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Review Article

The microbiota in breast cancer: dysbiosis, microbial metabolites, and therapeutic implications

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Abstract: The human microbiome plays a pivotal role in host health and disease, with emerging evidence underscoring its significant influence on the development and progression of breast cancer. Studies have revealed that dysbiosis in both the gut and breast tissue microbiota is strongly associated with an elevated risk of breast cancer. Distinct microbial profiles have been identified among healthy individuals, patients with benign breast conditions, and those with malignant tumors, with further variations observed across different ethnic groups and breast cancer subtypes. The complex interplay between breast cancer risk factors and microbial populations, coupled with the direct impact of microbial communities and their metabolites on inflammatory pathways and immune responses, underscores the importance of this field. Additionally, the interaction between gut microbiota and therapeutic modalities such as chemotherapy and radiotherapy is of particular interest, as these interactions can significantly influence treatment outcomes, either enhancing or diminishing efficacy. This review explores the effects of the Mediterranean diet, probiotics, prebiotics, and natural medicinal products on gut microbiota, emphasizing their potential as innovative therapeutic strategies. Notably, the use of engineered probiotics within the tumor microenvironment represents a promising frontier in breast cancer treatment. In conclusion, research on the human microbiome not only deepens our understanding of breast cancer pathogenesis but also lays the groundwork for the development of novel and targeted therapeutic interventions.

Keywords: Gut microbiome, breast cancer, metabolism, chemotherapy, radiotherapy, probiotics

Introduction

In 2020, breast cancer surpassed lung cancer as the most commonly diagnosed cancer worldwide, with approximately 2.3 million new cases, accounting for 11.7% of all cancer cases. It is also the fifth leading cause of cancer-related deaths globally, resulting in approximately 685,000 deaths (6.9%). Among women, breast cancer represents one-quarter of all cancer cases and one-sixth of cancer-related deaths, making it the second leading cause of cancer mortality in females. Globally, the age-standardized incidence rate of breast cancer is approximately 48/100,000, with significantly higher rates observed in economically developed countries compared to other regions [1]. Risk factors for breast cancer can be broadly categorized into reproductive and non-reproductive factors. Reproductive factors encompass the age at menarche, age at menopause, age at first childbirth, and number of childbirths. Non-reproductive factors include lifestyle elements such as obesity, alcohol consumption, and smoking, etc. [2-4]. Moreover, about 5-10% of breast cancer patients harbor hereditary genetic mutations, such as BRCA1, BRCA2, TP53, PTEN, and PALB2, etc. [5]. With the continuous advancement in diagnostic and therapeutic approaches, significant progress has been made in the fields of endocrine therapy and radio chemotherapy, leading to greatly improved cure rates and survival rates for breast cancer. However, given the vast patient population, we still need to seek more effective strategies to control the occurrence and progression of breast cancer.

The origin of microorganisms and cancer can be traced back to more than 4,000 years ago

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[6]. Although the number of microorganisms known to have carcinogenic potential is limited, their intricate connections with cancer risk factors are complex. An increasing body of research posits that bacteria, viruses, and fungi are key participants in cancer treatment. Recent studies suggest that the microbiome may be involved in the development of host breast cancer and may influence the response to cancer treatment and the efficacy of radio chemotherapy through chronic inflammation and immune responses [7-10].

The purpose of this review is to explore the mechanisms of host-microbiome interactions by summarizing existing research findings, thereby revealing the key role of the gut microbiota in the development and metastasis of breast cancer. In this article, we also discuss the dual nature of the microbiome and metabolites in chemotherapy and radiotherapy and outline the currently known methods that are beneficial for cancer treatment. We hope that these findings can provide new perspectives and breakthroughs to address the current bottlenecks in breast cancer treatment.

Microbiota is always present

The origins of microorganisms date back to 3.5 billion years ago, long before the emergence of humanity. Since Antonie van Leeuwenhoek first observed bacteria through a microscope, and Louis Pasteur coined the term “microbe”, the study of microorganisms by humans has been relentless and has deepened with technological advancements. Humans share a close symbiotic relationship with microorganisms, with more than 90% of our cells hosting them; bacteria and fungi are found throughout our skin, oral cavity, intestines, and other areas. These microorganisms aid in the digestion of food and the synthesis of essential nutrients in our intestines, establishing a mutually beneficial relationship with our body’s organs, thereby impacting both physical and mental health. However, despite the many benefits that microorganisms offer to the environment, a minority of pathogens, such as bacteria, fungi, parasites, and viruses, can lead to disease. Among carcinogenic microorganisms, viruses are particularly notorious; for instance, Human Papillomavirus (HPV) can cause cervical cancer, hepatitis viruses can lead to liver cell cancer, and HIV can result in various types of cancer. In recent years, researchers have discovered an increasing number of bacteria that are associated with the occurrence of tumors [11], such as *Helicobacter pylori* with gastric cancer, *Salmonella typhi* with gallbladder cancer, and *Fusobacterium nucleatum* with *Bacteroides fragilis* (ETBF) with colorectal cancer [12, 13]. These bacteria primarily exist within cells, including cancer cells and immune cells tumors [14], and bacterial DNA, RNA, and lipopolysaccharides have been found in many human solid tumors [11].

In humans, the gut microbiota has the most microorganisms and the largest number of species [15] compared to the rest of the body. The formation and reproduction of the gut microbiome begins at birth, and changes in its composition depend primarily on a variety of genetic, nutrient, and environmental factors. Changes in gut microbiota composition and function can alter intestinal permeability, digestion and metabolism, and immune response. Pro-inflammatory states caused by alternating balance of gut microbiota lead to the onset of many diseases, from gastrointestinal and metabolic diseases to immune and neuropsychiatric disorders [16], to tumorigenesis, which can be said to be involved in most disease processes in humans. Therefore, the exploration of the gut microbiome may be a key to solving human life science problems.

Gut microbiota in breast tumors

Breast cancer is the second most common cancer in the world and the most common malignancy in women [17]. Breast tumors have a richer and more diverse microbiome than all other tumor types. The bacterial load and abundance in breast tumor samples was higher than in normal breast samples from healthy subjects. In contrast, the normal breast tissue adjacent to the tumor has intermediate bacterial load and abundance, between the breast tumor and normal samples [11].

Health and malignancy, health and survivors, benign and malignant

Healthy VS Cancer patients. Highly representative populations in gut microbiota include *Firmicutes*, *Bacteroides*, *Actinomycetes*, and *Proteus*. Breast cancer patients have relative

abundance of *Bacillus* and *Staphylococcus (Firmicutes)* and *Enterobacteriaceae (Proteus phylum)* [18]. Among these, *Escherichia coli* and *Staphylococcus* can induce DNA double-strand breaks and promote chromosomal instability. Both mechanisms are closely linked to initiation and progression of cancer. In contrast, *Micrococcus*, a dominant microbial genus in the gut of healthy individuals, lacks such cancer-promoting capabilities. An unhealthy gut microbiome is prevalent in breast cancer patients, and in an analysis of 162 pre-operative faecal samples, delay in diagnosis was significantly associated with reduced α-diversity, variations in β-diversity, increased abundance of *Enorma massiliensis* species, and reduced abundance of *E. polymorphis faecalis* [19].

Healthy individuals exhibited considerably higher abundance of Lactobacillus, Thermal anaerobic bacilli, Candida, Cygnus, Anaerobic bacillus, Leuconostoc lactis, Lactococcus, Bacillus earthiformis and Methylbacterium compared to cancer patients containing large amounts of bacillus thermobacillus, Escherichia coli, Bacillus cereus and Shewanella. The normal tissues around tumors also exhibit similar microbiomes as tumorous tissue, with a significant difference compared with the healthy controls. In addition, it has been shown that histological grade of BC influences the microbial profile of tumors. As the tumor grade increases, the constituent abundance of the bacteria decreased [20]. Interestingly, using the same approach, Urbaniak C et al. did an analysis of different stages of tumour and degree of infiltration and found no significant differences in microbiome profiles by stage [18]. Based on studies of healthy populations versus patients with breast cancer and benign versus malignant breast cancers, we are more inclined to believe that the abundance of the microbiota is different for different grades of breast cancer, and that as the grading increases, the abundance decreases. The different results may be due to the fact that the microbiota is currently less measurable or less abundant and cannot be fully detected at the time of testing. Exploring more sensitive methods of measuring bacterial abundance may provide more definitive conclusions about the relationship between grade and changes in microbiota abundance.

Healthy VS Survivors. *Neisseria, Ruminococci, Lachnospiraceae, Faecalibacterium prausnitzii, Dolosigranulum pigrum, Corynbacterium durum, Mycobacterium kansasii, Clostridium baratii, and Rothia mucilaginosa* are mainly found only in survivors, while other bacteria such as *Lactobacillus salivarius* are abundant in healthy women [21]. In the gut microbial populations associated with survivors, the abundance of β-glucuronidase is significantly elevated. This enzyme modulates the bioavailability of estrogen, potentially contributing to the initiation and progression of breast cancer [22]. Compared to breast cancer survivors, the healthy control group had a higher proportion of *Firmicutes* and *Bacteroides*, and the ratio of *Firmicutes/Bacteroides* seems to be a risk factor for breast cancer [23]. Futhermore, compared with non-pathological complete response (non-PCR), PCR in patients with triple negative breast cancer who received neoadjuvant chemotherapy has more abundant α-diversity [24].

Malignant VS Benign patients. There is a significant difference in the composition of the microbiota between breast tissue from invasive cancer and benign disease [25]. Malignant breast tissue is rich in *Lactobacillus, Hydrogenophaga, Gluconacterobacter, Atopobium* and *Fusobacterium*, while the abundance of *MGS-260, Porphyromonas macacae, Staphylococcus epidermis, Prevotella timonensis, Clostridium sp ASF 356* and *Atopobium vaginae* is lower compared to benign disease [21]. *Fusobacterium* has been implicated in the development of various cancers, potentially through the secretion of virulence factors that induce a pro-tumorigenic and pro-inflammatory microenvironment. Additionally, *Fusobacterium* may contribute to cancer progression by engaging in multiple methionine-dependent metabolic pathways. Compared with benign breast cancer patients, malignant tumors have a higher ratio of *Firmicutes* to *Bacteroides*. This seems to contradict the higher proportion of *Firmicutes* and *Bacteroides* in the healthy control group previously obtained. We consider whether it is related to other factors such as the age and weight of the sample.

Different subtypes of breast cancer

According to the immunohistochemical classification of hormone receptor status in cancerous breast cells, there are 4 categories of breast cancer: endocrine receptor-positive (estrogen or progesterone receptors) (abbreviated

as BRER), human epidermal growth factor receptor 2-positive (HER2) (abbreviated BRHR), triple-positive (positive for estrogen, progesterone, and HER2 receptors) (abbreviated as BRTP), and triple-negative (lack of estrogen, progesterone, and HER2 receptors) (abbreviated as BRTN). These four types have specific prognosis and response to treatment. Endocrine therapy is effective against BRER, BRTP but not BRHR, BRTN, so BRER, BRTP shows a better prognosis, while BRHR, BRTN is more aggressive and has a poor prognosis [26]. BRTN is found in 15-20% of breast cancer patients, is non-responsive to treatment, highly angiogenic, proliferative, and has the lowest survival rate. It is the most aggressive type of all breast cancers [17].

Sagarika Banerjee and colleagues used genome-wide and transcriptome amplification and pan-pathogen microarray (PathoChip) strategies to summarize the microbial characteristics of different breast cancer types, revealing significant and decisive differences between the four breast cancer types. BRHR has the simplest microbial characteristics, while BRTP has the most complex microbial characteristics. Based on the status of estrogen receptors, BRER and BRTP with positive receptors have higher intestinal bacterial abundance. As previously reported, the main bacterial population in the cancer samples were *Proteus species*, followed by *Firmicutes species*. *Brevibacterium* and *Monera* are abundant in all subtypes. Bacterial characteristics of *Actinomyces* and *Bartonella* have been detected in all four cancer types, the hybridization signal intensity of *Actinomyces* in BRTN samples is significantly lower and the highest in BRHR, while the hybridization signal intensity of *Bartonella* in BRER samples is significantly lower. BRTN had the highest lactobacillus activity among all types, the breast carcinogenesis genes phospholipase A2, histone cluster 2, Crk-like, and cyclin D1, were significantly positive associated with the activity of *Lactobacillus*. In addition to bacteria, the presence and abundance of viruses, fungi, and parasites in breast cancer samples have also been observed, but the current research focuses on bacterial pathogens, so the impact of other microorganisms is still poorly understood. *Fungi*, in particular, can interact with bacteria through both physical and biochemical mechanisms [27]. Research by Narunsky-Haziza L et al. found that 96.5% of significant fungal-bacterial symbioses in breast cancer were positive, with *Aspergillus* and *Malassezia* being the center of inter-domain symbiosis [28]. Therefore, research on microorganisms such as fungi is also essential as they may be able to uncover new treatments and targets.

Racial disparities

According to statistics, black women have a lower lifetime risk of breast cancer than white or Asian women, yet they have the highest death rates. By performing genome and metagenomic analysis, Parida and others found that ethnic differences exist in both the immune microenvironment and the microbiota. Compared with white women, black women have higher activated dendritic cells (aDCs), B cells, epithelial cells, megakaryocytic-erythroid progenitors (MEPs), and lower endothelial cells, hematopoietic stem cells (HSCs), and smooth muscle cells. There is no clear difference between Asian women and black or white counterparts. Similarly, the α-diversity of Asian women was not significantly different from that of black and white women. In contrast, there were significant differences in both microbial α-diversity and β-diversity between blacks and whites. In this study, *Pseudomonas* and *Methylobacter* et al. were identified as biomarkers for breast tumors in Asian women, while *Genus Amycolatopsis* and *Anaerovorax* were identified as biomarkers for breast tumors in black women, white women were not mentioned [29]. *Pseudomonas aeruginosa*-mannose-sensitive hemagglutinin (PA-MSHA) exhibits significant antiproliferative effects on breast cancer cells and has been validated in clinical trials for breast cancer treatment. Furthermore, anaerobic bacteria may promote the initiation and progression of breast cancer by metabolizing putrescine into metabolites such as acetate, butyrate, hydrogen molecules, and ammonia.

Gut microbiota associated with risk factors

According to List of breast cancer risk factors as indicated by Cancer Research UK (January 2020), there are 25 factors that can influence the risk of developing breast cancer and they are either beneficial or harmful. Some of the more influential or well-known factors are age at menarche, menopausal status, unmarried

and infertile or having children at a later age, obesity, drinking and smoking.

There was no significant difference in the relative abundance of species in the gut microbiota of premenopausal breast cancer patients and premenopausal controls. In contrast, the relative abundance of 45 species differed significantly between postmenopausal patients and postmenopausal controls: postmenopausal patients were enriched for 38 species, including *Escherichia coli, Klebsiella, Prevotella, Enterococcus gallinarum*, and *Actinobacteria*, and seven species were less abundant in the postmenopausal period. Characterization of macrogenomic function showed that the intestinal macrogenomes of postmenopausal breast cancer patients were enriched in lipopolysaccharide biosynthesis, iron complex transport system, PTS system, secretion system, and β-oxidation encoding genes [30]. And the microbiota composition of postmenopausal breast cancer patients had higher β-diversity and lower α-diversity compared to premenopausal patients [31]. Thus, it is evident that microbiome changes in breast cancer patients occur mainly in the postmenopausal period and that the microbiome genes enriched in the postmenopausal period encode substances involved in multiple pathways that accelerate tumor progression.

The established literature identifies obesity as an important factor in the development of breast tumors, and a meta-analysis has shown that if women exercise regularly, their risk of breast cancer can be significantly reduced by approximately 25% [32]. The gut microbiota of obese patients has been found to be different from that of normal-weight populations. Mörkl et al. performed a 16S rRNA gene analysis of fecal DNA from normal-weight, overweight, and obese populations, as well as athletes, respectively, and demonstrated that obese subjects had exceptionally low α-diversity when compared to normal-weight subjects, while athletes exhibited the highest α-diversity [33]. α-diversity appears to be associated with a lower incidence rate and a higher survival period of breast cancer. Wiley Barton et al. also compared the microbiomes of athletes with those of sedentary healthy individuals at the metabolic level, with a relative increase in metabolic pathways (e.g., amino acid and antibiotic biosynthesis and carbohydrate metabolism) and fecal metabolites (e.g., microbially-produced short-chain fatty acid (SCFA) acetate, propionate, and butyrate) in the athletes and a significant difference in fecal microbiota differed significantly, with greater separation ratios at the macrogenomic and metabolomic levels [34]. The study by Wiley Barton et al. also showed that the microbiomes of different types of athletes are different. In addition, a meta-study showed that beta-glucuronidase was positively correlated with body mass index and total fat mass, and that beta-glucuronidase could increase circulating estrogen. Increased physical activity not only eliminates the risk of obesity for breast cancer, but also increases the diversity of the gut microbiome as well as improves metabolic levels, keeping the body in a healthier state.

There are many other factors that are also strongly associated with breast cancer, alcohol has been shown to increase the relative abundance of *Aspergillus, Enterobacter*, and *Streptococcus* and decrease the abundance of *Anaplasma* and *E. faecalis* [35]. The effects of smoking on the gut microbiome are multifaceted; on the one hand, tobacco contains a variety of potential pathogens such as *Fusobacterium, Bacillus, Burkholderia, Clostridium, Klebsiella* and *Pseudomonas aeruginosa*, who not only cause a wide range of diseases but also disrupt normal microbiota homeostasis [36]; on the other hand, the immunosuppressive substances contained in tobacco lead to an inhibition of the bacterial defense system is impaired, thus causing dysbiosis [37, 38]. Mice with vitamin D receptor (VDR) deficiency are more susceptible to breast cancer because VDR deficiency changes the microbiota profile from normal to oncogenic, disrupting intestinal permeability, causing inflammation, and ectopic bacteria [39]. Chronic diarrhea or constipation is positively associated with the risk of death from breast cancer [40] (**Figure 1**).

Regardless of the risk factors, their impact on the gut microbiome is not monolithic, so exploring treatments for breast cancer through a particular microorganism or class of microorganisms as an entry point is unrealistic, and searching for mechanisms of action between risk factors, the gut microbiome, and breast cancer from the macrogenome, the transcrip-

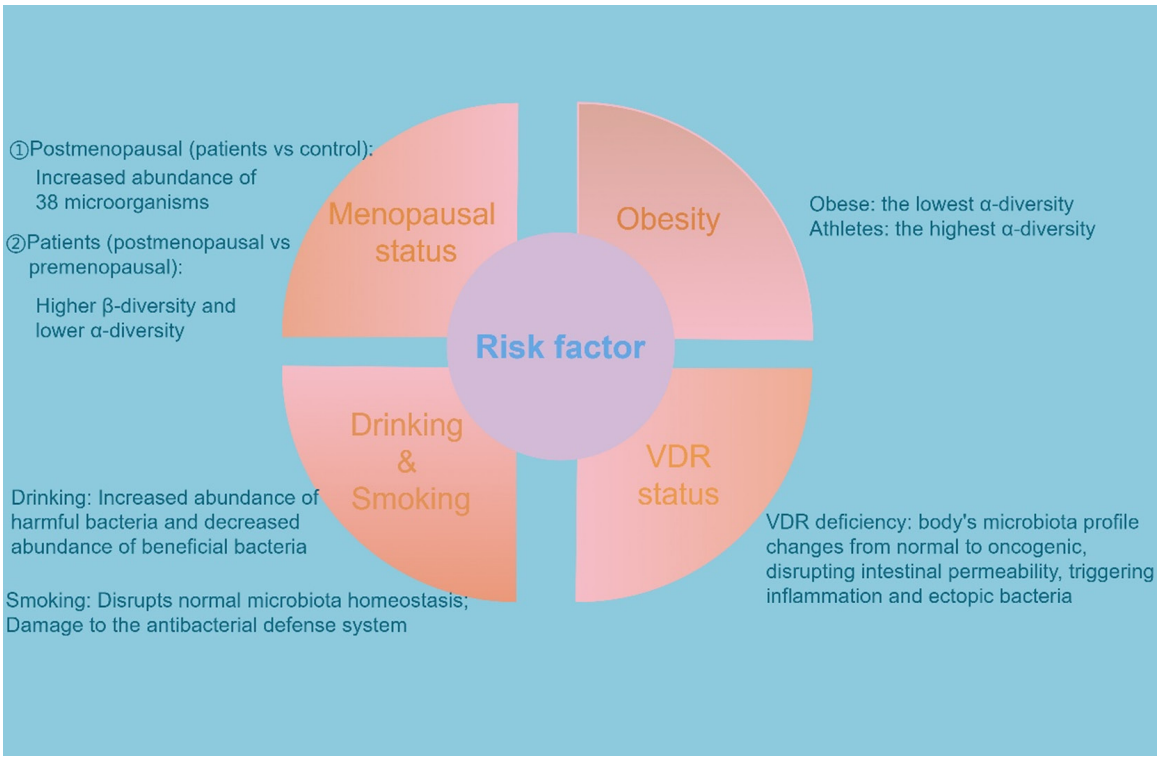

Figure 1. The impact of breast cancer-related risk factors on the gut microbiota (By Figdraw). Menopause, smoking, alcohol consumption, obesity, and vitamin D receptor (VDR) deficiency contribute to an increase in the abundance of harmful bacteria and a reduction in α-diversity, shifting the microbial profile from a normal to an oncogenic state and influencing the initiation and progression of breast cancer.

tome, and the clinical outcomes is the key to solving the problem.

β-glucuronidase and estrogen metabolism

In the liver, estrogens and their metabolites are bound either by glucuronidation or by sulfonation to permit excretion through bile, urine, and feces [41, 42]. Hepatic-bound estrogens excreted in the bile can be deconjugated by bacterial species with β-glucuronidase (BGUS) activity in the gut and thus reabsorbed into the circulation [43-45]. A variety of bacterial β-glucuronidase genes have been described in the human gut microbiota, most notably the *Bacteroidetes* and *Firmicutes* [45]. Fecal BGUS functional activity correlates directly with urinary estrogen and negatively with fecal total estrogen [46]. In addition, it is known that the activity of this enzyme can be modulated by diet and bacterial environment. Studies have shown that healthy individuals consuming high-fat and/or protein-rich diets exhibit increased fecal BGUS activity. In contrast, high-fiber diets significantly decreased BGUS activity [47-49]. Fat- and protein-rich diets stimulate symbiotic bacteria to metabolize bile acids to deoxycholic acid and lithocholic acid, which favors the growth of *Clostridium nucleatum, Aspergillus phylum, Escherichia coli, Enterobacteriaceae, Citrobacter,* and *Klebsiella*, whose dominance leads to the production of BGUS, which in turn leads to a significant increase in β-glucuronidase activity, resulting in estrogenic disorders. Studies have shown that the activity of β-glucuronidase is significantly elevated in both the gut and tumor microenvironment of breast cancer patients, which is associated with tumor aggressiveness and poor prognosis. Additionally, β-glucuronidase may indirectly promote the progression of breast cancer by modulating local inflammatory responses and the tumor microenvironment [50]. We believe that β-glucuronidase is a potential target for drug therapy, and it has been demonstrated that β-glucuronidase inhibitors inhibit the enzyme activity in gastrointestinal tumors, while attenuating the side effects of cancer drugs without affecting the metabolism kinet-

ics of the drugs [10]. Modulating probiotic levels to inhibit the reactivation of estrogen-related proteins has also demonstrated potential in reducing the risk of breast cancer [51]. Although the role of the microbiota in the pathophysiological mechanisms linking β-glucuronidase and breast cancer has not yet been fully elucidated, its significant contribution to these processes has been widely recognized. Future research should further explore and validate the development of β-glucuronidase inhibitors, as well as probiotic modulation strategies based on individual microbiota differences.

Metabolism of the gut microbiota in breast cancer

Nejman et al. showed that the most significant enrichment pathways in bacteria within ER + breast tumors are arsenate detoxification and mycothiol biosynthesis [11]. Arsenic, a class 1 carcinogen associated with lung, liver, bladder cancers, and others [52, 53], activates estrogen receptors, promotes the proliferation of estrogen-dependent breast cancer cells and increases the expression of estrogen-regulated genes. Additionally, arsenic may induce mutations that impair DNA repair, thereby elevating breast cancer risk [54]. Although the role of enzyme thiols in cancer remains unclear, mycobacteria utilize mycothiols to detoxify reactive oxygen species [55]. These findings suggest a functional link between intratumoral bacteria and their tumor microenvironment. The gut microbiota influences tumor progression by modulating the production of metabolites with either carcinogenic or anticarcinogenic properties. For instance, cadaverine (CAD), produced through lysine decarboxylation by the enzyme lysine decarboxylase (LDC), reverses endothelial-to-mesenchymal transition, inhibits cell motility and invasion, and reduces stem cell-like properties by decreasing mitochondrial oxidation [56]. Notably, genes associated with CAD and LDC are downregulated in early-stage breast cancer compared to healthy individuals, suggesting their potential role in regulating breast carcinogenesis. Lithocholic acid (LCA), another key metabolite, induces oxidative stress and reverses lipid metabolism, thereby slowing breast cancer cell proliferation. LCA activates the G-protein-coupled receptor (TGR5) and the constitutive androstane receptor (CAR), leading to decreased expression of nuclear factor-2 (NRF2) and increased expression of Kelch-like ECH-binding protein 1 (KEAP1). This imbalance reduces the expression of the antioxidant enzyme glutathione peroxidase 3 (GPX3) and increases inducible nitric oxide synthase (iNOS) expression, resulting in elevated lipid and protein oxidation and exerting a cytostatic effect [57]. Reduced serum LCA levels and a lower ratio of deoxycholic acid to LCA in early-stage breast cancer patients further support the role of LCA in tumor suppression [58].

Indolepropionic acid (IPA), a bacterial tryptophan metabolite, has been found to be inhibited in synthesis in early-stage breast cancer, especially at stage 0. Increased IPA levels reduce cancer stem cell populations, inhibit cancer cell proliferation and metastasis, and enhance antitumor immune responses by suppressing epithelial-to-mesenchymal transition and inducing oxidative and nitrosative stress [59]. Succinic acid, which accumulates abnormally in various cancers, reduces global 5-hydroxymethylcytosine (5hmC) levels and represses the transcription of epithelial-mesenchymal transition (EMT)-associated genes, promoting a mesenchymal phenotype and cancer stemness [60]. Additionally, succinic acid stabilizes the transcription factor HIF1α and reprograms cellular metabolism toward glycolysis [61]. In triple-negative breast cancer (TNBC), Wang et al. identified that the metabolite trimethylamine N-oxide (TMAO), derived from *Clostridium* spp., is significantly enriched in the immunomodulatory subtype (IM). Patients with higher TMAO levels exhibit better responses to immunotherapy, as TMAO activates the endoplasmic reticulum stress kinase PERK, inducing tumor cell pyroptosis and enhancing CD8+ T cell-mediated immune responses [62] (**Figure 2**).

Evidently, even if certain microorganisms do not come into direct contact with breast cancer cells, their metabolites can influence cancer development through various pathways. The important role of microbial metabolites in the process of tumorigenesis and development was revealed. Overall, the microbiota-metabolite-therapeutic axis would be a promising therapeutic strategy, and the possibilities of microbiota metabolism deserve further exploration.

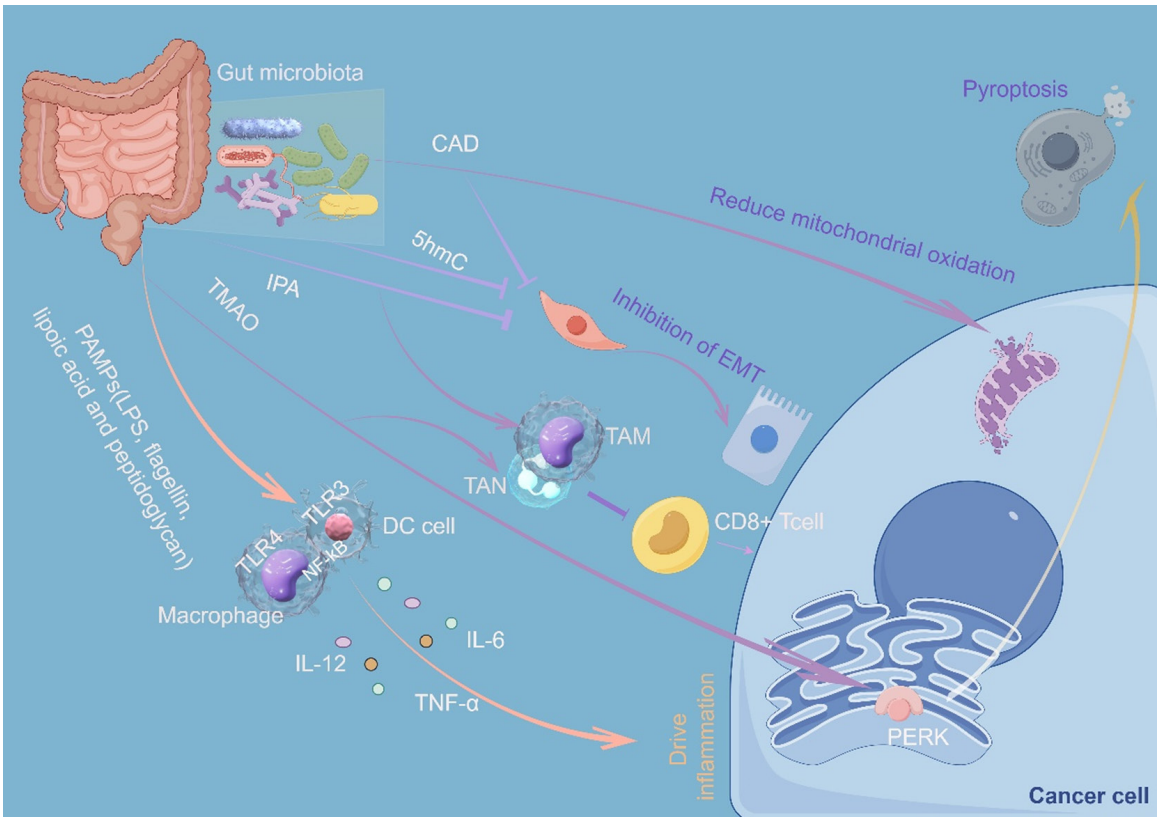

Figure 2. The regulatory network of gut microbiota and metabolism on tumor microenvironment and cancer cell behavior (By Figdraw). Cadaverine (CAD) inhibits tumor cell invasion and stem cell-like properties; indolepropionic acid (IPA) reduces cancer stem cells and enhances anti-tumor immunity; succinic acid promotes a mesenchymal phenotype and metabolic reprogramming; and trimethylamine N-oxide (TMAO) enhances the efficacy of immunotherapy; pathogenic microbe-associated molecular patterns (PAMPs) stimulate immune cells to produce pro-inflammatory cytokines, including IL-6, IL-12, and TNF-α.

Inflammatory and immune responses

One of the mechanisms by which gut bacteria promote BC is through chronic inflammation, which is associated with tumor development [63]. On the one hand, certain species of microorganisms digest nutrients such as cellulose, which the body is unable to digest and assimilate, into short-chain fatty acids, which have anti-inflammatory and immunomodulatory effect [64, 65]. On the other hand, the lipopolysaccharide and endotoxin of microorganisms can also react with the body to cause inflammation and immune response. When "leaky gut" occurs, the bacteria or metabolites associated with the bacteria travel with the bloodstream to all tissues of the body, causing a systemic reaction [66, 67]. Intestinal bacteria can upregulate Toll-like receptors (TLR) along with activation of NF-kB, which leads to the release of IL-6, IL-12, IL-17, and IL-18 as well as Tumor Necrosis Factor alpha (TNF-α), triggering an inflammatory mechanism in the tumor microenvironment [68-70]. It has been shown that symbiotic bacteria accelerate toll-like receptor-5 (TLR-5)-dependent malignant progression in IL-6-responsive tumors [71]. Systemic interactions between gut microbes, interleukin-6 (IL-6), and neutrophils have been reported in breast cancer patients. IL-6 can also drive inflammation by promoting insulin resistance and metabolic dysregulation [72]. In addition, IL-6 was positively correlated with the abundance of Lactobacillus species and the abundance of E. faecalis was negatively correlated with IL-6 levels [73].

Studies in early breast cancer have shown that the ratio of neutrophils to lymphocytes is positively correlated with the risk of breast cancer recurrence and the risk of death [74, 75]. Cytotoxic T-lymphocytes (CD8+ T) are consid-

ered to be the most effective immune cells for tumor eradication [76], and a significant reduction in the proportion of *Sphingomonas sphaericus* in the inflammatory process prevents the differentiation and functioning of CD8+ T cells [77, 78]. It is clear that neutrophils and lymphocytes are affected by the host microbiota and inflammation. Similarly, TLRs are able to activate pro-inflammatory cytokines produced by innate response cells by recognizing pathogenic microbe-associated molecular patterns (PAMPs), such as bacterial lipopolysaccharide (LPS), flagellin, lipoic acid, and peptidoglycan. Chronic activation of TLRs promotes tumor cell proliferation, invasion, and migration through the modulation of cytokines, metalloproteinases, and pro-inflammatory integrins [79]. Rather, *Bifidobacterium bifidum* upregulates immunoregulatory galactoglucan lectin-1 in Th2 and Th17 cells, providing a functional link between beneficial microbes and immunoregulation early in life [80].

Therefore, there are clear indications that the human microbiota is involved in the regulation of chronic inflammation and the host immune system during breast cancer development, and that they can be both anti-inflammatory and pro-inflammatory, and can inhibit as well as augment the immune response, and that better utilization of this feature of the microbiota to exploit its strengths and avoid its weaknesses will lead to great breakthroughs in the treatment of breast cancer.

Chemotherapy and radiotherapy

Intratumoral and gut microbiota have been shown to modulate the efficacy of chemotherapeutic agents through diverse mechanisms, thereby influencing therapeutic outcomes in breast cancer. Cyclophosphamide, a widely used chemotherapeutic agent for breast cancer, primarily exerts its anti-tumor effects by activating immune responses and modulating Th1 and Th17 cells [81, 82]. However, antibiotic use can lead to resistance by impairing Th1 and Th17 responses. Interestingly, supplementation with *Enterococcus* and *Barnesiella* can restore cyclophosphamide's anti-tumor efficacy by stimulating tumor-specific CD8+ and CD4+ T cells, as well as Th1 and Th17 cells [83]. Notably, cyclophosphamide administration reduces the abundance of *Thickettsia*, *Lactobacillales*, and *Enterococcaceae* species [83], underscoring the importance of timely supplementation with beneficial bacteria like *Enterococcus* during chemotherapy. Additionally, ectopic bacteria, particularly Gram-positive species, can migrate from the gut to lymphoid organs, inducing Th17 cell production and enhancing anti-tumor immune responses [83].

The enrichment of *Clostridium nucleatum* and other bacterial species has been observed in the feces of patients resistant to 5-fluorouracil chemotherapy, with higher *C. nucleatum* abundance correlating with poorer clinical outcomes in colorectal cancer [84-86]. Adriamycin, another chemotherapeutic agent used in breast cancer, is limited by its toxic side effects. However, gut *Streptomyces* species can inactivate adriamycin into a non-toxic form [87], offering a potential strategy to protect normal tissues during treatment. Recent studies using 16S rRNA sequencing in breast tumor tissues from patients undergoing neoadjuvant chemotherapy revealed that chemotherapy significantly increased *Pseudomonas aeruginosa* levels. Treatment with *P. aeruginosa*-conditioned medium enhanced the chemotherapeutic effects on breast cancer cells [88]. Conversely, in patients resistant to paclitaxel-based neoadjuvant chemotherapy, tumors harbored enterotoxin-producing *Bacteroides fragilis* (ETBF). Despite its low biomass, ETBF secretes the toxin BFT-1, which binds to NOD1, activates the NOTCH1-HEY1 signaling pathway, and promotes stemness and chemoresistance in breast cancer stem cells (BCSCs) [89]. These findings highlight the potential of targeting the microbiota to mitigate chemoresistance and optimize therapeutic outcomes.

Radiotherapy, a cornerstone of cancer treatment, exerts its effects by directly damaging tumor DNA and inducing reactive oxygen species (ROS)-dependent DNA damage. However, its efficacy varies among individuals, and emerging evidence suggests that the microbiota plays a critical role in modulating radiotherapy outcomes. Although research on the microbiota-radiotherapy relationship is less extensive than that on chemotherapy, significant progress has been made. Radiotherapy disrupts the gut microbiota, leading to dysbiosis, which in turn diminishes treatment efficacy and exacerbates gastrointestinal toxicity [90, 91].

For instance, Kim et al. observed that radiation treatment in mice significantly altered microbiome composition, increasing *Alistipes* and *Corynebacterium* while reducing *Mucispirillum* spp. [92]. Shiao et al. demonstrated the opposing roles of commensal bacteria and fungi in radiotherapy. Antibiotic treatment in mice with breast cancer cells (E0771) impaired radiotherapy efficacy and promoted fungal overgrowth, whereas antifungal treatment enhanced radiotherapy outcomes, delayed tumor growth, and improved survival [93].

A major side effect of chemotherapy and radiotherapy is mucositis, which compromises treatment efficacy and increases morbidity and mortality. The gut microbiota plays a pivotal role in regulating mucositis severity through mechanisms involving inflammation, oxidative stress, and intestinal barrier integrity [94]. Beneficial bacteria such as *Mucinobacteria*, *Bacteroides fragilis*, *Bifidobacterium* spp., *Corynebacterium*, and *E. faecalis* have been shown to mitigate chronic inflammatory diseases. In murine models of mucositis, elevated pro-inflammatory cytokines were associated with a reduced *Firmicutes/Bacteroides* ratio [95]. Radiotherapy-induced changes in gut microbiota composition have been linked to gastrointestinal toxicity. Patients with radiation-induced diarrhea exhibited reduced microbial diversity compared to those without diarrhea [96, 97]. Furthermore, pre-chemotherapy gut microbiota diversity was inversely correlated with the risk of severe hematological toxicity and neutropenia. Specific microbial taxa, such as *Synergistetes* and *Paenibacillales*, were associated with increased or decreased risks of severe neutropenia [98].

In conclusion, the microbiota plays a dual role in modulating the efficacy and toxicity of chemotherapy and radiotherapy in breast cancer. A deeper understanding of microbiota functions and their interactions with cancer therapies is essential for developing complementary treatments that mitigate adverse effects, improve patient quality of life, and enhance cure rates. Future research should focus on identifying promising microbial targets and optimizing microbiota-based interventions to maximize therapeutic benefits.

Treatments related to the gut microbiota

Mediterranean diet

In January 2020, U.S. News & World Report, the authoritative ranking organization in the U.S., released the new issue of the national diet ranking list, in which the “Mediterranean Diet” won the first place in the best diet ranking. The “Mediterranean Diet”, named after some countries around the Mediterranean Sea in Spain, Italy, France and Greece, is a healthy, light, simple and nutritious style of eating, which is known as a diet rather than a structured diet. It is characterized first and foremost by an adequate intake of fruits, vegetables and whole grains, and the diet will also include legumes, nuts, skim milk, olive oil and some fish, as well as small amounts of red meat, salt and carbohydrates. The Mediterranean diet has been shown to play a role in delaying and controlling cardiovascular and metabolic diseases, as well as certain cancers.

Adherence to the Mediterranean diet has been consistently associated with a reduced incidence of all breast cancer subtypes and a lower risk of breast cancer recurrence [99-101]. In contrast, findings from a Spanish cohort study indicate that a predominantly Western dietary pattern is positively correlated with an elevated risk of breast cancer [102]. Comparative studies in non-human primates have shown that monkeys consuming a Mediterranean diet exhibit significantly greater gut microbiota diversity, characterized by higher abundances of *Lactobacillus, Clostridium, E. faecalis*, and *Helicobacter* spp., and lower abundances of *Ruminococcus* and *E. faecalis* spp. compared to those on a Western diet [103]. These results suggest that long-term adherence to a Mediterranean diet can profoundly reshape the gut microbiome. Moreover, monkeys fed a Mediterranean diet displayed increased levels of bile acid metabolites and enhanced bacterial metabolism of bioactive compounds in their mammary glands [104], pointing to a potential connection between dietary patterns and the breast tissue microenvironment. Analysis of samples from women who adhered to the Mediterranean diet for three months revealed elevated fecal concentrations of short-chain fatty acids (SCFAs), particularly propionate and butyrate, which play a

crucial role in maintaining intestinal barrier integrity [105]. Notably, butyrate has been demonstrated to slow or inhibit tumorigenesis [106], underscoring the potential of dietary interventions in modulating cancer risk. Collectively, these findings suggest that diet can exert a direct influence on microbiota at distal sites, including the breast. Furthermore, the combination of probiotics with the Mediterranean diet significantly enhanced microbial biodiversity and reduced the *Bacteroides/Firmicutes* ratio compared to the Mediterranean diet alone [107], highlighting the synergistic benefits of integrating dietary and probiotic strategies.

Probiotics

Probiotics, defined as live microorganisms that confer health benefits to the host by colonizing the body, modulating mucosal and systemic immune responses, or regulating gut flora balance, have shown promising potential in breast cancer research. At the preclinical level, studies in animal models have demonstrated that administration of *Lactobacillus* species in breast cancer-implanted mice leads to increased serum and mammary cell levels of IL-10 and IL-12, reduced IL-6 cytokine levels, and suppressed tumor growth rates [108, 109]. Notably, regular *Lactobacillus* supplementation prior to tumor transplantation significantly improved overall survival in mice, suggesting its role in enhancing immune responses and potentially augmenting anti-tumor activity [110]. Specific strains, such as *Lactobacillus faecalis*, have been shown to inhibit breast tumor growth and metastasis by suppressing the IL-6/JAK/STAT3 signaling cascade, although its relative abundance is significantly reduced in breast cancer patients [111]. Other probiotics, including *Enterococcus faecalis* and *Staphylococcus mansoni*, exhibit anti-cancer properties by reducing cell proliferation, inducing apoptosis, and arresting the cell cycle at the G0/G1 phase in breast cancer cells [112].

Among the most extensively studied probiotics, *Lactobacillus rhamnosus* GG (LGG) is renowned for its anti-inflammatory properties, which include downregulating pro-inflammatory factors such as CXCL-2, IL-6, and IL-8 [113, 114]. In murine models, LGG administration mitigated 5-FU chemotherapy-induced intestinal epithelial damage and inflammation, preserved intestinal barrier integrity, and maintained microbiota homeostasis [115]. Additionally, *Saccharomyces boulardii*, a probiotic yeast used in food and pharmaceutical industries, has demonstrated anti-cancer potential by promoting apoptosis in breast cancer cells through inhibition of survivin gene expression in the MCF-7 cell line [116]. Despite these promising findings, clinical evidence remains limited. A Japanese study reported that regular consumption of *Lactobacillus casei* Hakuta and soy isoflavones from puberty was associated with a reduced risk of breast cancer in Japanese women, highlighting its chemopreventive potential [117]. However, only two registered clinical trials are currently ongoing, underscoring the need for further research to elucidate the role of probiotics in breast cancer prevention and control.

Probiotics have also been explored as adjuncts to chemotherapy. For instance, *Lactobacillus acidophilus* combined with cisplatin enhanced the expression of IFN-γ, GZMB, and PRF1, resulting in reduced tumor size and improved survival in mouse models [118]. Similarly, the combination of *Lactobacillus casei* CRL431 with capecitabine reduced chemotherapy-induced side effects, such as intestinal mucositis and mortality, while maintaining the anti-cancer and anti-metastatic efficacy of capecitabine [119]. Furthermore, the gut microbiome has been shown to influence the toxicity and efficacy of chemotherapeutic agents [120]. A recent randomized trial demonstrated that probiotics containing *Bifidobacterium*, *Lactobacillus*, and *Enterococcus faecalis* significantly reduced chemotherapy-associated cognitive deficits in women undergoing adjuvant chemotherapy [121]. Emerging evidence also suggests that the gut microbiota modulates the response to immune checkpoint inhibitors, such as CTLA4 and PD-L1/PD-1 [122]. For example, mice harboring specific microbiota (e.g., *Akkermansia* and *Bifidobacterium bifidum*) exhibited enhanced responses to anti-PD-L1 therapy, while patients with *Bifidobacterium anisopliae* showed reduced susceptibility to immune checkpoint inhibitor-induced colitis [123]. These findings suggest that microbiota modulation may enhance the efficacy of both chemotherapy and immunotherapy in breast cancer treatment.

Despite these potential benefits, the use of probiotics is not without risks. In severely immunocompromised individuals or patients with multiple organ failure, probiotics may increase the risk of bacterial translocation [124]. Additionally, a study on triple-negative breast cancer revealed that antimicrobial drug use negatively impacts survival outcomes [125]. The effects of different probiotic strains and dosages on breast cancer treatment efficacy remain poorly understood, and the potential side effects of probiotics are often overlooked. Future preclinical and clinical studies are needed to address these gaps. Nevertheless, the current evidence suggests that the benefits of probiotic therapy may outweigh the associated risks, highlighting its potential as a complementary strategy in breast cancer management.

Probiotics and symbiotics

Prebiotics are defined as "substrates that are selectively utilized by host microorganisms to confer health benefits". Common prebiotics include fructooligosaccharides (FOS), isomaltooligosaccharides (IMO), and xylo-oligosaccharides (XOS) [126], which are abundant in foods such as onions, asparagus, garlic, chicory, bananas, inulin, oats, wheat, and barley. These compounds have been shown to increase the abundance of beneficial gut bacteria, particularly *Lactobacillus* and *Bifidobacterium* [126-128]. FOS, a type of dietary fiber found in inulin and neosugar, enhances fecal volume, alleviates constipation, and increases fecal acidity. It is readily metabolized by *Bifidobacterium* and other microorganisms, promoting their growth [129, 130]. Preclinical studies in mouse models have demonstrated that inulin can inhibit the growth of melanoma and colorectal cancer [131]. Clinical trials have further revealed that IMO not only stimulates the growth of *Bifidobacterium* and *Lactobacillus* but also enhances local and systemic Th-1-like immune responses [132]. XOS, naturally present in fruits, bamboo shoots, vegetables, milk, and honey, is efficiently utilized by *Bifidobacterium adolescentum*, *Lactococcus lactis*, *Lactobacillus rhamnosus*, and *Lactobacillus plantarum*, highlighting its potential as a functional prebiotic.

Symbiotics, which combine probiotics and prebiotics, exhibit either complementary or synergistic effects. In symbiotic formulations, probiotics selectively utilize prebiotics as substrates for growth [133], thereby overcoming challenges related to probiotic survival in the gastrointestinal tract. Studies have shown that the combined use of probiotics and prebiotics is more effective than their individual application [134, 135]. Symbiotics have been observed to increase the abundance of *Bifidobacteria* and *Lactobacillus* in fecal samples while reducing coliforms. Additionally, they enhance the activity of digestive enzymes, such as lactase, lipase, sucrase, and isomaltase [136]. Currently, the combination of *Bifidobacterium* or *Lactobacillus* spp. with oligofructose is among the most widely studied symbiotic formulations. Research on prebiotics and synbiotics remains in its early stages, with no dedicated studies yet exploring their specific benefits in breast cancer. However, based on findings from research on other cancers, it is hypothesized that increased intake of prebiotics and synbiotics may enhance host health by reducing systemic inflammation, improving treatment efficacy, and maintaining microbial ecological balance in breast cancer patients during therapy. These potential mechanisms warrant further investigation to establish their role in breast cancer management.

Fecal mushroom transplantation

Fecal Microbiota Transplantation (FMT) was initially developed for the treatment of infectious and inflammatory diseases of the gastrointestinal tract. As research on FMT has advanced, its potential applications in extra-intestinal diseases have become increasingly evident. Currently, FMT has proven highly effective in treating *Clostridium difficile* infections [137, 138] and shows promise in managing conditions such as irritable bowel syndrome, inflammatory bowel disease, insulin resistance, and multiple sclerosis [139]. Although no experimental studies have directly investigated the relationship between FMT and breast cancer, FMT has demonstrated efficacy in alleviating intestinal symptoms and mucosal damage in patients with chronic radiation enteritis [140]. Furthermore, transferring microbiota from patients who have responded positively to anti-PD-1 therapy to non-responders or those with resistance has been shown to enhance anti-PD-1 efficacy and overcome treatment resistance [141, 142].

Despite these promising findings, the therapeutic benefits of FMT in cancer, particularly breast cancer, remain largely unexplored. Several critical questions need to be addressed: the optimal methods for transplantation, the potential use of alternative delivery carriers to enhance efficacy, the specific mechanisms of action post-transplantation, and the potential side effects or adverse reactions associated with the procedure. Addressing these questions will be essential to fully understand and harness the potential of FMT in breast cancer treatment.

Natural medicines and Chinese medicine

Numerous studies have shown that Chinese medicine can significantly regulate the intestinal flora, promote the growth of beneficial bacteria and inhibit the over-proliferation of harmful bacteria, thus maintaining a healthy intestinal environment [143, 144]. Natural medicines are also receiving more and more international attention, and the role it plays in the prevention and control of diseases is being more and more deeply explored, and a large number of natural medicines have been found to have a role to play in the treatment of cancer. Berberine has anticancer effects on a variety of cancers. In addition to inhibiting cell proliferation and metastasis, and inducing apoptosis and autophagy, berberine exerts anticancer effects by modulating the intestinal microbiota, such as increasing the ratio of Thick-walled Phylum *Firmicutes/Bacteroides*, and increasing the relative abundance of *Clostridium, Lactobacillus*, and *anabolic bacilli*. Berberine also improves the effects of antitumor drugs such as cisplatin and 5-fluorouracil, and increases radiation therapy sensitivity [145]. Ginseng and red rhizome extracts promoted the growth of probiotics such as *Lactobacillus* and *Bifidobacterium* and inhibited the growth of *Staphylococcus* and *Salmonella*, among others, in vitro [146]. Ganoderma lucidum extract reduced the high-fat diet-induced elevated percentage of *Bacteroides/anaplasma* phylum and the level of *Aspergillus* species, and also maintained the integrity of the intestinal mucosal barrier [147]. A natural nanotherapeutic agent derived from tea can directly treat breast tumors by promoting apoptosis and modulating the microbiota [148]. A study found that the classic Chinese medical formula Four Mow Formula significantly altered the composition of the gut microbiota and modulated factors associated with fat synthesis and inflammatory storms [149]. All of these studies provide favorable evidence that natural medicines are not limited to a single therapeutic pathway in oncology, and perhaps linking natural medicines to microbes will lead to surprising discoveries (**Figure 3**).

Conclusion and further directions

The gut microbiota, a complex and dynamic ecosystem within the human body, plays a pivotal role in maintaining host health. Its composition and functional alterations are closely linked to various diseases, including breast cancer. Recent studies have increasingly demonstrated a strong association between gut microbiota dysbiosis and the initiation, progression, metastasis, and invasiveness of breast cancer [7, 9]. While certain microbial imbalances may promote tumor development, other specific bacterial species exhibit significant tumor-suppressive effects, highlighting the dual role of the gut microbiota in breast cancer pathogenesis.

Risk factors such as diet, lifestyle, and genetic predisposition can induce dynamic changes in the gut microbiota during breast cancer development. These changes not only disrupt gut metabolic processes but may also exert systemic effects through circulating microbial metabolites, thereby influencing host biological functions. Chronic inflammation and immune dysregulation are two key mechanisms through which the gut microbiota impacts breast cancer. Chronic inflammation, a well-established driver of breast cancer, is closely modulated by the gut microbiota via its effects on the host immune response, underscoring the microbiota's role in cancer progression.

Despite advancements in surgical, chemotherapeutic, and radiotherapeutic interventions that have improved breast cancer survival rates, the disease remains a significant global health threat to women. Current diagnostic and therapeutic strategies require further refinement to address the needs of a large and diverse patient population. Emerging microbiota-targeted interventions, such as the Mediterranean diet, probiotics/prebiotics, fecal microbiota transplantation (FMT), and herbal therapies, have shown promising preliminary

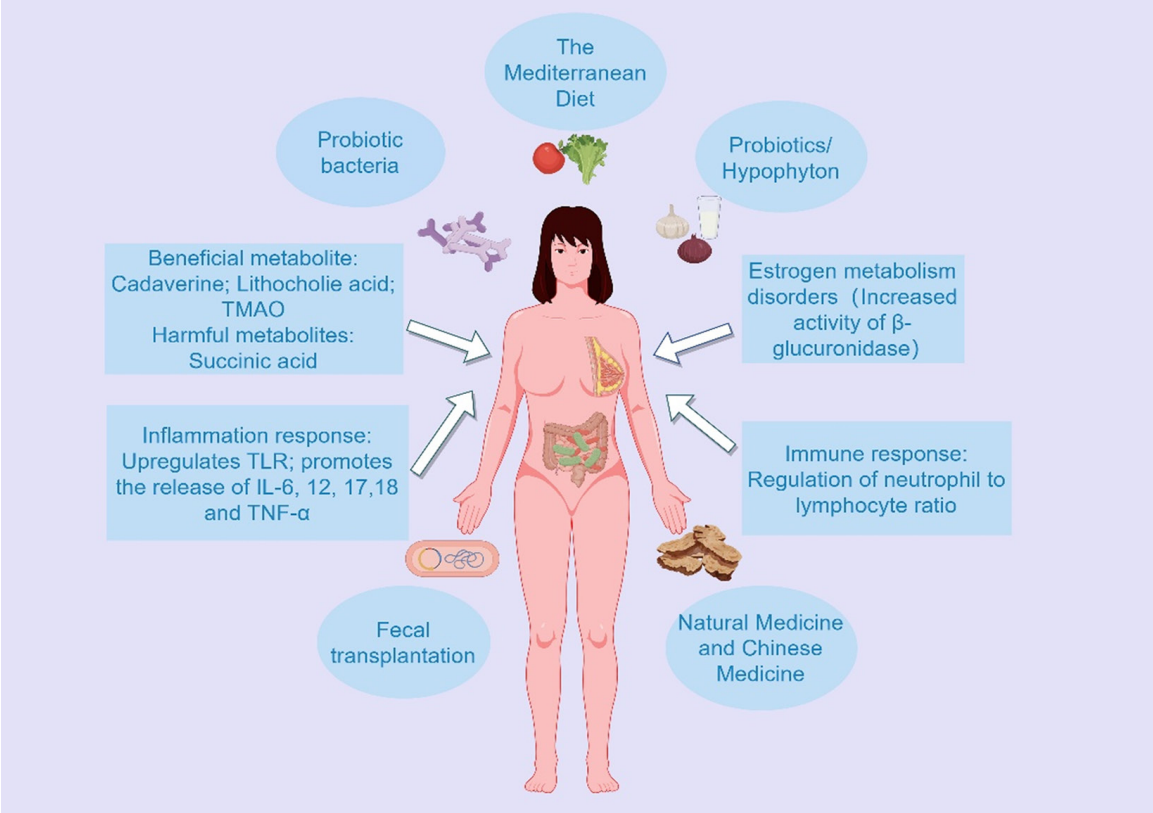

Figure 3. Pathogenesis and treatment options with gut microbiota as the intervention point (By Figdraw). The Mediterranean diet, probiotics and prebiotics, fecal transplantation, and natural medicines and traditional Chinese medicines modulate the composition and function of the gut microbiota, affects the production of metabolites and the inflammatory and immune responses, thereby exerting positive effects in the treatment and prevention of breast cancer.

results in cancer management. These approaches are cost-effective, associated with fewer side effects, and exhibit high patient compliance. Integrating these strategies with conventional therapies (e.g., chemotherapy and immunotherapy) holds potential for improving patient outcomes, reducing drug resistance, and mitigating chemotherapy-induced toxicity. However, large-scale, standardized clinical trials are essential to validate the efficacy and safety of such combinatorial approaches.

To fully harness the therapeutic and preventive potential of gut microbiota modulation in breast cancer, it is crucial to elucidate the underlying mechanisms of microbiota-breast cancer interactions. Current research primarily focuses on characterizing microbiota alterations in breast cancer patients, with limited exploration at the functional level. Key questions remain unanswered, including how specific microbial communities influence breast cancer pathogenesis and how gut microbiota modulation can suppress inflammation and enhance anti-tumor immunity. The rapid advancement of high-throughput technologies, such as metagenomics and metabolomics, offers unprecedented opportunities to explore these mechanisms, paving the way for innovative strategies in breast cancer management. Although this field remains underexplored, it represents a promising frontier in oncology research with the potential to revolutionize breast cancer treatment and prevention.

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Disclosure of conflict of interest

None.

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