can scavenge free radicals, increase the activity of antioxidant enzymes, chelate metal ions, and enhance host antioxidant metabolites such as glutathione and vitamins. Synbiotics combining *Lactobacillus* and *Bifidobacterium* strains with inulin or FOS have demonstrated efficacy in protecting the body from oxidative damage and improving plasma antioxidant capacity (Swanson et al., 2020).

In summary, probiotics and synbiotics act through a combination of competitive exclusion, enhancement of intestinal barrier function, immunomodulation, neurotransmitter production, and antioxidant activity. These mechanisms collectively contribute to the maintenance of gut health and the mitigation of chemotherapy-induced GI toxicity.

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CLINICAL EVIDENCE OF EFFICIENCY

The clinical application of probiotics and synbiotics during chemotherapy has garnered significant attention due to their potential to alleviate GI side effects and modulate systemic inflammation. Chemotherapeutic agents, while targeting rapidly dividing cancer cells, often damage the GI mucosa, leading to symptoms such as diarrhea, mucositis, nausea, and abdominal pain. These effects are exacerbated by chemotherapy-induced gut dysbiosis and immune dysfunction. Probiotics and synbiotics may counteract these outcomes by restoring gut microbial balance, improving mucosal integrity, and modulating immune responses (López-Gómez et al., 2023).

Probiotics in Chemotherapy: Clinical Evidence

Numerous randomized controlled trials (RCTs) have demonstrated the efficacy of probiotics in mitigating chemotherapy-induced GI toxicity. In one of the earliest and most influential studies, *Lactobacillus rhamnosus GG* was shown to significantly reduce the incidence of grade 3–4 diarrhea in colorectal cancer (CRC) patients undergoing 5-fluorouracil (5-FU)-based chemotherapy (Osterlund et al., 2007). This study also reported shorter hospital stays and reduced chemotherapy dose modifications in the probiotic group. Another meta-analysis of eight RCTs in CRC patients demonstrated that probiotics reduced abdominal distension (RR = 0.54) and radiation-induced diarrhea in patients receiving chemoradiotherapy, particularly with multi-strain formulations containing *Bifidobacterium* and *Lactobacillus* species (Yang et al., 2025).

Several clinical studies have explored the therapeutic effects of probiotics in pediatric oncology settings. For example, *Bifidobacterium breve* administered during chemotherapy was associated with beneficial modulation of the gut microbiota in children with malignancies. Another study using *Lactobacillus casei* for eight weeks post-treatment in children with leukemia suggested improvements in gut health and possibly bone mineral bioaccessibility (Šimiaková & Bielik, 2024).

Synbiotics in Chemotherapy: Clinical Evidence

Compared to probiotics, fewer clinical trials have investigated synbiotics in chemotherapy patients. However, emerging evidence suggests that synbiotics—combinations of probiotics and prebiotics—may offer synergistic benefits by enhancing the survival and activity of beneficial bacteria in the gut.

An early study evaluated a synbiotic formulation including *Lactobacillus rhamnosus GG*, *Bifidobacterium lactis*, and inulin in patients undergoing CRC surgery. The intervention improved intestinal barrier function and reduced systemic inflammation, as evidenced by decreased levels of endotoxemia and inflammatory cytokines (Rafter et al., 2007).

Patients with esophageal cancer showed improved intestinal microbiota diversity and reduced chemotherapy-induced diarrhea with synbiotic supplementation containing *Bifidobacterium breve* , *Lactobacillus casei* and galacto oligosaccharides given 2 days before the start of chemotherapy and continued during entire course of chemotherapy (Motoori et al., 2017).

Synbiotic supplementation with multistrain probiotic bacteria and FOS has been associated with significant reduction in inflammatory markers such as TNF-α and hs-CRP in breast cancer survivors. This reduction in inflammation is crucial as it can potentially improve the overall prognosis and quality of life for these patients (Raji Lahiji et al., 2021). During chemotherapy for autologous hematopoietic stem cell transplantation, synbiotic supplementation specifically *Bifidobacterium longum* and guar gum, may reduce GI toxicity, shorten the duration of severe diarrhea, and improve quality of life without severe adverse events (Mizutani et al., 2023).

Table 1: Comparision: Probiotic vs Synbiotic Interventions During Chemotherapy

Type	Strain(s)	Prebiotic (if synbiotic)	Duration	Patient Population	Reported Outcomes
Probiotic	*Lactobacillus rhamnosus* GG ($1 – 2 \times 10^{10}$ CFU)	N/A	24 weeks	Colorectal cancer (CRC)	Reduced grade 3–4 diarrhea, shorter hospital stay, fewer chemo modifications (Osterlund et al., 2007)
Probiotic	*Bifidobacterium breve* (1×10^{9} CFU)	N/A	6 weeks	Pediatric cancer patients	Improved gut microbiota modulation (Šimiaková & Bielik, 2024)
Probiotic	*Lactobacillus casei* (2×10^{10} CFU)	N/A	8 weeks	Pediatric leukemia survivors	Improved gut health, possibly enhanced bone

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					mineral bioaccessibility (Šimiaková & Bielik, 2024)
Probiotic (multi-strain)	*Lactobacillus spp.*, *Bifidobacterium spp.*	N/A	8 weeks to 6 months	CRC patients undergoing chemo-radiotherapy	Reduced radiation-induced diarrhea and abdominal distension (Yang et al., 2025)
Synbiotic	*Bifidobacterium breve* (1×10^8 CFU) *Lactobacillus casei* (1×10^8 CFU)	Galacto – oligosaccharides (15 gm/day)	6 weeks	Esophageal cancer	Reduced diarrhea, enhanced microbial diversity (Motoori et al., 2017)
Synbiotic	*Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* (c	Inulin (12 gm)	12 weeks	CRC patients post-surgery	Reduced systemic inflammation, improved intestinal barrier (Rafter et al., 2007)
Synbiotic	*Bifidobacterium longum* (5×10^9 CFU)	Guar gum (5 gm)	28 days	Hematologic malignancy (stem cell transplant)	Reduced GI toxicity, shorter duration of diarrhea, improved quality of life (Mizutani et al., 2023)
Synbiotic	*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, and Streptococcus thermophiles* (1×10^9 CFU / g)	FOS (35 mg)	8 weeks	Breast cancer survivors (overweight/obese)	Reduced inflammatory markers (TNF-α, hs-CRP) (Raji Lahiji et al., 2021)

Safety Consideration

The use of probiotics and synbiotics as supportive agents in patients undergoing chemotherapy has gained increasing attention, given their potential to alleviate GI side effects and improve quality of life. However, their safety, particularly in immunocompromised populations such as cancer patients, remains a critical area of concern. This section reviews the current evidence on safety considerations associated with probiotic and synbiotic supplementation during chemotherapy.

General Safety Profile

Probiotics are generally regarded as safe for healthy individuals, with most adverse effects being mild and self-limiting, such as abdominal discomfort, bloating, or flatulence (Hill et al., 2014). Synbiotics, which combine probiotics with prebiotics, are also considered safe, especially when using well-studied strains such as *Lactobacillus* and *Bifidobacterium* (Swanson et al., 2020). The majority of clinical trials in cancer patients have reported good tolerability, with few serious adverse events linked directly to probiotic or synbiotic use (Redman et al., 2014).

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Risk of Infection in Immunocompromised Patients

A primary safety concern in cancer patients is the risk of systemic infection caused by probiotic bacteria. Immunocompromised individuals, such as those receiving chemotherapy, are at increased risk for bacteremia, sepsis, or endocarditis due to probiotic translocation from the gut into the bloodstream. Although such events are rare, several case reports have documented instances of probiotic-associated infections in patients with underlying immune deficiencies or severe illness. For example, *Lactobacillus* and *Bifidobacterium* species, which are commonly used in probiotic formulations, have been implicated in cases of bloodstream infections in vulnerable populations (Sanders et al., 2016). Therefore, caution is advised when considering probiotic or synbiotic supplementation in patients with impaired immune function.

Adverse Effects and Reported Case Studies

Most patients tolerate probiotic and synbiotic supplementation well, with reported side effects typically limited to mild GI symptoms such as bloating, flatulence, or transient diarrhea. However, rare cases of more severe GI complications, such as bowel obstruction or severe discomfort, have been reported, particularly in patients with underlying GI disorders (Redman et al., 2014).

Allergic reactions to probiotics or synbiotics are rare but possible, particularly in individuals with known allergies to dairy products or specific microbial strains (Redman et al., 2014). Additionally, the quality and composition of commercial probiotic products can vary significantly, with some products containing microorganisms not listed on the label or potential contaminants (Sanders et al., 2016). This variability underscores the importance of selecting high-quality, well-characterized probiotic supplements for clinical use.

There is a theoretical risk that probiotic bacteria could transfer antibiotic resistance genes to other gut bacteria, particularly in the context of broad-spectrum antibiotic use, which is common in cancer patients (Sanders et al., 2016). While this risk is considered low, it remains a topic of ongoing research and regulatory scrutiny.

While probiotics and synbiotics are generally safe and well-tolerated in most cancer patients, their use during chemotherapy requires careful consideration of individual patient risk factors, particularly immune status. The risk of infection, although rare, is heightened in immunocompromised individuals, and caution should be exercised in this population. High-quality, well-characterized probiotic products should be selected, and patients should be monitored for adverse effects. Further research is needed to refine safety guidelines and identify optimal probiotic and synbiotic regimens for cancer patients undergoing chemotherapy.

Tolerability in Cancer Patients

The tolerability of probiotic and synbiotic supplementation in cancer patients, especially those undergoing chemotherapy, is a crucial aspect of their clinical utility. Tolerability refers not only to the absence of severe adverse effects but also to the acceptability and ease of use from the patient's perspective. Understanding how patients respond to these interventions is essential for determining their feasibility as supportive therapies in oncology.

Clinical trials and systematic reviews have generally reported that probiotics and synbiotics are well tolerated by cancer patients. Most studies describe mild and transient GI symptoms, such as bloating, flatulence, or mild diarrhea, which are often less severe than the GI toxicity induced by chemotherapy itself (Redman et al., 2014; Sanders et al., 2016). For instance, in a systematic review, the majority of included RCTs in CRC patients reported no significant differences in adverse events between probiotic/synbiotic and placebo groups. This suggests that these interventions do not add substantial risk or discomfort beyond what patients already experience due to cancer treatment (Kan et al., 2024).

However, tolerability can vary depending on the specific probiotic strain, dosage, and duration of supplementation. Some patients may experience mild discomfort, particularly during the initial days of supplementation, but these symptoms typically resolve without intervention. In rare cases, more severe GI symptoms, such as severe abdominal pain or bowel obstruction, have been reported, especially in patients with pre-existing GI disorders (Redman et al., 2014). Therefore, it is important for clinicians to monitor patients closely, particularly those with a history of GI complications.

The psychological impact of probiotic and synbiotic supplementation is another aspect of tolerability. Many cancer patients are willing to try complementary therapies to alleviate treatment-related side effects and improve their quality of life (Redman et al., 2014). The perception of taking a "natural" or "gut-friendly" supplement can provide psychological comfort, which may contribute to overall treatment adherence and satisfaction.

In summary, probiotic and synbiotic supplementation is generally well tolerated by cancer patients undergoing chemotherapy. Most adverse effects are mild and transient, and patient compliance is high. The ease of administration and low cost make these interventions attractive for supportive care. However, individual patient factors, such as pre-existing GI conditions, should be considered to ensure optimal tolerability and safety.

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CURRENT GUIDELINES AND RECOMMENDATIONS

The integration of probiotics and synbiotics into the supportive care of cancer patients is guided by a growing body of clinical evidence and expert consensus. However, formal guidelines are still evolving, and recommendations vary depending on the patient population, type of cancer, and specific treatment modalities.

Current expert consensus and systematic reviews suggest that probiotic and synbiotic supplementation may be beneficial for reducing GI side effects, such as diarrhea ,mucositis and faster return to normal gut function in patients, particularly those with CRC undergoing surgery or chemotherapy (Yao et al., 2024). These findings support the use of probiotics and synbiotics as adjunctive therapies in the perioperative and chemotherapy settings.

Despite these positive findings, clinical guidelines emphasize the importance of caution, particularly in immunocompromised patients. Current guidelines from the European Society for Medical Oncology (ESMO) acknowledge the potential of probiotics to reduce chemotherapy-induced diarrhea, particularly mild-to-moderate cases and in pelvic radiation patients (*Lactobacillus* strains may be considered preventive) (ESMO, 2017). However, ESMO emphasizes safety in immunocompromised patients and calls for further efficacy confirmation. While the American Society of Clinical Oncology (ASCO) lacks specific recommendations, it advocates cautious, evidence-based use of complementary therapies with rigorous risk-benefit assessments (ASCO, 2023). The International Scientific Association for Probiotics and Prebiotics (ISAPP) and other expert bodies recommend that probiotics and synbiotics should be used with caution in patients with severe immunosuppression, such as those undergoing intensive chemotherapy or stem cell transplantation (Hill et al., 2014). Collectively, these guidelines advocate a balanced approach, probiotics/synbiotics may alleviate GI toxicity but must be tailored to individual risk profiles, prioritizing safety in vulnerable groups.

Practical recommendations for clinicians include selecting high-quality, well-characterized probiotic strains with a proven safety record. The choice of strain, dosage, and duration of supplementation should be based on available clinical evidence and tailored to the individual patient's needs. For example, *Lactobacillus* and *Bifidobacterium* strains are among the most widely studied and are generally considered safe for use in cancer patients with mild to moderate immunosuppression (Hill et al., 2014; Sanders et al., 2016).

Patient education is also a key component of current guidelines. Clinicians should inform patients about the potential benefits and risks of probiotic and synbiotic supplementation, as well as the importance of using products from reputable manufacturers to minimize the risk of contamination or mislabeling (Sanders et al., 2016). Patients should be advised to report any new or worsening symptoms, particularly signs of infection, to their healthcare provider promptly.

CHALLENGES AND LIMITATIONS

Despite the promising potential of probiotics and synbiotics in the management of chemotherapy-induced gut toxicity, several challenges and limitations must be acknowledged. These factors influence the interpretation of clinical evidence, the practical implementation of these interventions, and the direction of future research.

One of the primary challenges is the heterogeneity among clinical studies. Differences in probiotic strains, dosages, intervention durations, and outcome measures make it difficult to compare results across trials and draw definitive conclusions. For example, systematic reviews have highlighted the variability in the types of probiotics used, the timing and duration of supplementation, and the criteria for assessing GI toxicity (Chen et al., 2024). This heterogeneity contributes to the risk of bias and limits the generalizability of findings.

Another limitation is the lack of large-scale, well-powered RCTs in specific cancer populations. Many existing studies have small sample sizes, which reduce their statistical power and increase the risk of type II errors (Hassan et al., 2018). Additionally, some trials have been terminated early or have high dropout rates, further compromising the reliability of their results (Redman et al., 2014). The need for more robust, multicenter RCTs with standardized protocols is widely recognized in the literature.

The safety of probiotics and synbiotics in immunocompromised patients remains a significant concern. Although most studies report good tolerability and few serious adverse events, the risk of probiotic-associated infections, such as bacteremia or sepsis, cannot be ignored, particularly in patients with severe immunosuppression (Sanders et al., 2016). This risk underscores the importance of careful patient selection and close monitoring in clinical practice.

Another challenge is the variability in the quality and composition of commercial probiotic products. Some products may contain microorganisms not listed on the label or may be contaminated with unwanted bacteria or fungi (Sanders et al., 2016). This variability complicates the interpretation of clinical outcomes and highlights the need for stricter regulatory oversight and quality control in the probiotic industry.

The lack of consensus on optimal probiotic strains, dosages, and duration of supplementation is another limitation. While certain strains, such as *Lactobacillus* and *Bifidobacterium*, have been extensively studied, the evidence for other strains is limited (Hill et al., 2014; Sanders et al., 2016). Furthermore, the optimal timing and duration of

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supplementation in relation to chemotherapy or surgery remain unclear, and more research is needed to address these questions

Finally, the cost-effectiveness and accessibility of probiotic and synbiotic supplements may be a barrier for some patients, particularly in low-resource settings. While these interventions are generally low cost and easy to administer, their widespread adoption may be limited by economic and logistical factors (McCallum et al., 2024).

In conclusion, while probiotics and synbiotics show promise as adjunctive therapies for chemotherapy-induced gut toxicity, several challenges and limitations must be addressed. These include study heterogeneity, small sample sizes, safety concerns in immunocompromised patients, variability in product quality, and the need for more robust clinical evidence. Addressing these challenges will be essential for optimizing the use of probiotics and synbiotics in oncology and improving patient outcomes.

FUTURE DIRECTIONS

The clinical application of probiotics and synbiotics during chemotherapy has demonstrated promising potential in alleviating GI side effects and improving treatment tolerance. However, several important gaps remain that need to be addressed through future research. Moving forward, a more rigorous, mechanistic, and individualized approach will be essential to establish standardized, safe, and efficacious use of these interventions in oncology.

One of the foremost future directions is the need for large-scale, multicenter RCTs that use standardized methodologies. Current studies vary significantly in terms of probiotic strains, dosages, formulations, and treatment durations, leading to heterogeneity that limits the generalizability of findings (Chen et al., 2024). Standardization of protocols, including the use of well-characterized strains and harmonized outcome measures (e.g., diarrhea grading, mucositis severity, quality of life indices), will help produce more comparable and reproducible data.

Another promising avenue involves the strain-specific evaluation of probiotics and synbiotics. The functional properties of probiotics are often strain-dependent, with some strains having immunomodulatory or barrier-protective effects, while others do not. Future research should focus on identifying and validating strains or combinations that are particularly effective in cancer patients undergoing chemotherapy (Hill et al., 2014). Furthermore, the development of genetically engineered probiotics designed to deliver therapeutic molecules or enhance mucosal immunity may represent an advanced application worth exploring (Han et al., 2024).

There is also a growing interest in personalized or precision probiotics, which considers individual microbiome composition, immune status, and cancer type. With advances in metagenomics and metabolomics, it is now possible to profile the gut microbiota in detail and tailor interventions to correct specific dysbiotic features (Pal & Shastry, 2023). Future studies should evaluate how baseline microbial diversity or composition affects the efficacy and safety of probiotic/synbiotic interventions and whether microbiome profiling could guide personalized supplementation.

In addition, mechanistic studies are needed to further elucidate the pathways through which probiotics and synbiotics modulate host physiology during chemotherapy. These include modulation of cytokine profiles, enhancement of tight junction protein expression, production of SCFAs, and neurotransmitter signaling (Markowiak-Kopeć & Śliżewska, 2020; Plaza-Diaz et al., 2019). Understanding these mechanisms may inform the design of next-generation synbiotics with targeted functionalities.

Safety profiling, particularly in immunocompromised patients, remains an essential research priority. While probiotics are generally safe, rare cases of bacteremia and sepsis underscore the importance of assessing host risk factors and identifying strains that are both effective and non-translocating (Sanders et al., 2016). Future safety studies should include pharmacovigilance, whole-genome sequencing of probiotic strains to screen for antibiotic resistance genes, and long-term follow-up to detect any delayed adverse events.

Another key area for future research is the impact of probiotic and synbiotic supplementation on chemotherapy efficacy and systemic outcomes. Preliminary findings suggest that gut microbiota composition can influence not only toxicity but also chemotherapy responsiveness and immune activation. For instance, butyrate-producing bacteria were shown to enhance oxaliplatin efficacy through $CD8^+$ T-cell activation in mice, with higher serum butyrate levels observed in human responders (He et al., 2021). It remains unclear whether manipulating the microbiome through supplementation could enhance therapeutic outcomes or synergize with immunotherapies—a hypothesis that warrants rigorous testing.

The development of regulatory guidelines and quality control standards is also needed. As the commercial probiotic market continues to expand, inconsistencies in strain identification, viability, and labeling persist (Sanders et al., 2016). Future efforts must aim at enforcing stricter manufacturing standards, ensuring strain authenticity, and establishing clinical-grade formulations for use in oncology.

Lastly, cost-effectiveness analyses and implementation research should be undertaken to understand the economic and logistical feasibility of incorporating probiotic and synbiotic therapy into routine cancer care. This includes assessing patient adherence, integration into treatment workflows, and acceptability among oncologists and dietitians.

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In summary, while current evidence supports the adjunctive role of probiotics and synbiotics during chemotherapy, future research should focus on standardization, mechanistic insights, safety validation, personalized approaches, and health system integration. Addressing these areas will help maximize therapeutic benefits, ensure patient safety, and pave the way for microbiota-targeted interventions in precision oncology.

CONCLUSION

Probiotic and synbiotic supplementation has emerged as a promising adjunctive strategy for managing chemotherapy-induced GI toxicity. Their multifaceted mechanisms—including modulation of the gut microbiota, enhancement of mucosal barrier integrity, immunomodulatory effects, and antioxidant activity—support their therapeutic potential in oncology. Clinical evidence from RCTs and meta-analyses indicates that these interventions can reduce the severity and incidence of side effects such as diarrhea, mucositis, and abdominal discomfort, thereby improving patient comfort, treatment adherence, and quality of life.

Despite these benefits, the implementation of probiotics and synbiotics in clinical oncology must be approached with caution. Safety concerns, particularly in immunocompromised individuals, underscore the need for careful strain selection, monitoring for adverse effects, and adherence to stringent quality control standards. Tolerability data remain largely favorable, with most patients experiencing only mild and transient GI symptoms. However, rare but serious adverse events highlight the importance of individualized risk assessment.

Current clinical guidelines support the cautious use of probiotics and synbiotics in selected cancer populations, but gaps remain in terms of standardization, regulatory oversight, and personalized recommendations. Challenges such as study heterogeneity, inconsistent product quality, and limited strain-specific data further complicate clinical decision-making.

Looking ahead, well-designed multicenter trials, mechanistic research, and personalized supplementation strategies are essential to fully realize the potential of microbiome-targeted interventions in cancer care. With continued scientific rigor and clinical vigilance, probiotics and synbiotics may become integral components of supportive oncology, contributing to safer, more effective, and patient-centered treatment paradigms.

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COMPLIANCE WITH ETHICAL STANDARDS

It is not applicable

CONFLICT OF INTEREST

Authors have declared no conflict of interest.

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