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# Microbial Biomarkers Helpful in Early Detection of Cancer: Prognosis and Suitable Treatment

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## ABSTRACT

The significance of microbial biomarkers in cancer detection and prognosis garners heightened interest, with considerable implications for early diagnosis, tailored treatment, and enhanced patient outcomes. Microbial dysbiosis, especially within the gut microbiome, is associated with multiple cancers, including gastrointestinal, colorectal, and pancreatic malignancies. Notwithstanding the expanding corpus of research, the methods through which microbial biomarkers affect cancer development and treatment response remain inadequately comprehended, and their clinical use is currently being explored. This review consolidates information on microbial biomarkers in cancer, emphasizing their significance in early detection, prognosis, and therapy results. The review rigorously assesses studies investigating microbial fingerprints as prospective diagnostic instruments and scrutinizes the constraints of current research, encompassing challenges associated with repeatability, validity, and clinical integration. Recent research highlights key results about new microbial biomarkers that demonstrate potential for early detection and may impact patient prognosis and therapy efficacy. The review identifies critical gaps in the field, notably the necessity for standardized methodology, expanded clinical trials, and an enhanced mechanistic comprehension of microbiome-cancer interactions. The analysis ultimately proposes actionable recommendations for future research, emphasizing the integration of microbiome data with improved diagnostic tools and tailored therapy strategies. This review seeks to address existing research gaps to facilitate the creation of microbiome-based diagnostic systems that enhance traditional cancer screening and improve clinical outcomes.

## INTRODUCTION

Microbial biomarkers for cancer's early detection and prognosis have attracted broad interest in oncology in the past decade. Cancer remains one of the biggest single killers of patients on a global scale, and timely detection is important for treatment efficacy and patient prognosis (Draz et al., 2018). Microbiome analysis as a diagnostic tool is a hot topic because microbial dysbiosis or upsets in the microbiota contribute to cancer initiation and progression (Radziejowska et al., 2023). Although

the microbiome and its relationship to cancer have been intensively studied, the underlying mechanisms remain poorly defined, and microbial biomarker-based applications in cancer early detection and therapy remain nascent (Peng et al., 2017). This review aims to provide a narrative review of the current literature on microbial biomarkers involved in cancer, specifically early diagnosis, prognosis, and treatment, with a strong focus on gastrointestinal cancer.

Recent studies have shown that gut bacteria may significantly influence cancer prognosis and treatment response (Kamil Reza et al., 2017). Research indicates that specific microbial signatures are associated with tumor formation, immune regulation, and patient outcomes in colorectal, gastric, and pancreatic malignancies (Yang & Rhee, 2021). Nevertheless, whereas these investigations have yielded helpful insights, they also expose a significant deficiency in knowledge. There is inadequate comprehension of how these microbial biomarkers might be dependably utilized in clinical environments for early detection and tailored treatment (Huh & Roh, 2020). Addressing this deficiency is crucial for advancing microbiome-based diagnostic systems that may enhance conventional cancer screening techniques and optimize patient care (Sarojini et al., 2012).

This review aims to fill this gap by thoroughly examining the existing research on microbial biomarkers in cancer. This review synthesizes existing findings and critically evaluates the methodology employed in this field, emphasizing the limitations of prior studies, especially regarding reproducibility and clinical applicability (Park et al., 2021). This review presents a fresh approach by analyzing the integration of microbial biomarker profiles with sophisticated cancer detection technologies, providing new insights into the potential clinical applications of these biomarkers (Adam-Artigues et al., 2021). This study addresses existing gaps and establishes a framework for future research to enhance microbial biomarkers' diagnostic and therapeutic potential in oncology (Löwenmark et al., 2020).

## Role of the Gut Microbiome in Cancer Detection and Prognosis

The role of microbial biomarkers, particularly in colorectal cancer(CRC), has been recently emphasized using available technologies to assess the prognostic potential of microorganisms for human cancers. Previous studies have revealed that certain microbial signatures, such as the enrichment of Fusobacterium nucleatum, are linked to CRC progression and poor prognosis in patients with CRC (Negrut et al., 2023). On the other hand, Fusobacterium has been associated with worse tumor grade and inflammation and could, therefore, be a prognostic marker (Gethings-Behncke et al., 2020). Moreover, changes in gut microbiota diversity are associated with treatment responses among patients with CRC, suggesting a role for microbiota composition in therapeutic responses (Sillo et al., 2023). These findings imply that microbial profiling could be used as a noninvasive diagnostic approach for CRC, thus improving the early detection and personalized treatment of CRC and potentially other gastrointestinal cancers (Chen et al., 2020).

The potential of microbial biomarkers in cancer diagnostics, particularly in gastrointestinal cancers and other solid tumors, has been increasingly recognized. Common microbiota signatures such as Fusobacterium nucleatum (for CRC detection with high sensitivity and specificity (Stasiewicz et al., 2021). Moreover, studies have shown that microbial dysbiosis occurs in many types of cancers, thereby raising the possibility of identifying common biomarkers as shown in Figure 1(Liu et al., 2019; Dai, 2023). Compounding this challenge is that microbial profiles may differ between cancers and, even with a similar cancer, vary significantly at the individual patient level, making standardization of these biomarkers for clinical use problematic (Dai et al., 2024). Although multi-cancer biomarker panels may improve diagnostic accuracy, it remains unclear whether such approaches will yield increased diagnostic performance after validation (Alrahawy et al., 2022).

Although microbial biomarkers hold great potential as prognostic indicators for cancer, achievement remains elusive because of the high variability in microbiota composition between patients, the absence of an established methodology for biomarker identification, and translatability issues from experimental animal models to humans. The heterogeneity of individual microbiota profiles according to diet and lifestyle makes the identification of universal biomarkers

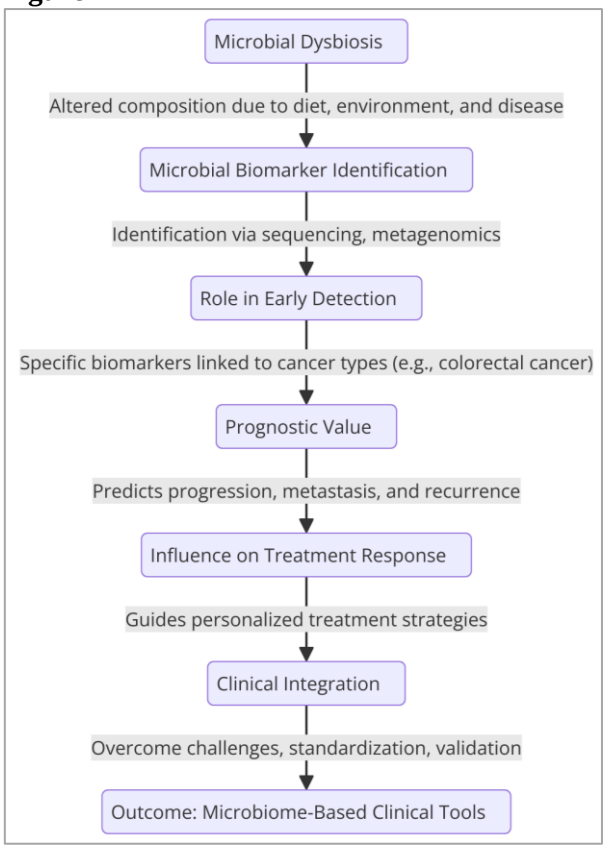
challenging (Pan et al., 2024). In addition, because there are no harmonized guidelines for their identification and validation, data from studies on these biomarkers tend to vary (Ting et al., 2022). Finally, the translation of results also faces hurdles, as the clinical relevance of microbial biomarkers can be compromised by a lack of correspondence between animal models and humans (Ren et al., 2017). Such restrictions reduce the clinical utility of microbial biomarkers and inhibit their use for personalized cancer prognosis (Wardill et al., 2021).

Gut microbiota dysbiosis, defined as an imbalance of microbial composition, is believed to contribute an important environmental factor in the development and progression of cancer. Some researchers have found that dysbiosis can drive chronic inflammation, a positive factor for carcinogenesis, as inflammatory cytokines may stimulate cell mutations and tumors (T. Liu et al., 2020). Evidence from key studies has shown that high-fat diets aggravate dysbiosis by promoting adenoma progression to adenocarcinoma through immune modulation and macrophage polarization (Wang et al., 2019). Indeed, alterations in the gut microbiota can also modify the integrity of the intestinal barrier, leading to a state of permeability and bacterial translocation, further triggering inflammation and cancer development. In this context, knowledge of microbial dysbiosis is important for developing specific therapeutic and preventive interventions related to cancer (T. Liu et al., 2020).

Research has shown that the gut microbiome plays an important role in the efficacy of cancer treatments, such as chemotherapy and immunotherapy. Certain microbial communities can upregulate or downregulate the response to treatment through various means, such as immune modulation or metabolism of antineoplastic agents (Sun et al., 2020). Dysbiosis is an imbalance in the gut microbiome and has been associated with treatment resistance, and vice versa; a diverse gut microbiome has been linked to better responses to immune checkpoint inhibitors (Khan et al., 2020). Previous studies have shown that some bacteria can alleviate chemotherapy toxicity (e.g., Faecalibacterium prausnitzii), thereby facilitating the treatment of patients (Zhang et al., 2020). In contrast, an unbalanced microbiome can enhance detrimental effects and decrease treatment effectiveness, emphasizing the necessity for individualized microbiome-directed therapeutic approaches (Maddern et al., 2023).

Animal models have been invaluable in determining the microbiome's contribution to cancer progression, and findings have revealed microbial dependencies and key species associated with tumor development. In particular, some bacteria (Fusobacterium nucleatum) were found to drive colorectal cancer via inflammatory pathways (Islam et al., 2022). These observations are also corroborated by findings from clinical trials, where different microbiome profiles among patients have shown disparities in responses to immunotherapy (Kleber et al., 2022). These studies suggest that a balanced microbiome that promotes treatment and dysbiosis can worsen outcomes (Sethi et al., 2018). Therefore, testing the microbiome in cancer treatment can maximize patient intervention and prognoses for these patients.

**Figure 1**




This flowchart defines the role of microbial biomarkers in cancer detection, prognosis, and therapy efficacy. It establishes essential steps,

encompassing microbial dysbiosis, biomarker identification, clinical integration, and the potential for tailored treatment.

**Oral Microbiome in Cancer Detection and Prognosis**

Dysregulation of the oral microbiome has emerged as a potential diagnostic biomarker for head and neck cancer (HNC). Certain microbial changes, including increases in Fusobacterium nucleatum and Streptococcus mutans, have been linked with oral squamous (Hao et al., 2022). Such changes in microbial communities can result in a chronic inflammatory state that can promote carcinogenesis (Tsai et al., 2022). Because saliva features a microbiome signature of HNC that is detectable but noninvasively sampled (Tsai et al., 2022). These microbial alterations may have potential as early phenotype lesion detection candidates (Chattopadhyay et al., 2019). Therefore, oral microbiome profiling would provide the most clinical utility in facilitating early diagnosis and thus improving patient outcomes in managing HNC.

Studies comparing oral microbiota composition in cancer patients, especially those with head and neck cancers (HNC), to non-cancer patients or healthy individuals indicate that the microbiota differs. For example, in patients with cancer, pathogenic bacteria (Fusobacterium nucleatum and Porphyromonas gingivalis) are more abundant, whereas beneficial bacteria (Streptococcus mitis) are less abundant (Nie et al., 2022). Such changes in the microbiome could, therefore, act as a potential biomarker in order to assist with diagnosis and give an indication of prognosis, as a unique oral microbiome profile is associated with the presence and status of cancer (Chattopadhyay et al., 2019). Exploiting such contrasts between tumor and normal cells may allow gene expression patterns to be utilized for non-invasive diagnostic purposes, which would help with the early detection of HNC and, therefore, timely treatment (Lim et al., 2018).

The role of the oral microbiome is crucial for the prognosis and therapeutic efficacy of cancers, especially head and neck cancers. Changes in microbial composition have also been shown to correlate with tumor progression and poor treatment responses, such as increased Fusobacterium nucleatum and Porphyromonas gingivalis (Yamamoto et al., 2023). For example, Fusobacterium has been associated with increased tumor progression and resistance to therapy. Changes in the oral microbiome can also be associated with the intensity of treatment-related complications, such as oral mucositis, that can adversely affect the quality of life of patients and compliance with treatment, such as oral mucositis (Morsy et al., 2023). By exploiting these microbial alterations, novel biomarkers can be identified to diagnose early HNC and develop personalized therapeutic approaches (Irfan et al., 2020).

In contrast, saliva is a perfect, noninvasive body fluid for the diagnosis of cancer, with particular reference to head and neck cancers. It is simple, noninvasive, and can be easily collected from clinical settings, making it more accessible to patients (Farag et al., 2021). Saliva, which represents systemic changes, is anticipated to contain relevant cancer biomarkers even before the development of clinical symptoms. Various salivary metabolites and promising miRNAs have been associated with the early diagnosis and monitoring of treatment responses in oral squamous cell carcinoma (Rapado-González et al., 2019). Using saliva for microbiome characterization can aid in gaining further insights into cancer progression and treatment response, ultimately facilitating personalized therapy (Farag et al., 2021).

Recent evidence of microbiome DNA in saliva and its health-disease links has shown the potential of DNA and metabolites as salivary biomarkers for detecting early cancer. Certain salivary metabolites and microbial profiles enable the distinction between patients with cancer and healthy individuals, establishing their diagnostic potential (Kuwabara et al., 2022). Salivary biomarkers, especially miRNA, demonstrate good specificity and sensitivity, revealing an association with cancer existence and development, and salivary volatile organic compounds are promising biomarkers (Fadhil et al., 2023). Saliva provides a less-intrusive and easily accessible medium with reliable results and, therefore, is a more desirable candidate than biopsy and blood tests for early-

stage cancer detection and monitoring (Poehls et al., 2018).

There are some limitations in using the oral microbiome as a diagnostic tool for cancer, which is currently the subject of ongoing research. Molecular differences between some individuals make searching for a universal biomarker difficult, as some organisms may be found in certain individuals and not others (Sami et al., 2023). Moreover, the contamination of urine specimens and processing of samples will further bias the results and yield objectionable data (Wang et al., 2021). Further, as highlighted in extensive meta-analyses and systematic reviews, methodological inconsistencies between studies, such as sampling strategies and analyses, limit comparability and reproducibility (Bernard et al., 2022). Further studies are needed to standardize protocols, use larger and more diverse populations, and combine multi-omics approaches to improve the reliability of oral microbiome biomarkers of cancer for future diagnosis and prognosis (Radziejowska et al., 2023).

**Microbial Signatures in Cancer Immunotherapy Response**

The gut microbiome is an important immune checkpoint inhibitor (ICI) efficacy modulator in cancer therapy. Thus, certain microbes, such as Akkermansia muciniphila and Lactobacillus, have been linked to improved responses to PD-1 inhibitors by affecting tumor immune cell infiltration and activity (Jin et al., 2019). Diversity of gut microbiome is associated with better treatment outcomes, while dysbiosis may give rise to resistance against ICIs (Zheng et al., 2019). This may indicate that knowledge of the gut microbiome composition could contribute to the development of personalized cancer therapies by tailoring ICI treatment to suit the specific gut microbiome composition of cancer patients and perhaps avoid suboptimal prognoses (X. Liu et al., 2020).

Recently, differences in the gut microbiota between responders and non-responders to immunotherapy have been reported. The gut microbiome of responders is more diverse and enriched in certain taxa, including Faecalibacterium prausnitzii and Akkermansia muciniphila, which are associated with greater immune responses (Shi et al., 2020). Such microbial traits may act as predictive biomarkers for treatment outcomes by indicating which patients are more likely to respond to PD-1 inhibitors and related therapies (Huang et al., 2019). For example, studies have demonstrated that gut microbiome diversity is associated with the enhanced efficacy of immune checkpoint inhibitors, indicating that microbiome profiling could be utilized for personalized medicine in cancer (Hou et al., 2022).

The gut microbiome may affect immunotherapy responses via T cell activation and immune function modulation pathways. Some bacterial species, such as Bifidobacterium and Akkermansia, increase T-cell responses and favor antitumor immunity (Hou et al., 2022). In contrast, dysbiosis has the potential to enable tumors to evade the immune system and facilitate their progression (Kim & Lee, 2021). Recent research has shown that certain gut microbiota can generate molecules that modify immune pathways, affecting the efficacy of immune checkpoint inhibitors (ICI) (Chervin & Gajewski, 2020). A deeper understanding of these interactions is essential to create patient-specific immunotherapy strategies because certain microbiome profiles may identify patients who will respond to therapy and, therefore, may guide treatment choices (Li et al., 2021).

The impact of the microbiome on resistance to immunotherapy involves its effects on tumor immune evasion and therapeutic efficacy (e.g., ICIs). Decreased microbial diversity due to dysbiosis correlates with the failure of patients to respond successfully to ICIs (Huang et al., 2021). Certain gut bacteria can improve immune suppression or the tumor-enhancing effect to achieve immune escape (Sillo et al., 2023). Recent studies have indicated that antibiotics can alter the microbiome's composition, causing a diminished response to immunotherapy (Preissner et al., 2023). Knowledge of such mechanisms is necessary to develop strategies to modulate the microbiome to enhance immunotherapy responses in resistant patients (Kim et al., 2020).

The potential to manipulate the microbiome provides a novel strategy for overcoming resistance

to immunotherapy. In this regard, manipulating the gut microbiota with probiotics, prebiotics, and selective antibiotics can enhance immune responses, thereby improving treatment outcomes. For example, the enhancement of beneficial bacteria arms T-cells for better activity while decreasing tumor immune evasion, as observed with the probiotic (Manfredi et al., 2023). Fecal microbiota transplantation (FMT) has also been suggested to restore effective immune responses in patients resistant to immune checkpoint inhibitors (Koulouris et al., 2022). The clinical implications of our findings support the idea that microbiome modulation can serve as a complementary strategy to improve the success of cancer immunotherapy (Liu et al., 2019).

Microbiome-based strategies have enormous clinical ramifications for enhancing the efficacy of immunotherapy. Recent advances in gut microbiome profiling can aid in selecting an immunotherapy regimen and anticipate patients' responses to particular regimens based on distinct microbiota signatures correlated with treatment response (Preissner et al., 2023). Clinical trials in the current era have shown that cancer patients with a diverse microbiome enriched in the genera of Akkermansia and Faecalibacterium were associated with enhanced responses to immune checkpoint inhibitors at least in mice (Liang et al., 2022). For example, fecal microbiota transplantation from responders to non-responders increased the treatment efficiency in melanoma (Sillo et al., 2023). These results highlight the potential of microbiome modulation as an adjunct strategy for improving immunotherapy in patients with cancer (Abdul Rahman et al., 2021).

**Probiotics, Prebiotics, and Cancer Treatment: A Microbial Biomarker Perspective**

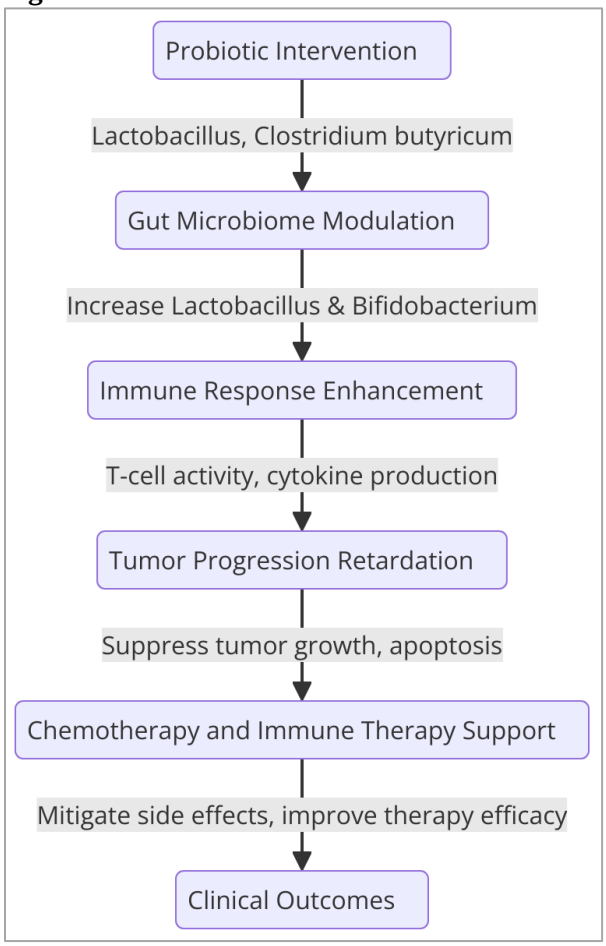
Probiotics can potentially affect cancer development and outcomes by mediating the gut microbiome as shown in Figure 2. Noteworthy, but more specifically, they can boost immune responses, retard tumor progression, and ameliorate treatment effects. An example is the probiotic Lactobacillus rhamnosus, which studies have shown to suppress tumor growth and induce apoptosis of cancer cells (Zhang et al., 2022). Probiotic supplementation during chemotherapy is associated with fewer side effects and a higher quality of life in patients (Lu et al., 2022). Studies have also shown that probiotics like Clostridium butyricum can improve the efficacy of immune checkpoint inhibitors, which will serve as the basis for their application in cancer (Tomita et al., 2020). This emphasizes the potential of probiotics as antidotes for cancer therapy.

Probiotic interventions are associated with significant modulation of microbial biomarkers related to cancer prognosis and treatment response as shown in Figure 2. Supplementation has been shown to increase the abundance of specific species, such as Lactobacillus and Bifidobacterium, which are associated with enhanced immune responses and lower tumor progression (Sivamaruthi et al., 2020). For example, a systematic review showed that probiotic supplementation could improve gut microbiome diversity and tolerance to chemotherapy in cancer patients. However, information about specific species, such as Lactobacillus rhamnosus, still needs to be provided(Wierzbicka et al., 2021). In addition, Clostridium butyricum has a potential role in increasing immune checkpoint inhibitors, but evidence in cancer patients is still lacking (Deleemans et al., 2021). These findings imply that probiotics could be adjunctive therapies to modulate the microbiome and enhance clinical outcomes during cancer treatment (Wierzbicka et al., 2021).

Probiotics have recently been evaluated in clinical trials as adjunctive anticancer therapies with promising results. Liu et al. (2022) showed that probiotics such as Lactobacillus rhamnosus mitigated oral mucositis due to chemotherapeutic agents, which can lead to improved quality of life for patients undergoing cancer therapy, with greater treatment compliance required for a successful therapeutic journey (Liu et al., 2022). In another trial, gut microbiome diversity was increased by PF supplementation, which was positively correlated with immune responses and lower treatment-related adverse events (Lu et al., 2022). Nevertheless, variable probiotic strains and dosages limit their generalizability (van Ruissen et al., 2019). The results indicated that probiotics

could be helpful not only as a nutritional supplement but also as part of the standard course of treatment and thus deserve wide application in clinical practice (Liu et al., 2022).

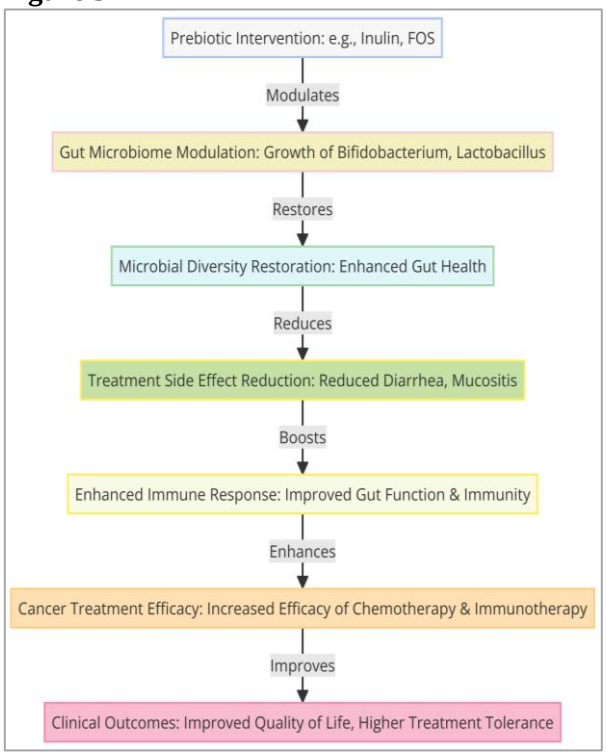
**Figure 2**




This flowchart illustrates the mechanisms through which probiotics influence cancer treatment. It outlines the process from probiotic intervention, through gut microbiome modulation, immune response enhancement, tumor progression retardation, to supporting chemotherapy and immune therapy, ultimately leading to improved clinical outcomes.

Prebiotics are essential in assisting cancer patients to have an ideally balanced gut microbiome through minimal induction of microbial diversity and, subsequently, a decrease in the side effects of chemotherapy as shown in Figure 3. They promote the growth of good gut bacterial species, including Bifidobacterium and Lactobacillus, which can enhance microbial diversity and improve immunity and gut function (Chen et al., 2023). For instance, prebiotics have been shown to reduce diarrhea and help restore the gut in colorectal cancer patients undergoing chemotherapy (Chen et al., 2023). In another trial, prebiotics contributed to the higher stability of the microbiome, which was associated with better tolerance to treatment and lower levels of inflammatory markers (Sun et al., 2019). These results indicate that prebiotics could improve patients' outcomes and quality of life in cancer care (Siddiqui et al., 2022).

**Figure 3**




This flowchart illustrates the role of prebiotics in enhancing cancer treatment by modulating the gut microbiome. It shows how prebiotics, such as inulin and fructooligosaccharides, promote the growth of beneficial bacteria, improve microbial diversity, reduce chemotherapy side effects, and enhance immune responses, ultimately improving treatment efficacy and clinical outcomes.

These are of great interest because recent studies have pointed out the clear impact of prebiotics on microbial biomarkers and the beneficial effects of prebiotic supplementation for improving cancer treatment outcomes. Prebiotics, such as inulin and fructooligosaccharides,

stimulate the growth of protective gut bacteria, such as Bifidobacterium and Lactobacillus, and may help restore microbial diversity and improve immune function (Zhang et al., 2023). For example, one study showed that prebiotic supplementation decreased the side effects of chemotherapy and enhanced patients' quality of life (Yang et al., 2023). Moreover, prebiotics have been shown to improve immunotherapy efficiency through gut microbiome modulation and improve treatment efficacy (Yang et al., 2023). These results support the prospect of implementing prebiotics in cancer treatment to improve therapeutic efficacy.

To gain the most from these advances in clinical care, further studies are needed to establish the optimal types and doses of prebiotics for beneficial effects in different cancer patient demographics. More studies should be undertaken to determine what prebiotic combinations promote diversity and immune function during chemotherapy or immunotherapy. In addition, research on the combined use of prebiotics with current cancer treatment modalities may have implications for individualized treatment regimens (Mishra et al., 2023). Future clinical trials should evaluate the effect of prebiotics on treatment endpoints, toxicity, and quality of life in cancer patients and guide the implementation of prebiotics in the routine clinical management of cancer (Anelli et al., 2021).

## CONCLUSION

This review emphasizes the increasing importance of gut microbiota as a pivotal element in cancer detection, prognosis, and treatment, particularly regarding its potential as a biomarker for early diagnosis and its influence on treatment results. Recent studies have highlighted the significance of microbial dysbiosis in cancer advancement, particularly in gastrointestinal malignancies, and its influence on immune regulation, which can markedly impact therapeutic effectiveness, particularly in immunotherapy. This study examined promising developments in microbiome-based therapeutics, including probiotics and prebiotics, which may improve patient outcomes by reestablishing microbial equilibrium and mitigating treatment side effects. Notwithstanding these advancements, significant gaps persist, notably the necessity for extensive, longitudinal clinical trials to authenticate microbiome biomarkers across varied populations and cancer types, alongside more comprehensive mechanistic investigations to thoroughly comprehend the intricate interactions between the microbiome and cancer treatment. The heterogeneity of microbiome composition among diverse populations, attributable to factors such as nutrition, genetics, and the environment, necessitates additional investigation to enhance the generalizability of microbiome-based diagnoses and therapies. This review highlights the need for established procedures in microbiome research as impediments to translating findings into clinical practice. Future research should concentrate on confirming microbiome biomarkers for clinical use, examining how the microbiome affects cancer progression, and investigating the potential of microbiome regulation alongside traditional cancer therapy. This study highlights the revolutionary potential of microbiome-based strategies in oncology, which could improve cancer diagnosis, treatment, and individualized care. However, hurdles persist in properly integrating these advances into clinical practice.

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