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REVIEW ARTICLE

Exploring the Gut Microbiota as a Promising Target for Breast Cancer Treatment

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Abstract: Breast cancer is a heterogeneous disease and highly prevalent malignancy affecting women globally. Breast cancer treatments have been demonstrated to elicit significant and long-lasting effects on various aspects of a patient's life, including physical, emotional, social, and financial, highlighting the need for comprehensive cancer care. Recent research suggests that the composition and activity of the gut microbiota may play a crucial role in anticancer responses. Various compositional features of the gut microbial population have been found to influence both the clinical and biological aspects of breast cancer. Notably, the dominance of specific microbial populations in the human intestine may significantly impact the effectiveness of cancer treatment strategies. Therefore, the manipulation of the microbiota to improve the anticancer effects of conventional tumor treatments represents a promising strategy for enhancing the efficacy of cancer therapy. Emerging evidence indicates that alterations in the gut microbiota composition and activity have the potential to impact breast cancer risk and treatment outcomes. In this paper, we conduct a comprehensive investigation of various databases and published articles to explore the impact of gut microbial composition on both the molecular and clinical aspects of breast cancer. We also discuss the implications of our findings for future research directions and clinical strategies.

Keywords: Breast cancer, gut microbiota, gut flora, microorganism.

1. INTRODUCTION

Breast cancer (BC) remains a significant global health challenge, with high prevalence rates and ranking as the fifth leading cause of cancer-related mortality worldwide [1]. In recent decades, there has been a steady rise in the mortality rate of breast cancer cases among women, indicating the need for effective prevention and treatment strategies [2]. Four major subtypes of BC are luminal A, luminal B, human epidermal growth factor (HER2)-positive, and triple-negative BC (TNBC), which have distinct clinical, pathological, and molecular features [3]. Estrogen receptor (ER) is a critical biomarker in breast cancer, as it is expressed in approximately 70-75% of all cases, making it a crucial target for endocrine therapies [4]. The progesterone receptor (PR) is frequently co-expressed with ER in BC, with more than 50% of ER-positive BC cases also expressing PR [5]. Both ER and PR are widely recognized as essential diagnostic and prognostic biomarkers in BC [6]. HER2 overexpression is observed in approximately 15-25% of BC cases, and its detection is vital for identifying patients who may benefit from targeted anti-HER2 therapies [7]. TNBC represents approximately 15-20% of all BC cases and is defined by the absence of ER, PR, and HER2 expression [8].

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1.1. BC Treatment

The results of clinical trials have shown that breast cancer therapies can have significant and enduring impacts on multiple dimensions of a patient's quality of life, encompassing physical, emotional, and social well-being, underscoring the importance of a holistic and integrated approach to cancer care [10]. Despite the remarkable advances in BC diagnosis and therapy, there is an urgent need to explore novel therapeutic modalities to overcome drug resistance and improve outcomes [11].

Advances in microbiome research have provided compelling evidence supporting the involvement of the human microbiota in the pathogenesis of cancer and highlighted the multifaceted role of the microbiome in cancer biology [12, 13]. Human microbiota or flora, including bacteria, viruses, protozoa, fungi, and other microorganisms, has numerous important functions in the body [14]. Emerging evidence from preclinical and clinical studies has shed light on the potential impact of the gut microbiota composition and function on the host's anticancer immune response, suggesting a significant role for the microbiome in modulating cancer development and progression [15]. Manipulating the gut microbiota composition and activity may represent a promising strategy to enhance the effectiveness of BC treatment [16].

This review aims to explore how modifying gut microbiota through probiotics or dietary changes can boost the effectiveness of current BC treatments. Additionally, it seeks to identify specific microbial profiles linked to various stages of BC, which could serve as valuable biomarkers for prognosis and treatment response. The study will also delve into the molecular mechanisms by which gut microbiota influences BC biology. Ultimately, the goal is to translate these findings into clinical applications that enhance treatment outcomes for patients with BC by incorporating microbiota-based strategies into standard care. We conducted a comprehensive literature review of databases including PubMed, Google Scholar, Embase and Scopus using the keywords “gut microbiota”, “ gut microbial population/composition”, “cancer treatment”, “breast cancer”, “breast cancer treatment”, “breast cancer prognosis”, “gut microbial alteration”, “prebiotics”, “symbiotics”, “postbiotics” and “microbial supplementation” aiming to elucidate the role of gut flora and its alteration in population in the determination of BC treatment response and prognosis.

2. THE INTERPLAY BETWEEN GUT MICROBIOTA AND HOST HEALTH

The human microbiota is a complex and dynamic collection of microorganisms that resides in diverse body sites such as the skin, the mucosa, the oral cavity, the mammary gland, the nasal cavity, the gastrointestinal tract, the respiratory tract, and reproductive organs, and serves critical functions in preserving optimal health and physiological balance [17, 18]. More than 97% of the human microbiota reside in the gastrointestinal tract, predominantly in the colon with the capacity to metabolize non-digestible substrates and utilize intestinal mucins as an energy source [19, 20]. The characteristics of the human microbiome are shaped by a multitude of host-related factors, such as age, lifestyle, dietary habits, antibiotics, antigen exposure, hormonal variations, and host genetics [21].

The latest scientific breakthroughs have unveiled the diverse and complex effects of the microbiota on host physiology, encompassing a range of processes such as the modulation of host cellular function and metabolism, regulation of circadian rhythmicity, and nutritional responses [22, 23]. The intricate interplay between microbial signals and the host immune system is essential for the proper development and maintenance of major components of both the innate and adaptive immune systems [24]. The modulation of the host adaptive immune system through the targeting of T cell receptor (TCR) and B cell receptor (BCR) by the gut microbiota is a critical factor in the maintenance of immune homeostasis and the prevention of chronic inflammatory diseases [25].

The intestinal microbiota was found to play essential roles in the maintenance of the mucosal immune system [26]. Disturbances in the homeostasis of microbiota or microbiome-immune interactions can result in significant alterations in overall physiological balance, leading to dysregulation of the metabolic and immune systems and contributing to the development of numerous diseases [27].

Gut dysbiosis, which refers to a state of imbalance in the composition and function of the gastrointestinal microbiota, has been associated with various pathological conditions and diseases, including diarrhea [28], allergies [29], multiple sclerosis [30], type 1 and 2 diabetes [31], inflammatory bowel diseases [32], cardiovascular diseases [33, 34], rheumatoid arthritis [35], Alzheimer's disease [36], Parkinson's disease [37], autism [38], obesity [39], liver diseases [40], atherosclerosis [41], and cancers [27, 42-44].

The use of antibiotics, probiotics, synbiotics, prebiotics, and fecal microbiota transplantation (FMT) has been identified as effective approaches to correct dysbiosis, and restore the composition and activity of the gut microbiota [45, 46]. Studies have shown that variations in the composition of the human microbiome may influence tumor development and therapeutic outcomes in patients with cancer [47]. This microorganism, by targeting immune checkpoint inhibitors, can regulate phenotypes of tumor somatic mutations.

Fusobacterium nucleatum, a member of the oral microbiota and a known periodontal pathogen is implicated both in the maintenance of human health and in the development of oral cancer [48]. *Helicobacter pylori* is widely recognized as the primary microorganism residing in the human stomach, and is implicated in a range of gastric disorders, including hypochlorhydria, gastritis, and gastric cancer [49, 50].

Lachnospiraceae, a family of gut microbiota, has been linked to the maintenance of gut health, and emerging evidence suggests that it may also play a protective role in the development of colorectal cancer [51, 52]. *Ruminococcaceae* is widely recognized as the dominant bacterial family within the healthy human intestinal microbiome [53]. *Bacteroidota*, including *Clostridia* and *Bacteroidia*, are recognized as important constituents of the gastrointestinal microbiota, serving as a vital source of nutrients for other coexisting gut microbes, while their potential pathogenic effects may vary with their specific location in the host [54]. An imbalance in the *Firmicutes/Bacteroidetes* (F/B) ratio is implicated in the development of obesity, whereby an increase in *Firmicutes* and a decrease in *Bacteroidetes* populations may promote weight gain and metabolic dysfunction [55]. The presence of *Bacteroides massiliensis* has been linked to varying risk factors in the development of prostate cancer, highlighting the potential role of this microbe in the pathogenesis of the disease [42].

Fig. **1** visually illustrates the interrelationship between the gut microbiota and the health of the host.

Research findings indicate that the microbiota can exert influence on the genetic and epigenetic architecture of the host genome (regulation of non-coding RNAs (ncRNAs), modifications of DNA or histones) without altering the underlying genetic code, thereby promoting tumorigenesis in colorectal cancer through targeted interactions [56, 57].

Emerging evidence suggests that modulation of the gut microbiota and targeting tumor-associated bacteria may hold great promise as a strategy to enhance the efficacy and reduce treatment complications [58].

3. BACTERIAL MICROBIOME IN CANCER TREATMENT

The ability of bacteria to modulate the effectiveness of chemotherapeutic drugs and immunotherapy is well documented. Previous documentation has indicated that the loss of gut microbiota is associated with unfavorable therapy outcomes. This suggests that the gut-residing microbial flora plays a crucial role in modulating anticancer immune responses through several mechanisms. Components produced by different bacteria may affect the growth of cancer cells or modulate anticancer immunosurveillance. Toxins with anticancer properties, ligands of pattern recognition receptors (PRRs) that affect antitumor immunity, and metabolites that alter the metabolism of

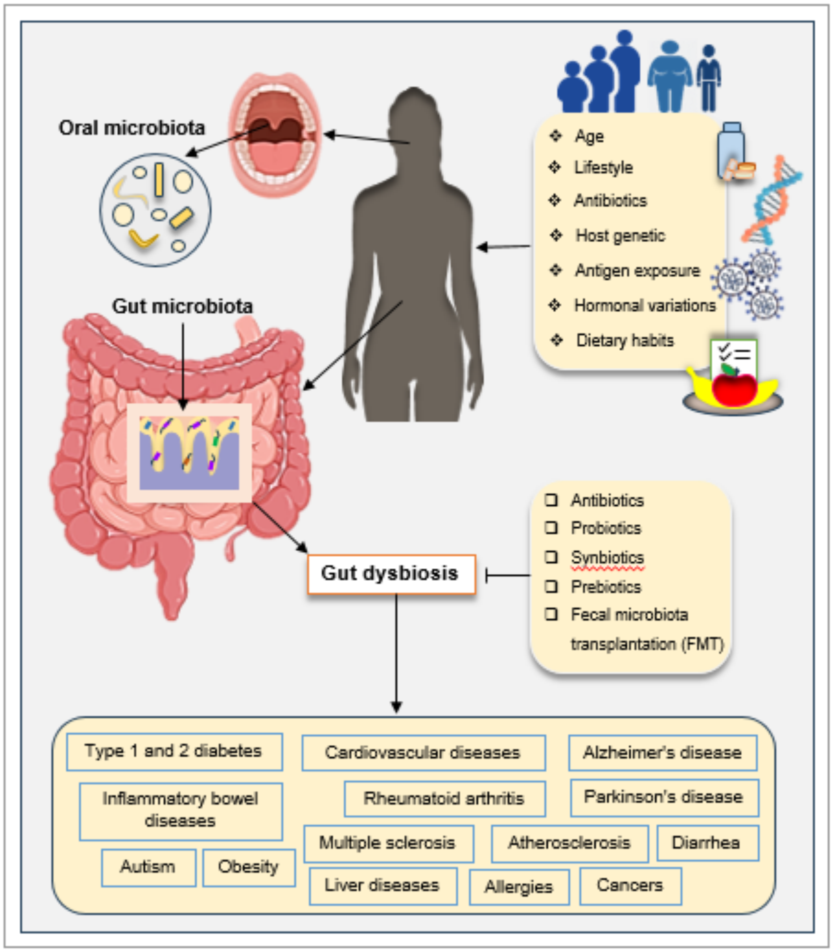

Fig. (1). The connection between gut microbiota and the health of the host. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

the host are some examples [59]. In addition, several interventions such as FMT, antibiotic treatment, administration of prebiotic and/or probiotic formulations, some kinds of medications (e.g., metformin) and dietary-based interventions, such as caloric restriction modulate the resident gut microbiota in cancerous situations resulting in specific outcomes [59].

4. ANIMAL MODEL STUDIES

There has been a pile of research conducted in animal models of cancer to reveal the role of gut flora composition and its importance. Here, we indicate some remarkable ones divided by type of therapy approach.

4.1. Chemotherapy

In mice, cyclophosphamide (CTX), a chemotherapeutic drug, altered the composition of intestinal microbiota, causing selected species of Gram-positive bacteria to translocate into secondary lymphoid organs, stimulating the production of "pathogenic" T helper 17 (pT(H)17) cells and memory T(H)1 immune response [60, 61]. In mice of germ-free state due to antibiotic treatment, removing the gut microbiota resulted in a decreased effect of CTX [60]. Iida *et al*. demonstrated that the response of subcutaneous tumors to platinum-based therapy is impaired in mice with a disrupted gut microbial population [62]. By creating platinum DNA adducts and intrastrand cross-links, the platinum compounds oxaliplatin and cisplatin cause tumor cytotoxicity [63]. Reactive oxygen species (ROS) are crucial for DNA damage and apoptosis in response to platinum compounds [64]. In contrast to cisplatin, oxaliplatin also causes immunogenic cell death, which drives antitumor T cell immunity [65, 66]. Oxaliplatin-induced DNA damage and apoptosis were reported to be prevented in mice by antibiotic cocktail therapy by lowering ROS after some of the DNA adducts had formed. Data specifically demonstrated that most of the ROS needed for oxaliplatin genotoxicity are produced by inflammatory cells residing in the tumor tissue. This finding implies that by affecting the related inflammatory cells and the synthesis of ROS, gut microbiota influences the antitumor potential of oxaliplatin [62]. A study on the adjuvant 5-fluorouracil (5-FU)-based chemotherapy, including FOLFOX (5-FU, leucovorin calcium, and oxaliplatin) regimen in a colorectal cancer model showed this therapeutic approach induces mucositis and this involves changes in gut microbiota *Firmicutes* and *Bacteroidetes* and might be “driven” by NF-κB pathway activation. Activated NF-κB results in apoptotic signal release and production of inflammatory mediators, which sequentially contribute to gastrointestinal tissue injury. By modulating gut microbiota and proinflammatory responses with suppression of intrinsic apoptosis, probiotic *Lactobacillus casei* variety *rhamnosus* (*Lcr35*) mitigated FOLFOX-induced mucositis. These results indicated that *Lcr35* may be utilized as a replacement therapeutic strategy to prevent or regulate chemotherapy-induced mucositis [67].

4.2. Radiation Therapy

A recent study by Guo *et al*. showed that a gut microbiome-metabolome network in mice can suggest substantial protection against tissue injury caused by radiation therapy. They showed that the presence of *Lachnospiraceae* and *Enterococcaceae* is associated with relief in the hematopoietic and gastrointestinal systems following radiation. These two taxa were also found to be more prevalent in patients with leukemia undergoing radiotherapy who experienced milder gastrointestinal adverse effects. Moreover, metabolomic investigations revealed elevated fecal concentrations of microbially derived propionate and tryptophan metabolites (^{1}H-indole-3-carboxaldehyde (I3A) and kynurenic acid (KYNA)) in so-called elite survivors. Administration of these metabolites resulted in long-term radioprotection as well as mitigation of hematopoietic and gastrointestinal defects and reduced proinflammatory responses following radiotherapy [68].

4.3. Immunotherapy

Previous research supports the role of *Alistipes* in stimulating tumor necrosis factor (TNF) production via activating Toll-like receptor 4 (TLR-4), mainly through priming the tumor-associated myeloid cells. The ability of tumor-associated myeloid cells to generate TNF is restored and the antitumoral responses are improved with oral administration of bacteria *Alistipes shahii* in mice who have already undergone antibiotic treatment [62, 69].

Recent studies have demonstrated that the composition of intestinal flora is capable of predicting the efficacy of allogeneic stem cell transplantation, and they play a key role in creating systemic immune responses [70]. Therefore, one of the key mechanisms for tumor immunotherapy is patients' immune system regulation by microbiota. Current studies on cancer immunotherapy focus on antibodies against immune checkpoint inhibitors (ICIs) such as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), and antibodies against CD8+ T-cell programmed death factor programmed death-1 (PD-1)/PD-L1 [71]. There is a straight link between the efficacy of CTLA-4 inhibition and the activation of T cell responses facilitated by specific microbiota constituents, such as *Bacteroides fragilis* or *Bacteroides thetaiotaomicron*. These results imply that the gut microbiota is necessary for the antitumor immunity produced by CTLA-4 blockade. Tumors in germ-free mice did not respond to therapies blocking CTLA-4 signaling [72].

Moreover, Li *et al*. reported that mice without RNF5 (a ubiquitin ligase regulating ER stress response) expression showed impaired activation of the unfolded protein response (UPR) components, increased levels of inflammasome elements, recruitment and activation of dendritic cells, and decreased expression of antimicrobial peptides in the intestinal epithelial tissue.

Reduced UPR expression was also seen in murine and human melanoma tumor specimens that responded to immune checkpoint therapy. Transfer of bacterial strains, including *B. rodentium*, enriched in Rnf5-/- mice, augments antitumor immune response and restricts melanoma growth in germ-free wild-type mice. Also, in Rnf5-/- mice, altered UPR signaling is associated with altered gut microbial population and antitumor immunity [73].

A recent study found that microbiota-derived short-chain fatty acids (SCFAs) such as butyrate improved the memory potential of activated CD8+ T cells, showing that microbiota may potentiate antitumor immune response by promoting CD8+ T cells' long-term survival as memory cells [74]. *Faecalibacterium prausnitzii*, a butyrate-producing species, could function as a negative regulator of colorectal cancer progression. The underlying mechanism relies on the anti-inflammatory property of butyrate, which has been shown to contribute to the differentiation and accumulation of Tregs. Butyrate also inhibits histone deacetylase and consequently reduces transcription and translation of oncogenic genes, as well as stimulation of CD8+ T cells to release effector antitumor mediators [59, 75].

4.4. Human Studies

Clinical findings also indicate the role of gut microbiome in cancer therapy. Interestingly, a randomized clinical trial showed that a probiotic combination in patients with nasopharyngeal carcinoma receiving concurrent chemoradiation could significantly enhance host immunity and reduce oral mucositis (OM) via modifying the gut microbiota [76]. However, there is no previous documentation about the influence of intestinal flora on radiotherapy outcome and efficacy. The gut microbiota derived from patients suffering from pancreatic adenocarcinoma (PDAC) bears the capacity to modulate the composition of the tumor microbiota and impact tumor development. The gut microbiomes of long-term and short-term survivors of patients with PDAC who underwent surgery are different in composition and abundance, which may be used as a prediction factor. In addition, in preclinical murine models, the transplantation of specific gut microbiomes from long-term survivors can improve the immune response to tumors [77]. Metagenomics of stool samples from patients with non–small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) receiving anti-PD-1 treatment revealed that reduced levels of *Akkermansia muciniphila* resulted in unfavorable anticancer response, which is positively correlated with recruitment of CCR9+CXCR3+CD4+ T lymphocytes. Therefore, primary resistance to ICIs can be associated with abnormal gut microbiome composition [78].

5. GUT MICROBIOTA AND BREAST CANCER

The influence of microbiota that inhabit the human intestine on cancers could be stated via diverse aspects such as disease progression, therapy efficacy, prediction of treatment response and therapy toxicity modulation [79]. Data inferring the impact of gut microbiota on BC is divergent and ranges from preclinical research to clinical trials which are still recruiting the patients. Therefore, it is possible that there is a causal link between the gut microbiome and BC.

5.1. Gut Microbial Population and Breast Cancer

In the case of BC, interruption in the community of gut microbial taxa has been reported in many studies. The term “alpha-diversity” describes the richness (abundance of certain taxa) or evenness (the relative number of the taxa) in a sample obtained from different habitat flora like gut or skin. Generally, higher alpha diversity is associated with a healthier body status. In a study by Goedert *et al*., the gut microbiota of postmenopausal patients with BC was more homogeneous and presented lower alpha diversity. The relative quantity of *Faecalibacterium*, *Ruminococcaceae* and *Clostridiaceae* were higher, along with decreased abundance of *Dorea* and *Lachnospiraceae* [80]. Gut microbial genes involved in the iron complex and cobalamin transport system, lipopolysaccharide biosynthesis and phosphotransferase system, all of which are related to inflammatory states, were also enriched in postmenopausal BC cases [81]. Parida *et al*. showed that there are considerable diversities between the gut microbial makeup of patients with BC and normal individuals. This diversity also existed between survivors and healthy counterparts. A couple of studies have demonstrated that gut microbial diversity is reduced in patients with BC compared to healthy people. Moreover, metabolites produced by the altered microbiota influence BC development and treatment [82, 83]. Producing biogenic metabolites occurs abundantly by the intestine resident bacteria. Cadaverine is an amine molecule synthesized by the members of the genera *Enterobacter*, *Escherichia*, *Proteus*, *Shigella* and *Streptococci*. Cadaverine inhibits BC cell proliferation, invasion and migration and is reduced in early-stage patients with BC due possibly to diminished synthesis by the microbiome following dysbiosis [84].

Dysbiotic gut may lead to a disrupted inflammatory immune response and promote carcinogenesis at distant sites. In vivo, the gut microbiome appeared to rely on neutrophils to propagate tumorigenesis in breast tissue. Thus, an intact intestine lining with tight junctions is necessary to prevent tumorigenesis [84, 85]. In addition, it is evident that dysbiosis leads to increased gut permeability and circulating lipopolysaccharide fostering monocyte-activated endothelial adhesion of circulating breast tumor cells and BC metastasis [86]. However, *Faecalibacterium prausnitzii* inhibits BC cell growth by suppressing the IL-6/STAT3 pathway, bringing a potentially promising treatment strategy [87]. Lithocholic acid (LCA), a secondary bile acid synthesized by the gut bacteria, is shown to suppress the BC cell growth and invasiveness along with the propagation of antitumor immunity. Interestingly, serum levels of LCA were decreased among early patients with BC compared to normal individuals with a reduction of LCA-producing enzyme 7α/β-hydroxysteroid dehydroxylase gene in the fecal DNA of the patients [88]. It is reported that the uptake of ^{18}F-FDG by intestinal cells as a marker for mucosal inflammation is affected by the gut microbial composition. By assuming the gut dysbiosis as a contributor to intestine epithelial inflammation, Yoon *et al*. reported that the physiologic intestinal uptake of ^{18}F-FDG (which was measured by PET/CT scanning) was positively correlated to *Citrobacter* genus of the *Enterobacteriaceae* family relative abundance in patients with BC. At the same time, the relative quantity of unclassified *Ruminococcaceae* depicted a negative correlation [89]. A pilot study was performed by Wu *et al*. to probe the association between gut microbiome and BC tumor features. In this study patients with HER2$^+$ tumors depicted lower alpha-diversity and decreased relative abundance in *Firmicutes* phylum as well as increased *Bacteroidetes* phylum relative quantity. In addition, patients experiencing early (ages ≤ 11) menarche had a lower number of species and diminished abundance of *Firmicutes* phylum. However, no difference in alpha-diversity and phyla was detected among patients with different tumor stages, grades and ER/PR status [90]. In a case-control study by Bobin-Dubigeon *et al*., a lower diversity of gut microbiota was shown in treatment-naïve patients with BC compared to controls. Depletion in *Bacteroidetes* amount and *Firmicutes* phylum enrichment were also outlined by this group. The relative abundance of *Butyricimonas, Coprococcus*, and *Odoribacter* species was lower among the patients with BC, as well [91]. Conversely, Fruge *et al*. demonstrated that diversity in gut microbiota is linked to obesity, underscoring *Akkermansia muciniphila* prevalence in stage 0 to II patients with BC. The elevated relative quantity of *Akkermansia muciniphila* was associated with a higher abundance of genera *Lactobacillus* and *Prevotella* [92]. Moreover, dysbiosis and modification of gut resident microbes were revealed in premenopausal BC cases; He *et al*. reported a substantially increased *Firmicutes/Bacteroidetes* ratio in patients with BC than normal controls. Also, the abundance of different bacteria species which produce SCFA such as genera *Fusobacterium* and *Pediococcus* was significantly decreased in patients with BC. As SCFA-producing genera, *Desulfovibrio* and *Pediococcus* depicted probable reference value to detect premenopausal patients with BC. Reduced SCFA formation by gut microbiota in patients with BC along with the fact that SCFAs butyrate and propionate suppress the BC cell growth in vitro, SCFA receptor targeting may be a considerable treatment approach in premenopausal BC [93].

Cachexia occurring during cancer plays a crucial role and is a remarkable challenge in the disease prognosis. An altered gut microbial community is observed among patients with cancer who suffer from cachexia. Ubachs *et al*. found that genus *Veillonella*, phylum *Proteobacteria* and an unknown genus from the *Enterobacteriaceae* family were abundantly present in patients with cancer cachexia (including cases with BC). However, alpha-diversity was not significantly different comparing cachectic and non-cachectic individuals. Finally, fecal calprotectin levels, as an inflammation indicator, depicted a positive correlation with *Peptococcus*, *Veillonella* and unknown *Enterobacteriaceae*. Also, SCFA was lower in the feces of patients with cachexia [94].

It is now clear that certain BC tumor types rely on estrogen for their growth, and elevated blood estrogen levels are a significant risk factor for the development of BC. Estrogen metabolism involves enterohepatic circulation, where conjugated estrogen loses its glucuronic moiety and is reabsorbed into the bloodstream. The enzyme beta-glucuronidase, produced by specific members of the gut microbiota—collectively referred to as the "estrobolome"—plays a crucial role in this process by facilitating the reabsorption of estrogen. *Ruminococcacea* and *Clostridia* families and *Escherichia/Shigella* group include several beta-glucuronidase bacteria. There is also an association between estrogen metabolism and gut microbial diversity in postmenopausal patients with BC [95, 96]. Beta-glucuronidase enzyme presents a diversified nature with differing potential in estrogen deconjugation. Considering the sub-cellular localization of this enzyme and its physicochemical features, bacteria producing beta-glucuronidase are more diverse in patients with BC compared to healthy counterparts. Recently, Muccee *et al*. performed an in-silico study to characterize features of this enzyme (e.g., physicochemical attribute, 2D and 3D structure, conserved motifs and sub-cellular localization) among the gut microbiota of patients with BC and normal people [97]. The gut microbial population may be associated with quality of life in patients with BC. In a randomized control trial conducted by Smith *et al*. among obese and non-obese BC survivors, mental health, physical function and vitality represented a negative correlation with *Ruminococcus* and *Dorea* genera regardless of obesity status. Moreover, non-obese survivors had increased relative abundance in genera *Streptococcus*, *Roseburia*, *Ruminococcus* and *Dorea* [98]. Eventually, in a recent study of the TNBC model by Hossain *et al*., obesity produced via a "Western" diet was correlated to loss of diversity in the gut microbiota with a reduction in *Bacteroides* species. Metabolic interactions among the intestinal microbiome were also influenced by obesity [99].

5.2. Diagnostic Implications

Utilizing the intestinal microbiota status has appeared to present favorable competence to be a part of the detection approach of BC. Investigating varied populations and the performance of estrobolome in normal individuals relative to estrogen-dependent patients with BC may pave the way to introduce microbiome-based biomarkers and interventions to reduce the risk of BC [84, 100].

The gut microbial profile may hold potential for detecting breast cancer in patients. In the study by He *et al*., the genus *Desulfovibrio*, belonging to the phylum Proteobacteria, was notably prevalent among patients with BC, while *Pediococcus* was the most characteristic genus found in healthy individuals. The application of a random forest algorithm revealed that the abundance of these two genera could effectively differentiate between patients and healthy individuals, suggesting their potential as diagnostic indicators [93]. The diversity between the gut microbial population of pre/postmenopausal patients with BC and normal samples found in previous investigations exhibit the probability and advantage of developing a reference profile in which gut microbiota dysbiosis patterns act as a biomarker for BC detection [101]. In order to develop microbial markers in pre- and postmenopausal patients with BC compared to healthy counterparts, Hou *et al*. reported that alpha diversity in the intestinal microbial population was remarkably reduced in the patients. Beta-diversity was also significantly different between patients and controls. They suggested 14 bacterial taxa as markers in different statuses. The abundance of *Bifidobacterium bifidum*, *Bifidobacterium adolescentis* and *Bifidobacterium longum* fluctuated by age but was more significantly reduced in the premenopausal BC group. Also, *Bacteroides fragilis* was particularly found in young premenopausal patients with BC and *Klebsiella pneumoniae* in older cases. The percentage status of 10 bacterial taxa in premenopausal individuals and 7 bacterial taxa in the postmenopausal individuals depicted good discriminating value for patients and controls after calculating area under the curve (AUC) in receiver operating characteristic (ROC) diagram. This study introduced potential menopausal-specified diagnostic microbial markers for BC [102]. There is an ongoing case-control observational study being conducted by Plaza-Diaz *et al*., which aims to assess the contribution of gut bacteria, archaea, fungi and viruses' alteration in BC development. This investigation would elucidate probable risk factors of BC associated with gut microbial dysbiosis and may bring more accurate microbiota-related diagnostic markers [103]. Intriguingly, gut microbial status has been reported to be variable between patients with benign and malignant breast tumors. In the study by Yang *et al*., relative distribution for 31 bacterial genera like *Brachybacterium, Clostridium, Lachnospira* and *Faecalibacterium* was found to be different between benign and malignant groups. Genera *Romboutsia, Fusicatenibacter, Erysipelotrichaceae, Faecalibacterium, Clostridium, Xylophilus* and *Lachnospira* were more plentiful in the benign group. However, the proportion of *Citrobacter* was significantly elevated in the malignant group. The population features of the gut bacteria were also correlated to clinical and pathological items like hormone receptors and Ki-67 expression. For instance, species *Roseburia, Prevotellaceae, and Megasphaera* depicted higher abundance in patients with ER^+ tumors [104]. This pilot study also brings promising insights into the application of gut microbial elements as a diagnostic factor alone or in combination with previous modalities. Besides the intestinal microbiota, the tumor microbiome, so-called "oncobiome", for different breast cancer subtypes may also have clinical implications. Like previous similar studies, Banerjee *et al*. attempted to introduce microbial signatures for BC tumor subtypes and found that the microbial makeup of different tumor subtypes is significantly diverse and associated with disease grade and staging. The tumor bacterial diversity affected prognostic values such as disease-free survival time and therapy response in the BC subtypes [105]. Recently, a study conducted by Nguyen *et al*. in a Vietnamese BC population demonstrated that a longer gap in disease detection is correlated with reduced alpha-diversity and abundance of *Enorma massiliensis* species and decreased number of *Faecalicoccus pleomorphus* among the intestinal microbiome bringing novel insights to the field of BC diagnosis [106]. Table **1** summarizes the reports about the diagnostic implications of intestinal flora in BC.

5.3. Prognostic Implications

In addition, the intestinal bacterial makeup has been reported to be correlated with prognostic and predictive parameters like lymph node metastasis and clinicopathological response to multiple methods of BC treatment. A study including non-metastatic patients with BC (before and after treatment) and normal controls by Terrisse *et al*. revealed that health-linked commensal bacteria such as *Eubacteriaceae* family, *Methanobrevibacter smithii* and species that belong to the *Coprococcus* genus were correlated with no axillary node involvement and smaller tumor size. Also, metabolites produced by the gut microbiome appeared to be correlated with clinical outcomes. They found a similarity between cancer-free individuals and patients with BC without axillary lymph node spread. Following eight cycles of adjuvant chemotherapy consisting of taxans and anthracyclines, commensal microbes associated with favorable outcomes (e.g., *Dorea formicigenerans*) expanded in quantity. The mentioned regimen also increased the alpha-diversity of the gut bacteria. An abundance of fecal bacterial species and families associated with unfavorable prognoses were discovered to be prevalent among patients who experienced chemotherapy-induced neurological side effects, highlighting the predictive capacity of the gut microbiome in anticipating adverse effects of therapy [107]. As another model for the predictive value of the intestinal bacterial population, Guan *et al*. demonstrated an association between gut bacteria and progression-free survival (PFS) period in metastatic $HER2^-$ patients with BC that, as an independent predictive factor, the median PFS was shorter in patients with the microbial composition of *Slackia*.

In contrast, the patients with species *Blautia obeum* had extended PFS time. Additionally, the authors reported that two capecitabine-consisting chemotherapy regimens (metronomic versus conventional dosage) could cause different profiles in gut microbiota, affecting upcoming outcomes [108].

Table 1. Diagnostic implications of the gut microbial status in patients with BC.

Study	Year	Findings
He *et al.* [93]	2021	Genus *Desulfovibrio* was the most particular in the BC cases, while the most characteristic genus among the normal individuals was *Pediococcus/*
Hou *et al.* [102]	2021	Alpha-diversity was lower in the patients/ Abundance of *Bifidobacterium bifidum*, *Bifidobacterium adolescentis* and *Bifidobacterium longum* were more significantly reduced in premenopausal cases/ *Bacteroides fragilis* was particularly found in young premenopausal cases and *Klebsiella pneumoniae* in older patients/
Yang *et al.* [104]	2021	Relative distribution for 31 bacterial genera was different between benign and malignant cases/ The proportion of *Citrobacter* was higher in the malignant group/ Gut bacterial status was correlated to clinical and pathological determinants
Banerjee *et al.* [105]	2021	Bacterial make-up of different subtypes was diverse and is associated with tumor grade and disease staging
Wenhui *et al.* [109]	2022	Cases with BM, BM-free cases and normal controls have distinct gut microbial profile; Absence of genera *Akkermansia* and *Megamonas* was related to BM
Nguyen *et al.* [106]	2024	Delay in the disease spotting is correlated with reduced alpha-diversity and abundance of *Enorma massiliensis* species and decreased number of *Faecalicoccus pleomorphus* among the intestinal flora

The most frequent site for BC metastasis is bone. Bone metastasis (BM) occurrence reduces the patients' life expectancy and worsens their quality of life, remaining a vicious event. A recent study conducted by Wenhui *et al*. revealed that patients with BM, those without BM, and individuals without BC (normal controls) exhibit distinct gut microbial profiles, suggesting the potential for utilizing gut microbiota as a discriminatory factor in distinguishing different BC subgroups. The dominant taxa in BM-positive and BM-free patients were reported to be divergent in that families *Pasteurellaceaea* and *Planococcaceae* and genera *Lysinibacillus*, *Neisseria* and *Haemophilus* were dominant in the BM-positive cohort. The absence of genera *Akkermansia* and *Megamonas* in the BM-positive group compared to BM-free and healthy individuals was considered related to BM. Also, an increase in the abundance of taxa *Campylobacter, Moraxellaceae, Streptococcus* in the patients compared to the controls could be regarded as a risk factor for BC progression [109]. Preoperative gut microbial population status may also predict the probability of chronic postoperative pain (CPP) development in BC survivors. Surgically treated patients with BC who experience chronic pain following the surgery exhibit a discernibly unique intestinal microbial profile, indicating a potential association between the gut microbiota and the development of persistent pain in this patient population. This diversity in multiple taxonomic rank levels depicted a reliable potential for discrimination of patients experiencing CPP and others using the ROC curve [110]. Previously, it was observed that the diversity of gut bacterial composition in BC survivors who had completed their chemotherapy/radiation regimens displayed a correlation with cardiorespiratory fitness indicators, such as peak O_2 uptake, suggesting a potential link between the gut microbiota and the physical fitness levels of BC survivors [111]. Emerging evidence suggests that the gut microbiota may exert an influence on anxiety and depressive disorders, including chemotherapy-induced psychological distress, through the gut microbiome-brain axis. In a recent study by Okubo *et al*., notable connections were established between specific intestinal microbes and fear of cancer recurrence (FCR) in BC survivors. The authors reported that heightened FCR was associated with a reduction in gut microbial diversity. Additionally, a decrease in the abundance of *Firmicutes* and an increase in the relative quantity of *Bacteroidetes* at the phylum level, along with a low relative abundance of the genera *Ruminococcus* and *Bacteroides*, were identified as being linked to the experience of FCR [112].

Proportional and metabolic characteristics of the intestinal microbiota may influence the outcome of BC therapeutic strategies and their adverse outcomes. The gut microbiome could affect drug metabolism and therapy-induced antitumor immunity, among other mechanisms to modulate the overall disease fate [113]. The recombinant monoclonal antibody trastuzumab (Herceptin®), which targets the extracellular domain of HER2 molecule, is nowadays the primary choice for early and advanced HER2$^+$ patients with BC [114]. However, trastuzumab resistance remains an inevitable hazard in the course of therapy. Considering the fact that trastuzumab exerts its function by augmenting antitumor immunity, Modica *et al*. probed the influence of gut microbiota on trastuzumab efficacy. They reported that antibiotic treatment alters the gut microbial profile, leading to changes in the tumor immune microenvironment with a reduction in the number of effector cytotoxic T-cells and NK cells in HER2$^+$ mouse models of BC. Subsequently, a human study of early patients with HER2$^+$ tumors undergoing trastuzumab-containing neoadjuvant treatment further supported the results. The gut microbial composition of responder and non-responder cohorts was different in that taxa *Bifidobacteriaceae, Turicibacteraceae,* *Clostridiales, Bacteroidales* were enriched in the cases with pathological complete response. Interestingly, stool microbial beta diversity was positively correlated with activated $CD4^+$ T-cells and dendritic cells in the tumor microenvironment [115]. More recently, a similar study was conducted by Li *et al*. to show the relation between gut microbiome and response to neoadjuvant chemotherapy. Among the early patients with BC, three signature taxa, including *Dorea, Coprococcus*, and uncultured *Ruminococcus* served as reliable factors to distinguish responder and non-responder cases. There was also a positive association between the signature bacteria taxa and the number of effector T-cells in both tumor tissue and peripheral blood, representing the tumor immunity modulation as a mechanism of impact on the therapy efficacy [116]. The response of BC to immune checkpoint inhibitors (ICIs) may be influenced by the composition of gut bacteria, highlighting the potential role of the gut microbiota in modulating the efficacy of ICIs in BC treatment. In a study of epithelial-derived cancers, Routy *et al*. showed that patients with a history of antibiotic consumption showed inferior response to PD-1 blocking agents. Non-responder patients had a decreased level of *Akkermansia muciniphila*. Transplantation of the responders' fecal microbes to the mouse models resulted in enhanced $CD8^+$ T-cell priming [117]. Immune destruction of the tumor tissue mediated by cytotoxic T lymphocyte-associated antigen 4 (CTLA4) inhibition has been found to rely on diverse *Bacteroides* species with *B.fragilis* and *B.thetaiotaomicron* being associated with favorable outcomes [118]. In a recent in vivo study using breast carcinoma models, the administration of the oral Hedgehog inhibitor vismodegib resulted in dynamic changes in the composition of gut commensal microbes. Remarkably, this treatment exhibited beneficial effects on the proliferation of cytotoxic T-cells, promoting an immune response against the tumor, while no significant adverse effects were observed [119]. Gut microbial dysbiosis is relevant to the development of chemotherapy-induced toxicities, especially neuropsychiatric adverse events in different cancer types, including BC [120]. In a recent study by Nguyen *et al*. gut microbial profile of patients with BC before chemotherapy was linked to therapy-related toxicities. Elevated alpha-diversity and high abundances of 29 distinct taxa (mostly from *Ruminococcaceae*, *Oscillospiraceae* and *Lachnospiraceae*) were associated with a lower risk of hematological events and neutropenia. Moreover, a significant correlation between taxa from *Sporanaerobacteraceae*, *Fusobacteriaceae*, *Lachnospiraceae* and *Bacteroidaceae* and severe neutropenia was reported. Moreover, the enrichment of species *Odoribacter laneus* and L-proline biosynthesis II pathway depicted a negative correlation with severe nausea and vomiting among the patients. However, higher diversity and Chao1 index and species related to the family *Oscillospiraceae*, *Ruminococcaceae* and *Lachnospiraceae* had a positive association with gastrointestinal adverse events [121]. Table **2** mentions the above information about the prognostic impacts of gut flora on the course of BC (Fig. **2**).

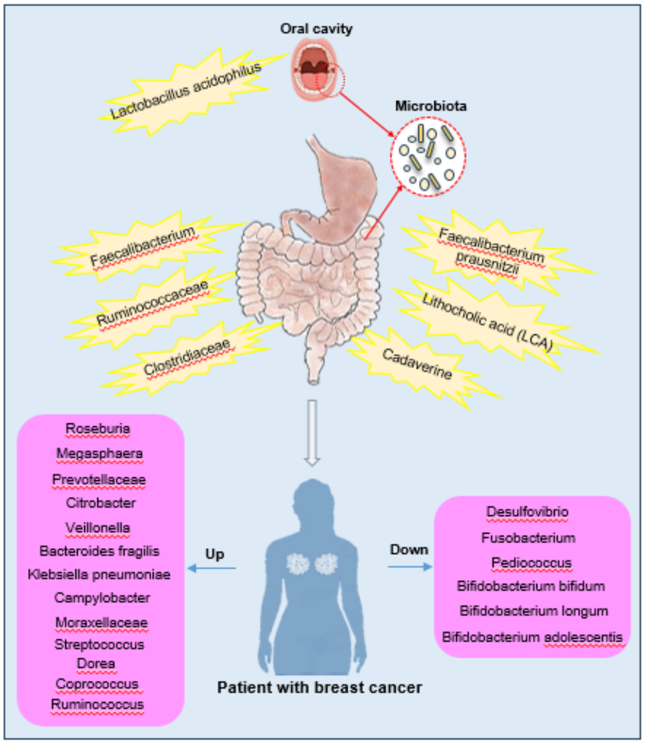

Fig. (2). The potential of oral cavity to gut microbiota axis as a promising resource in the fight against breast cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.4. Predictive Implications

Interestingly, recent investigations have probed the efficacy of gut microbial status as a parameter to predict the response of cancer and, especially, patients with BC to specific therapies. However, this landscape of research needs to be expanded and the studies have to be further verified. The potential of the gut flora population to determine the efficacy of immunotherapy regimens in multiple tumor types has brought the reliability of this factor in therapy response prediction [122]. In a study of advanced cancer cases treated with ICIs (either PD-1 or CTLA-4 inhibitor or a combined regimen), Chang *et al*. found that the distribution of the gut flora of the patients who benefited from the therapy was more similar to healthy counterparts than cases with poor response. Linear Discriminant analysis showed that the genus *Lachnospiracea incertae sedis* and *Fusicatenibacter* and species *Fusicatenibacter saccharivorans* were more abundant in the cases with favorable response. However, alpha diversity was associated with longer OS in cases receiving checkpoint inhibitors, indicating the potential of this parameter as a prognostic factor instead of a predictive value [123]. Formerly, Liang *et al*. provided a machine learning algorithm and shotgun metagenomic data analysis after obtaining baseline gut microbial data in patients with cancer undergoing ICI therapy to predict

Table 2. Prognostic implications of the gut microbial status in patients with BC.

Study	Year	Findings
Carter *et al.* [111]	2019	Diversity of the gut bacterial composition is correlated with cardiorespiratory fitness
Okubo *et al.* [112]	2020	Gut microbiota may influence anxiety and depressive disorders; high FCR is associated with lower microbial diversity, decreased *Firmicutes*, *Ruminococcus* and *Bacteroides* and increased *Bacteroidetes* is related to FCR
Guan *et al.* [108]	2020	Median PFS was limited in patients with the microbial composition of *Slackia*/ Patients with species *Blautia obeum* had longer PFS time/ Capecitabine-consisting chemotherapy regimen could affect gut microbiota
Di Modica *et al.* [115]	2021	Among patients with HER2$^+$ tumors receiving trastuzumab-containing neoadjuvant treatment, microbial status of responder and non-responder cases were different; *Bifidobacteriaceae*, *Turicibacteraceae*, *Clostridiales*, *Bacteroidales* were associated with pathological response
Banerjee *et al.* [105]	2021	Tumor bacterial diversity affected prognostic values like DFS and therapy response
Terrisse et al. [107]	2021	Commensal bacteria were correlated with no axillary node spread and smaller tumor/ Commensal bacteria were associated with favorable chemotherapy outcomes/ Fecal bacterial taxa related to poor prognosis were higher in patients with chemotherapy-related neurological side effects
Wenhui *et al.* [109]	2022	An increase in abundance of taxa *Campylobacter*, *Moraxellaceae* and *Streptococcus* in the patients compared to the controls could be regarded as a risk factor for BC
Yao *et al.* [110]	2022	Preoperative gut microbial status may predict the probability of chronic postoperative pain
Li *et al.* [116]	2022	Three signature taxa *Dorea*, *Coprococcus* and *Ruminococcus* were reliable in distinguishing responder and non-responder early cases receiving neoadjuvant chemotherapy
Nguyen *et al.* [145]	2023	Baseline gut microbial population was linked to the therapy-related gastrointestinal and hematologic toxicities; taxa from *Sporanaerobacteraceae*, *Fusobacteriaceae*, *Lachnospiraceae* and *Bacteroidaceae* were related to severe neutropenia
Nguyen *et al.* [121]	2024	Higher alpha-diversity and high abundances of specific distinct taxa (mostly *Ruminococcaceae, Oscillospiraceae* and *Lachnospiraceae*) was associated with diminished hazard of hematological events and neutropenia/ Significant correlation between taxa from *Sporanaerobacteraceae, Fusobacteriaceae, Lachnospiraceae* and *Bacteroidaceae* and severe neutropenia was observed/ Negative correlation between *Odoribacter laneus* species abundance and nausea and vomiting and higher numbers in *Oscillospiraceae, Ruminococcaceae* and *Lachnospiraceae* families was linked to adverse events in gastrointestinal system

the clinical outcome. Their study suggested two groups of microbial genera enriched in responders and non-responders introducing novel strategies in using gut flora composition in ICI response augury [124]. Also, the implication of gut-residing flora in the therapy efficacy forecast of patients with BC has been reported so far. Recently, Schettini and colleagues revealed that certain bacterial species may serve as efficacy predictors in metastatic BC cases receiving CDK4/6 inhibitor-based treatment, which is almost a novel approach. At the phylum and species level, no significant difference was found in alpha-diversity among responders and non-responders. Moreover, species *Ruminococcus callidus* and *Bifidobacterium longum* remarkably discriminated against the responders and species *Schaalia odontolytica* and *Clostridium innocuum* were enriched in the non-responder cases with an AUC of greater than 0.9. Even though other differentially-enriched taxa were observed among the responders and non-responders, they were not reported to be statistically significant [125]. Furthermore, the favorable outcome has been linked to the higher relative level of *Odoribacter splanchnicus* and reduced baseline population of *Blautia wexlerae* in patients with metastatic hormone receptor-positive BC treated with eribulin alone or combined with PD-1 inhibitor pembrolizumab indicating more potentials of the intestinal flora in therapy response forecasting [126]. Finally, certain intestinal microbe populations may be associated with and predict immunotherapy toxicity in patients of different cancer types. However, the determination of the specific taxa in BC cases and the quantitative predictive value calculation needs additional investigations and larger study samples [117].

5.5. Supplementation

The profit of dietary supplementation with specific useful microbial types to modify the intestinal microbiome has brought encouraging consequences. Through the oral delivery of *Lactobacillus acidophilus* (*L. acidophilus*) prior to the transplantation of BC cells and continuously during the disease period in mouse models, a significant expansion in their survival time was achieved. This effect was attributed to the augmentation of antitumor immunity, facilitated by the production of proinflammatory cytokines such as interferon-gamma (IFN-γ). Further animal studies confirmed the anticancer effect of *L. acidophilus* in the context of BC [127].

Diet mixed with probiotic agents regulates the gut microbial profile and function via interaction with the commensal population and microbial enzyme synthesis. To assess the effect of probiotics on the gut microbiome composition, Pellegrini *et al*. randomized BC survivors to receive a Mediterranean di*et al*one or in combination with probiotics, including *Lactobacillus rhamnosus* and *Bifidobacterium longum*. The gut bacterial diversity increased in the patient's receiving probiotics. Also, *Bacteroidetes/Firmicutes* ratio significantly diminished in this cohort of patients. The addition of probiotics was associated with improved metabolic profile, as well [128]. Lymphedema, characterized as an inflammatory complication that arises after BC treatment, exerts a detrimental influence on the quality of life experienced by affected patients. The supplementation of a low-calorie diet with synbiotics in obese BC survivors demonstrated favorable effects, as evidenced by the elevation of anti-inflammatory markers, including TGF-β, adiponectin, and IL-10, in the patient's serum. Additionally, this intervention resulted in a reduction in edema volume, providing further support for the potential benefits of synbiotic supplementation in managing inflammation and edema in obese BC survivors [129]. Due to the fact that synbiotics bear antioxidant properties, Navaei *et al*. conducted a double-blind placebo-controlled study and reported that receiving synbiotics could significantly decrease serum malondialdehyde levels in parallel to the enhancement of superoxide dismutase concentration among obese BC survivors. This indicates the protective antioxidant feature of the synbiotics. However, in this study synbiotics had no significant effect on the size of arm edema [130]. Intriguingly, in a study by Lahiji *et al*., the addition of synbiotics to the diet of obese postmenopausal hormone-positive BC survivors demonstrated insignificant effects on glycemic control and sex hormones after eight weeks of trial [131]. Another randomized placebo-controlled research by Lahiji *et al*. revealed that supplementation with synbiotics may attenuate the inflammatory state in postmenopausal obese BC survivors through an increase in adiponectin and TNF-α reduction [132]. Eventually, cognitive impairment appears to be an inevitable and worrisome event in patients with BC undergoing chemotherapy. Probiotic supplementation has been suggested recently by Juan *et al*. as a potential preventing modality through modulating plasma metabolites like p-Mentha-1,8-dien-7-ol in a double-blind trial of patients with BC receiving adjuvant chemotherapy [133].

6. CLINICAL TRIALS ASSESSING THE ROLE OF GUT MICROBIOTA IN BREAST CANCER THERAPY

Research shows that gut microbiota can significantly impact how effective various cancer treatments are, including immunotherapy and chemotherapy. For example, certain microbial profiles have been linked to treatment responses in patients with HER2-positive metastatic breast cancer receiving chemotherapy, suggesting these profiles could serve as predictive biomarkers for treatment outcomes [117, 134].

Currently, clinical trials are exploring how modifying gut microbiota through methods like probiotics, prebiotics, and FMT might enhance treatment responses and minimize side effects for patients with BC. These approaches aim to boost immune responses and improve overall patient outcomes [12, 117]. Studies have found notable differences in gut microbiota composition between patients with BC and healthy individuals, with specific microbial species associated with either tumor progression or regression. A reduction in microbial diversity has been particularly linked to more aggressive BC forms [135]. Integrating microbiome analysis into clinical practice could lead to more personalized treatment strategies for patients with BC. This includes identifying unique microbial signatures that may act as biomarkers for predicting how well patients will respond to treatments, allowing for tailored therapies. These insights highlight the gut microbiota's potential as a novel target in BC therapy, paving the way for innovative strategies that leverage the relationship between the microbiome and cancer biology [12, 117].

7. PITFALLS AND FUTURE PROSPECTS

Not only is cancer affected by the intestinal microbial community, but other disorders, including inflammatory diseases and neurological deficits, appear to be influenced by gut microbial dysbiosis. Many studies have illustrated the consequential role of gut bacterial dysregulation in the pathogenesis and progression of inflammatory bowel disease (IBD) and neurological conditions such as Parkinson's and Alzheimer's diseases and multiple sclerosis through deviations in the inflammatory status and metabolic properties, among other mechanisms [136, 137]. Even there is a potential association between specific kidney stone formation and proinflammatory gut dysbiosis [138]. Numerous potential associations have been suggested thus far in the context of cancers, particularly BC. However, discrepancies in reported bacterial taxa and the limited availability of validated data from human studies underscore the need for further dedicated efforts to comprehensively understand the role of the microbiota in BC and its implications for diagnosis, treatment, and prevention. Investigations exploring the influence of intestinal dysbiosis on various aspects of BC encompass a broad range of taxonomy levels within the resident bacterial community, including phylum and species classifications. The vast diversity within each taxonomic group further complicates the data, posing challenges for comprehensive analysis and the formulation of reliable conclusions. To obtain more conclusive and robust findings, future studies in this field should strive to harmonize methodologies and incorporate larger sample sizes, allowing for a more comprehensive understanding of the complex relationship between gut microbiota and BC. Fortunately, several ongoing clinical trials hold promise in providing additional insights into the intricate connections between the gut microbiota and the development and treatment of BC. These trials aim to elucidate the potential benefits of "biotics" supplementation, such as probiotics or synbiotics, in the context of BC. The outcomes of these trials have the potential to enhance our understanding of the role of gut microbiota in BC pathogenesis and treatment, paving the way for potential therapeutic interventions and personalized approaches in managing this type of cancer [103]. This would enable the incorporation of gut microbial status assessment and dietary incubation with probiotics into the standard diagnosis and treatment guidelines for BC. Such inclusion holds the potential to enhance the precision and effectiveness of BC management by considering the interplay between the gut microbiota and the disease, allowing for personalized therapeutic approaches and improved patient outcomes. Also, the heterogeneous available evidence requires comprehensive and multi-aspect analysis to develop microbiota-related patterns in the BC care landscape. Machine learning and deep learning techniques are employed to introduce robust biomarker panels for the detection and prognosis prediction of diseases using datasets and experimental evidence directionally [139]. Employing a machine learning approach, Ciaramella *et al*. have recently proposed a signature panel encompassing 13 transcribed-ultraconserved regions of long ncRNAs (lncRNAs) exhibiting distinct expression patterns in bladder cancer tissues compared to normal tissues. This panel demonstrates the potential to discriminate between patients with bladder cancer and healthy individuals while also offering predictive capabilities for estimating patients' survival time [140]. To date, a multitude of research papers have presented findings on the utilization of artificial intelligence (AI) methodologies, including both machine learning and deep learning, to explore the clinical correlations between gut microbial status and diverse disorders, such as IBD, obesity, diabetes, and various types of cancer. Evaluating the performance of AI algorithms on microbiome-related data, the most frequently reported metrics were AUC and accuracy, showcasing their effectiveness in discerning and predicting disease associations based on gut microbiota profiles [141]. Recently, Mao *et al*. have suggested a 15-microbe signature to predict progression-free and overall survival in patients with BC [142]. The microbiome presents a compelling opportunity to leverage AI techniques, among other approaches, in constructing microbial profiles to elucidate clinical aspects of BC. Beyond the scope of gut resident bacteria, the population of intestinal commensal fungi has also emerged as a potential influencer of BC. These gut-inhabiting fungi are implicated in immune system regulation and may exert an impact on various human diseases, further emphasizing the need to unravel their role in BC pathogenesis and treatment through comprehensive investigations and integrative analytical methods [143]. In a study utilizing murine BC models, Shiao *et al*. demonstrated that commensal bacteria play a role in enhancing antitumor immunity following radiation therapy. Notably, depletion of these commensal bacteria led to the expansion of commensal fungi, which in turn reduced tumor immune destruction by activating protumor macrophages, thereby suggesting a complex interplay between the gut microbiota, immune response, and tumor progression in the context of BC [144]. Hence, there is a compelling need to investigate the impact of intestinal fungi on the landscape of BC pathogenesis and treatment in parallel.

Table **1** provides an overview of the clinical implications associated with the gut microbial status in patients with BC, emphasizing the importance of comprehensively understanding the role of both bacterial and fungal components of the gut microbiota in BC-related processes.

CONCLUSION

Collectively, the intestinal microbial population emerges as a pivotal player in governing the characteristics of BC. Dysregulation in the relative abundance of gut microbial taxa has been shown to modify BC progression and metastasis, ultimately influencing patient outcomes. Extensive research has elucidated the systemic effects of dysbiotic gut bacteria on BC features through the production of metabolic intermediates and modulation of the immune system. Furthermore, the detailed analysis of the gut microbiota holds great diagnostic and prognostic potential in patients with BC, which can be implemented in disease detection and treatment strategies pending validation through large-scale human studies. Additionally, incorporating commensal gut microbes, such as probiotics and synbiotics, into the patients' diet has the potential to improve BC prognosis and mitigate therapy-related side effects. Ultimately, the development of bacterial "panels" using AI approaches and big data analysis, as well as the exploration of the impact of gut commensal fungi in the BC landscape, may yield promising outcomes in the field of managing this life-limiting cancer.

LIST OF ABBREVIATIONS

HER2 = Human epidermal growth factor
BC = Breast cancer
TNBC = Triple-negative BC
TCR = T cell receptor
BCR = B cell receptor
FMT = Fecal microbiota transplantation
ncRNAs = Non-coding RNAs
PRRs = Pattern recognition receptors
CTX = Cyclophosphamide
ROS = Reactive oxygen species

5-FU = 5-fluorouracil
TNF = Tumor necrosis factor
TLR-4 = Toll-like receptor 4
ICIs = Immune checkpoint inhibitors
CTLA-4 = Cytotoxic T lymphocyte-associated antigen-4
PD-1 = Programmed death-1
UPR = Unfolded protein response
SCFAs = Short chain fatty acids
OM = Oral mucositis
PDAC = Pancreatic adenocarcinoma
NSCLC = Non-small cell lung cancer
RCC = Renal cell carcinoma
LCA = Lithocholic acid
AUC = Area under the curve
ROC = Receiver operating characteristic
PFS = Progression-free survival
BM = Bone metastasis
CPP = Chronic postoperative pain
FCR = Fear of cancer recurrence
ICIs = Immune checkpoint inhibitors
CTLA4 = Cytotoxic T lymphocyte-associated antigen 4
IFN-γ = Interferon-gamma
IBD = Inflammatory bowel disease
lncRNAs = Long ncRNAs
AI = Artificial intelligence

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: study conception and design were provided by Mahrokh Abouali Gale Dari and Hossein Abouali, data was collected by Farhoodeh Ghaedrahmati and Fatemeh Jamshidi, analysis and interpretation of results were presented by Atefeh Bahmani and Arash Moalemnia and manuscript draft was prepared by Farhoodeh Ghaedrahmati, Bartosz Kempisty, Mojtaba Zehtabi and Maryam Farzaneh. All authors reviewed the results and approved the final version of the manuscript

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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