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Role of Probiotics in Breast Cancer: From Experimental Models to Clinical Translation

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ABSTRACT: In spite of considerable advances in its management, breast cancer continues being an important medical issue affecting predominantly reproductive females. Recent investigations have suggested that microbiotas of the gut and breasts may contribute to the onset of breast cancer and further breast cancer development and treatment. In the current review, the epidemiologic, mechanistic, preclinical, and clinical literature about the relationship between the gut microbiota dysbiosis and breast cancer will be analyzed especially in regard to the gut-breast connection and probiotic use. Using novel methods of sequencing, researchers found that there were differences in microbiota profiles in the breast and disturbances in the compositions of both gut and breast microbiotas could participate in carcinogenesis, immunity failure, and abnormality in estrogen metabolism. Mechanisms behind these relationships may involve the following processes: reactivation of estrobolome, inflammation regulation, changes in intestinal barrier, transfer of microbe-associated metabolites, and epigenetics control. The dysbiosis of the microbiota is characterized by the decrease in the microbiota diversity, the reduction in the abundance of short chain fatty acid-producing bacteria, and an increase in pro-inflammatory microbes. Probiotics like Lactobacillus and Bifidobacterium could be useful in breast cancer treatment due to microbiota alteration, suppression of cancer-promoting enzymes, assistance in the process of detoxification of carcinogens, immunomodulation, oncogenic signaling modulation, and strengthening the integrity of the intestinal barrier. Preclinically, positive effect on tumor development and angiogenesis as well as better immune responses were expected. However, the necessity in further clinical trials exists.

INTRODUCTION OUTLINING THE GLOBAL BURDEN OF BREAST CANCER AND THE SCIENTIFIC RATIONALE FOR INVESTIGATING PROBIOTICS AS ADJUNCTS IN ITS MANAGEMENT

Breast cancer is the most common cancer in the world amongst women, and it is a growing health issue of concern with a significant socioeconomic burden. Modern epidemiological statistics show that the level of incidence and mortality has been steadily high in the past several decades, and in the developing countries, there are disproportionately high increases. Women in the reproductive age group (15-49 years) are a specific demographic because this age is critical for reproductive and family building. The diagnosis of breast cancer among this cohort not only affects physical health, but also has a complex effect on reproductive potential, mental health, socioeconomic stability, and hence increases the overall burden of the disease, both on the whole society and on the individual (Cai Y et al.,2025).

Between 1990 and 2021, there were significant changes in the epidemiological trends of breast cancer among women of reproductive age, with changing geographic distributions as well as changing risk factor profiles. There is a big difference in

the frequency and mortality rates between the country and rural versus urban areas, which signifies the complex interaction between environmental exposure, lifestyle, healthcare, and genetics. With such differences, there is still a gaping research void on the particular age group that investigates the specific determinants and implications of breast cancer in this age group, which is critical (Cai Y et al.,2025; Halvaei S et al.,2020).

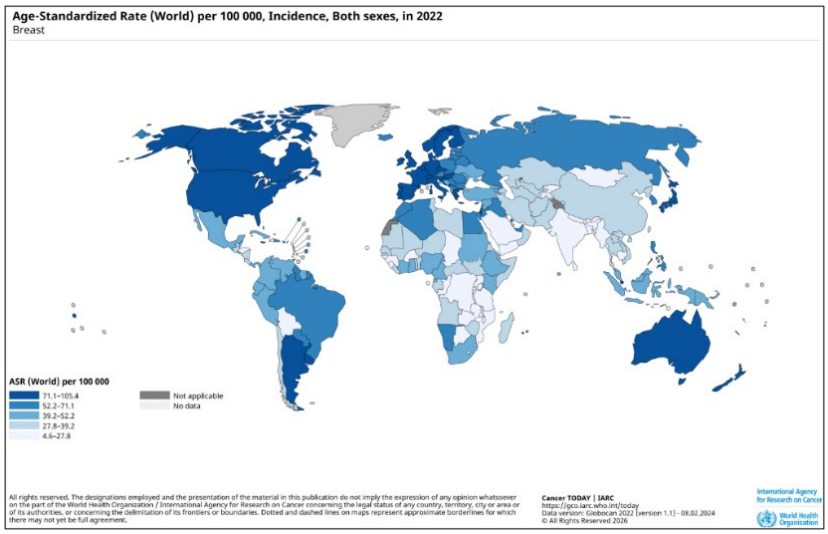
Breast cancer is the most frequently diagnosed cancer in women around the world and has a rate of over 2.3 million new cases every year. Despite the progress in early diagnosis and systemic therapy, recurrence, resistance to the therapy, and the toxicity of treatment are all important complications. In parallel with developments in the field of oncology, studies of the human microbiome have changed the comprehension of the host-disease relationship. The gut microbiota shows an effect on the immune system, metabolic homeostasis, systemic inflammation, and metabolism of estrogen in the pathophysiology of breast cancer (Sung H et al.,2020).

Probiotics, which refer to live microorganisms that bring health benefits to the host when taken in sufficient quantities, have gained popularity other than the traditional use in gut health. In recent studies, probiotics have been proposed to have major applications in the therapy of cancer, due to their capacity to regulate immune responses, alter the microbiota of the gut, and have anti-inflammatory properties. The properties are especially pertinent to the case of oncology since the development of cancer and the treatment process tend to interfere with immune functioning and homeostasis of microbial communities(Thu MS et al.,2023; Nama ASA et al.,2025).

Research has established that probiotics are able to increase the effectiveness of chemotherapeutic agents, decrease the effects of treatments, and improve the overall quality of life of cancer patients. As an example, Lactobacillus and Bifidobacterium strains have demonstrated a potential to regulate tumor microenvironment through cytokine production and the increased tumor microenvironment of natural killer (NK) cells and cytotoxic T lymphocytes. Besides, probiotics might be used to improve some adverse effects of chemotherapy, like mucositis and diarrhoea, through restoring the integrity of the intestinal wall and restoring the balance of the microbial flora(Debela DT et al.,2021).

Epidemiology

Breast cancer is a worldwide health issue, which is the most diagnosed cancer among women and the second most diagnosed cancer in general. It is estimated that in 2022 breast cancer cases worldwide made 2.3 million people, and the number of annual deaths is 670,000. Such a substantial load is not evenly distributed among the nations of the world (Nazeer HA et al.,2025; Penjišević A et al.,2025). Greater incidence rates are reported in the countries that have very high Human Development Index (HDI), which comprises the countries in Australia, North America, New Zealand, and Northern Europe, with approximately 1 in 12 women being diagnosed in their lifetime. On the contrary, in the countries with a low HDI, which have a lower rate of incidence (e.g., 1 in 27 women in a lifetime), the burden of mortality is disproportionately (high Penjišević A et al.,2025). **Figure 1** shows the Age Standardized Prevalence of Breast Cancer around the world.



Graph 1: Standardized Incidence of Breast Cancer [Source: Globocan, 2]

Life time risk of breast cancer is high, and 1 out of 20 women is likely to develop cancer, and 1 out of 70 to succumb to cancer across the globe. Though the majority of cases and deaths in the world are seen in people over 50 years of age, almost half (47 %) of the breast cancer cases in Africa are identified among women below the age of 50 years, which implies a great difference in the manner in which the disease manifests and impacts in this region. There will be an increase in death rates by 38-69% globally with reduced HDI. Although the rates of incidence of this disease have been on the rise by 1-5% every year in most high HDI nations from 2008 to 2017, mortality rates have declined in 29 of the 46 high HDI countries (Joanne Kim et al.,2025).

OVERVIEW OF THE HUMAN MICROBIOME AND THE GUT–BREAST AXIS, EMPHASIZING ITS RELEVANCE ACROSS DIVERSE POPULATIONS AND HEALTHCARE SETTINGS

Breast microbiome

The breast tissue had always been thought of as being sterile, but evidence has recently shown it to actually possess a specific microbiome, which is different in composition from that of other tissues, like the gut. Since the breast consists of much adipose tissue that has extensive vascular and lymphatic systems, it provides a good environment for microbes to colonize (O'Connor H et al.,2018). Early studies were mainly on the topic of oncogenic viruses with a possible linkage of breast cancer (BC) with the viral infections (Akil N et al.,2008). Several studies have associated human papillomavirus (HPV) with BC, and Epstein-Barr virus (EBV), otherwise referred to as human herpesvirus-4 (HHV-4), has also been identified in about a third of mammary tumors (Fina F et al.,2001). Nevertheless, such results are still dubious, and later experiments did not find consistent correlations.

According to mechanistic studies, there is a potential interaction between HPV infection, signal transducer and activator of transcription-3 (STAT3) activation, and high levels of interleukin-17 (IL-17). HPV-induced activation of STAT3 enhances the expression of IL-17, which could facilitate pro-inflammatory conditions in breast tissue that could underlie the advancement of BC. In spite of these findings, it is clear that the role of the breast virome in the preservation of breast tissue homeostasis or in the promotion of the carcinogenesis process is poorly comprehended and requires further study (Hieken TJ et al.,2016).

The development of next-generation sequencing has facilitated the in-depth description of the microbiome of the breast. Colonization of the breast tissue by microbes can take place via a number of pathways, such as nipple-areola contact during breastfeeding, skin contact, sexual intercourse, or translocation of bacteria of the gut. The cumulative evidence shows that the BC tissue has local dysbiosis as compared to non-cancerous tissue. Bioinformatic studies of large-scale samples show that the microbiome composition of the breast differs by ethnicity, disease, BC type, and even in nipple biopsy samples of individuals who have survived cancer and healthy people (Urbaniak C et al.,2014).

Urbaniak et al. described numerous novel unidentified species and phyla of bacteria in breast tissue, the most prevalent of which were Proteobacteria and Firmicutes. It is possible that they are preeminent due to the adaptation to the lipid-rich microenvironment of the breast. A number of bacterial groups in these phyla are more abundant in BC tissues. Though other studies have found no significant bacterial presence on BC, others have found reduced microbial diversity and abundance in malignant tissues. It was found that the relative abundance of Enterobacteriaceae, Bacillus, and Staphylococcus species was increased in BC through 16S rRNA analysis. Notably, Escherichia coli and Staphylococcus epidermidis were observed to cause a process of breaking the DNA of the breast cancer cells in laboratory experiments, which may be thought of as contributing to genomic instability (Banerjee S et al.,2015).

Comparison between benign and malignant breast tissues shows that they have a significant difference in the composition of microbiomes. Despite similarities in the dominance of Bacteroidetes and Firmicutes, the Bacteroidetes and Firmicutes in normal tissues are enriched by low-abundance taxa (Fusobacterium, Atopobium, Gluconacetobacter, Hydrogenophaga, and Lactobacillus) in malignant tissues. Also, specific microbial signatures have been found in triple-negative breast cancer (TNBC), which has potential diagnostic and treatment implications, but the involved functional implications are not well understood (Xuan C et al.,2014).

Quantitative studies indicate that tissues in tumors have less bacterial DNA as compared to the normal tissues surrounding them. *Methylobacterium radiotolerans,* is overgrown in tumors, and Sphingomonas yanoikuyae overgrows in healthy tissue, indicating the possible presence of a protective or probiotic effect. Lower concentrations of S. yanoikuyae are associated with

a decrease in antimicrobial and innate immune gene expression, such as TLRs, IL-12A, BPI, and MPO (Laborda-Illanes A et al.,2020).

The cumulative evidence is that microorganisms that are breast-associated could be playing a role in ensuring tissue homeostasis by stimulating immunity. BC can be promoted by dysbiosis or depletion of microbes of benefit. Although the exact mechanism of carcinogenesis of the breast microbiome is unclear yet, these findings bring to the fore crucial diagnostic, prognostic, and therapeutic implications that need to be clarified further (Urbaniak C et al.,2014).

Table 1: Overview of the breast microbiome and the related implications regarding to breast cancer from different studies

Aspect	Key Findings	Implications	Reference
Presence of breast microbiome	Breast tissue is not sterile and harbors a distinct microbiome different from the gut	Suggests tissue-specific microbial communities	(O'Connor H et al.,2018)
Factors supporting microbial colonization	Lipid-rich adipose tissue with extensive vascular and lymphatic networks	Favors microbial survival and colonization	(O'Connor H et al.,2018)
Viral associations	HPV and EBV (HHV-4) detected in a subset of breast cancer tissues	Possible but inconsistent viral involvement in BC	(Akil N et al.,2008; Fina F et al.,2001)
HPV-mediated mechanisms	HPV activates STAT3, increasing IL-17 expression and pro-inflammatory signaling	May promote tumor-supportive inflammation	(Hieken TJ et al.,2016)
Routes of microbial entry	Breastfeeding, skin contact, sexual contact, and gut bacterial translocation	Explains microbial diversity in breast tissue	(Urbaniak C et al.,2014)
Microbial dysbiosis in BC	Breast cancer tissues show altered microbiome compared to normal tissue	Dysbiosis may contribute to carcinogenesis	(Urbaniak C et al.,2014)
Dominant bacterial phyla	Proteobacteria and Firmicutes are predominant	Adaptation to lipid-rich breast environment	(Banerjee S et al.,2015)
Bacterial species enriched in BC	Enterobacteriaceae, Bacillus, Staphylococcus spp.	Potential role in DNA damage and genomic instability	(Banerjee S et al.,2015)
Genotoxic effects	*E. coli* and *S. epidermidis* induce DNA breaks in vitro	May contribute to mutagenesis	(Banerjee S et al.,2015)
Benign vs malignant tissue microbiome	Distinct microbial composition despite shared dominant phyla	Indicates disease-specific microbial signatures	(Xuan C et al.,2014).
TNBC-specific microbiome	Unique microbial signatures identified in TNBC	Potential diagnostic and therapeutic relevance	(Xuan C et al.,2014).
Microbial abundance in tumors	Tumor tissues contain less bacterial DNA than adjacent normal tissue	Suggests microbial depletion in malignancy	(Laborda-Illanes A et al.,2020)
Protective bacterial species	*Sphingomonas yanoikuyae* enriched in healthy tissue	Possible probiotic or immune-protective role	(Laborda-Illanes A et al.,2020)
Immune modulation	Reduced beneficial microbes linked to lower expression of TLRs, IL-12A, BPI, MPO	Impaired innate immune responses	(Laborda-Illanes A et al.,2020)

Gut-Mammary axis

Gut microbiota has a highly complicated microbial community in the gastrointestinal tract of humans and consists mainly of bacteria and archaea, viruses, and fungi. This microbiota plays a critical role in host physiology and metabolism as well as immune functions. The colon is an extremely concentrated microbial habitat, and it contains approximately bacterial cells per milliliter (O'Connor H et al.,2018; Akil N et al.,2008; Fina F et al.,2001). Together, these microorganisms constitute the gut microbiome, which carries a total of more than three million genes, which is many times greater than the human genome volume, in illustration of its huge metabolic and functional potential (Nazeer HA et al.,2025). Gut microbiota can act as a symbiotic superorganism that interacts directly with the host in a two-way communication system, involving neural, endocrine, metabolic, immune, and humoral contact. Consequently, host genetics has an effect on a variety of physiological processes, along with the activities of microorganisms (Nazeer HA et al.,2025; Hong W et al.,2023).

The gut microbiota, as well as metabolic functions, plays a regulatory role in immunologic homeostasis. It controls the development of immune cells, immune tolerance, and boosts host defense against pathogens by close interactions with the gut-associated lymphoid tissue (GALT). Since it is a systemic regulator, any changes in gastric microbial homeostasis can have an extraintestinal effect on other body organs and cause illnesses like breast cancer (Nazeer HA et al.,2025;Thu MS et al.,2023). Mechanisms connecting Gut Microbiota to the Physiology and Cancer of Breast Tissues. Short-chain fatty acids (SCFAs), metabolites of estrogen, genotoxins, and derivatives of tryptophan, are released by the gut microbiome and enter the circulatory system. Those bioactive compounds can control the activity of the immune system, modify the tumor microenvironment, and gain access to the breast tissues in order to influence cancer-related events, including epigenetic controls and immune surveillance. The movement of microbial metabolites and immune components along the gut to the breast is depicted through arrows to indicate the systemic aspect of the gut in development, progression, and reports of breast cancer to therapy (Nazeer HA et al.,2025). The role of Gut-Mammary Axis has been illustrated in **Figure 2**.

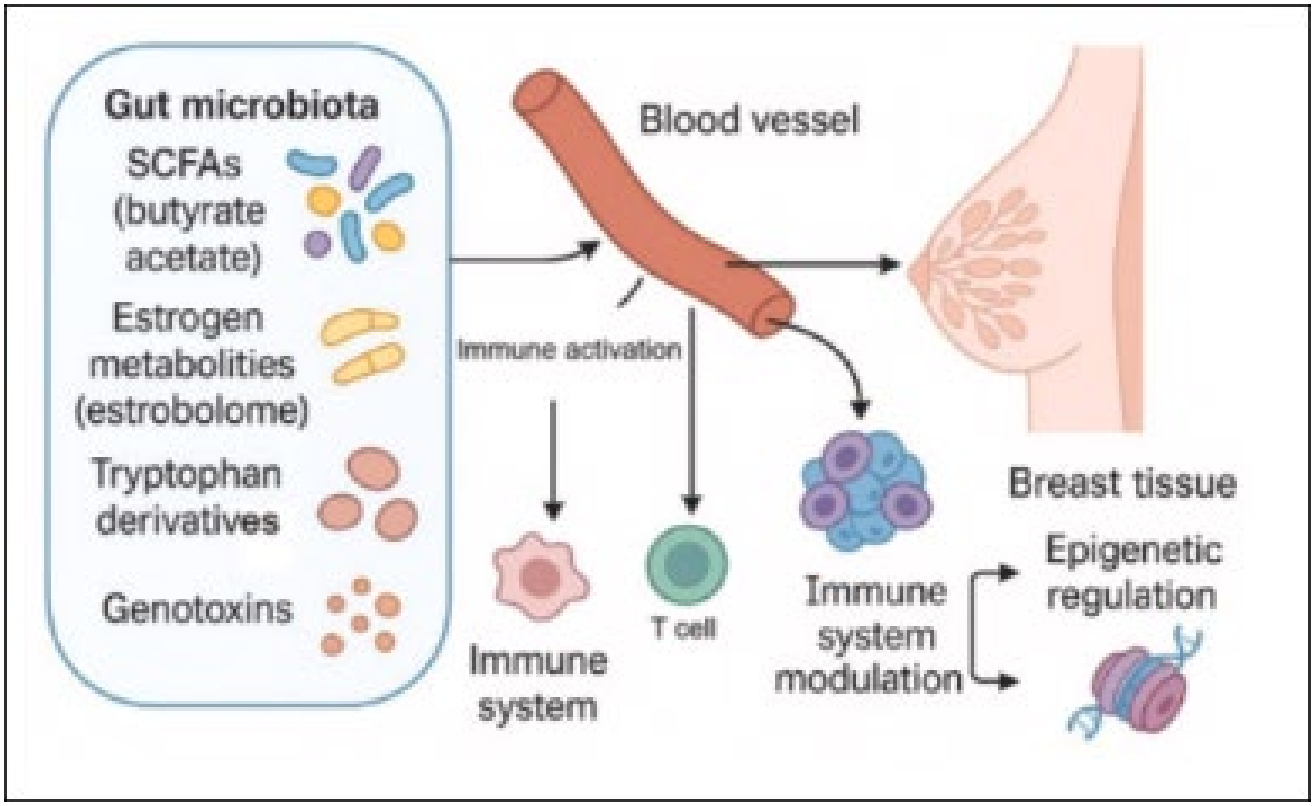


Fig. 2. Gut-Mammary Axis: Mechanisms linking the gut microbiome with the physiology and carcinogenesis of mammary tissue. Based on Nazeer et al. (2025).

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GLOBAL LANDSCAPE OF MICROBIAL DYSBIOSIS IN BREAST CANCER, HIGHLIGHTING EPIDEMIOLOGICAL AND MECHANISTIC INSIGHTS FROM DIFFERENT REGIONS

Microbial dysbiosis in breast cancer globally

Recent studies have shown that microbial dysbiosis, the lack of balance in microbial composition and diversity, is a common feature in the process of breast cancer development and is observable both locally in breast tissue and systemically in the microbiome of the gut. The numerous studies of various geographic areas also indicate that women with breast cancer have a specific microbial signature that is different than that of healthy controls, and this reflects a universal trend of dysbiosis associated with disease processes (Cai Y et al.,2025).

Systematic reviews stated that breast cancer patients experience low microbes in the breast and gut compared to healthy individuals (Bose C et al.,2025). These changes can be found among various cohorts, such as case-control as well as cohort studies that have been conducted across continents and ethnicities, indicating that dysbiosis has no specific population or location (Yamada M et al.,2025).

On the gut level, it is common to find an increase in the relative abundance of major bacterial phyla (Firmicutes) and a decrease in the relative abundance of major bacterial phyla (Bacteroidetes), and a reduction in overall diversity of the microbiota among breast cancer patients, which can impact immune regulation, estrogen metabolism, and systemic inflammation, which are all processes implicated in breast carcinogenesis. In the clinical and pre-clinical studies, it was observed that the fusobacterium and pathobionts are associated with carcinogenic and pro-inflammatory pathways (Bose C et al.,2025;Yamada M et al.,2025).

In breast tissue, there are unique microbial communities, which are found between tumor and normal tissue. The profiles of microbiota have been established in malignant breast tissue using 16S rRNA and reported unique profiles of microbiota in malignant tissues (Atopobium, Fusobacterium, and other low-abundance microbes), indicating that malignancy is linked to local dysbiosis (Mishra P et al.,2025).

Although these world observations were made, another set of research findings also highlights the heterogeneity in dysbiosis patterns among populations and the lack of replications in certain microbial signatures, in many cases, because of a variance in sampling methods, analytical platforms, and demographic variations (Cai Y et al.,2025; Bose C et al.,2025).

BIOLOGICAL MECHANISMS THROUGH WHICH PROBIOTICS INFLUENCE BREAST CANCER DEVELOPMENT AND PROGRESSION, INCLUDING IMMUNE MODULATION, HORMONAL REGULATION, INFLAMMATORY CONTROL, AND METABOLIC EFFECTS

Interaction between gut microbes and breast cancer

The interaction between gut microbiota and breast cancer formation is complex and includes hormonal regulation, immunity regulation, and metabolic signalling. Growing evidence indicates that there are discrete microbial activities and metabolites that coordinate multifaceted interactions with the host endocrine and immune systems and have a direct effect on tumorigenesis (Beaud D et al.,2005).

Estrogen metabolism

The gut microbiota-estrobolome-breast cancer connection is among the most commonly examined mechanistic pathways through which estrogens in the body are regulated due to the activity of the estrobolome, a subgroup of the gut microbiota that can metabolize estrogens. Estrogens are hepatically conjugated and are excreted into the bile as inactive glucuronides. These estrogens are deconjugated in the gut by bacterial β-glucuronidase enzymes, which are mostly Bacteroides, Clostridium, Escherichia, and Ruminococcus in nature (Plottel CS et al.,2011). High levels of 2-glucuronidase have been correlated with the rise of high levels of estrogen in the body, which is considered a risk factor for hormone-receptor-positive breast cancers. The elevated systemic levels of estrogen may increase the growth of estrogen receptor-positive (ER+) breast cancer cells through estrogen response element (ERE)-mediated transcription (Fuhrman BJ et al.,2014). Research has found that postmenopausal women whose gut microbial diversity is lower and whose abundance of β-glucuronidase-producing bacteria is higher experience high levels of plasma estrogen. These data indicate that dysbiosis of the estrobolome has the potential to either increase the risk of breast cancer or manipulate the treatment response in ER+ subtypes (Belkaid Y et al.,2014).

Immune system modulation

Antigen presentation, preserving the mucosal integrity, and producing cytokines help in controlling the immune responses. The systemic inflammation and tumor surveillance may be the downstream outcome of such immunological changes. Lactobacillus, Bifidobacterium, and A. muciniphila are commensal bacteria that facilitate regulatory T cells differentiation and anti-inflammatory cytokines, including IL-10, production, which ensures immune homeostasis. On the other hand, such pathogenic taxa as E. coli and Fu. nucleatum may stimulate TLRs and release pro-inflammatory cytokines (e.g., IL-6, TNF-alpha) and cause chronic inflammatory conditions contributing to the development and progression of tumors (Naqash AR et al.,2021). The inflammation triggered by chronic inflammation through microbial dysbiosis leads to immune evasion through the increase of myeloid-derived suppressor cells (MDSCs) and Treg accumulation in the tumor microenvironment. This repressive environment downregulates the functions of cytotoxic T lymphocytes, hence enabling the survival of tumours. Additionally, bacterial constituents, e.g., LPS, are able to pre-dispose NF-KB signaling and Cyclooxygenase-2 (COX-2) expression, hence increasing the inflammatory cascades linked with breast cancer progression (Parida S et al.,2019).

Hormonal and gut health

Gut dysbiosis is defined as a change in the functional ability and composition of the gut microbiome, whereby there is a decrease in both the microbial diversity and the numbers of beneficial commensals, and an increase in the numbers of pathogenic or pro-inflammatory taxa. Such disproportion may significantly disrupt systemic homeostasis, which leads to chronic inflammation, oxidative stress, and hormonal imbalance, which are the processes that play an important role in the pathophysiology of breast cancer. Mechanistically, gut dysbiosis may be a possible cause of breast cancer through regulation of estrogen metabolism via the estrobolome, activation of immune signaling pathways resulting in the creation of a pro-tumorigenic microenvironment, and alterations in the intestinal production of metabolites that modify host epigenetics and cell growth. The preclinical and clinical evidence support the presence of the gut microbiota as a mediator and biomarker of breast cancer risk (Álvarez-Mercado AI et al.,2023;Zhang J et al.,2022).

The development of high-throughput sequencing and metagenomic studies has made a detailed characterization of gut microbial changes in breast cancer by disease stages and subtypes possible. It has led to a group of taxa dysbiotic phenotype with the loss of short-chain fatty acid (SCFA)-producing commensals (e.g., Roseburia and Eubacterium rectale), and the acquisition of proinflammatory taxa (e.g., Prevotella, Desulfovibrio, and some Clostridium species). The changes lead to perturbation of mucosal immunity, destabilizing the barrier of the intestines and chronic low-grade inflammation that initiates tumorigenesis. The functional metagenomic analyses also depict enrichment of microbial pathways related to xenobiotic metabolism, estrogen conversion, lipopolysaccharide synthesis, and bile acid metabolism that affect the immune activation and hormonal homeostasis (Beaud D et al.,2005;Abolhassani A et al.,2025).

The microbial DNA and its metabolites are translocated to extraintestinal sites like the microenvironment of the breast tumor beyond the gut, where they control phenotypes of immune cells, cytokine balance, and tumor cell functions. The abnormality of estrobolome, especially high levels of 2-glucuronidase, increases estrogen reactivation and systemic exposure, which favors the progression of estrogen receptor-positive breast cancer. Simultaneous inflammatory taxa enhancement and immunoregulatory commensal depletion enhance immune dysregulation and maintain a pro-tumorigenic environment. Combined with the other places, the emphasis on gut dysbiosis as a multi-axis primary cause of breast cancer formation, progression, and resistance to treatment (Beaud D et al.,2005;Zhang W et al.,2022).

Table 2 shows the various mechanisms which are associated with the gut microbes for breast cancer development.

Table 2: The mechanistic pathway associated with gut microbes for development of breast cancer

Mechanistic pathway	Key gut microbial components	Molecular / cellular mechanisms	Impact on breast cancer	Reference(s)
Estrogen metabolism (Estrobolome)	*Bacteroides, Clostridium, Escherichia, Ruminococcus*	β-glucuronidase–mediated deconjugation of estrogen glucuronides → increased systemic estrogen levels	Promotes proliferation of ER+ breast cancer via ERE-mediated	(Plottel CS et al.,2011; Fuhrman BJ et al.,2014; Belkaid Y et al.,2014)

			transcription	
Gut microbial dysbiosis	Reduced microbial diversity; enrichment of β-glucuronidase-producing taxa	Enhanced estrogen reactivation and altered endocrine signaling	Increased risk and progression of hormone receptor–positive breast cancer	(Belkaid Y et al.,2014)
Immune homeostasis maintenance	*Lactobacillus, Bifidobacterium, Akkermansia muciniphila*	Induction of Treg differentiation; production of anti-inflammatory cytokines (IL-10)	Supports immune surveillance and suppresses tumor-promoting inflammation	(Naqash AR et al.,2021)
Pro-inflammatory immune activation	*Escherichia coli, Fusobacterium nucleatum*	TLR activation; increased IL-6, TNF-α secretion	Chronic inflammation and tumor promotion	(Naqash AR et al.,2021)
Immune evasion in tumor microenvironment	Dysbiosis-associated microbial signals	Expansion of MDSCs and Tregs; suppression of cytotoxic T lymphocyte activity	Facilitates tumor survival and progression	(Parida S et al.,2019).
Inflammatory signaling pathways	LPS-producing gut bacteria	Activation of NF-ϰB and COX-2 pathways	Sustained inflammatory cascades enhancing tumor growth	(Parida S et al.,2019).
Loss of SCFA-producing commensals	*Roseburia, Eubacterium rectale*	Reduced SCFA production → impaired gut barrier integrity	Increased systemic inflammation and tumor initiation	(Beaud D et al.,2005;Abolhassani A et al.,2025)
Enrichment of pro-inflammatory taxa	*Prevotella, Desulfovibrio, Clostridium spp.*	Promotion of low-grade chronic inflammation	Supports carcinogenesis and disease progression	(Beaud D et al.,2005;Abolhassani A et al.,2025)
Metabolic reprogramming	Dysbiotic gut microbiome	Altered xenobiotic metabolism, bile acid metabolism, estrogen conversion	Influences immune activation and hormonal imbalance	(Beaud D et al.,2005;Abolhassani A et al.,2025)
Microbial translocation beyond gut	Microbial DNA, LPS, metabolites	Migration to breast tumor microenvironment; modulation of immune cell phenotypes	Alters cytokine balance and tumor cell behavior	(Beaud D et al.,2005;Zhang W et al.,2022)
Treatment resistance and progression	Estrobolome dysregulation and inflammatory taxa	Persistent estrogen exposure and immune dysfunction	Promotes tumor progression and therapy resistance	(Beaud D et al.,2005;Zhang W et al.,2022)

Preclinical evidence from in vitro studies worldwide evaluating probiotic strains and their metabolites in breast cancer models

Breast cancer (BC) is one of the most complicated disorders, and it is the main cause of death among women worldwide. Different species of probiotics could be used in the treatment of this disease. Although the effects of potent probiotics on

BC, as well as its risk factors, have been previously studied, especially Lactobacillus and Bifidobacterium, it is important to mention that the effects of probiotics are strain-specific. The exact mechanism of various Lactobacillus strains in the prevention and/or management of BC complications has not been adequately researched, despite the extensive study of Lactobacillus, particularly in vitro and in vivo. To this effect, there is a significant promotion of immune responses and anti-cancer effects of Lactobacillus strains against BC by the oral administration of Lactobacillus acidophilus (L. acidophilus), Lacticaseibacillus casei (L. casei), Lacticaseibacillus helveticus (L. helveticus), Ligilactobacillus lactis (L. lactis) and Lactiplantibacillus plantarum (L. plantarum). Furthermore, several Lactobacillus strains that are available in the form of oral capsule supplements that include Lactobacillus rhamnosus (L. rhamnosus) with Lactose acidophilus coupled with Bifidobacteria or prebiotics (a synbiotic) are also proven as effective. In addition, certain anti-carcinogenic activity of Lactobacillus strains might be more distinguished than others, which helps in curing cancer complications. They involve interactions with the gut microbiota, immune system modulation, apoptosis induction, anti-inflammatory effect, effects of probiotic-derived agents, and epigenetics (Nguyen MR et al.,2023).

The gut microbiome has the potential to affect tumor growth and the efficacy of cancer treatment, thus it is a potential site of tumor prevention/treatment. The preventive and therapeutic capacities of a probiotic strain, Lacticaseibacillus rhamnosus Probio-M9 (Probio-M9), were studied in a pilot study against murine mammary cancer. A total of thirty-six female mice were randomly selected to three groups (n = 12 per group) as follows: control (without tumor transplantation), model (tumor transplantation; without probiotic administration), and probiotic (30-day oral gavage of probiotic, beginning seven days before tumor transplantation). The alterations in the tumor size were noted, and the end of the trial was followed by blood, tumor tissue, and stool samples that were collected. Compared to the model group, the probiotic group had an extremely lower tumor volume, a higher fecal microbiota Shannon diversity index, and a substantial change in the gut microbiota structure, and more Bacteroidales bacteria 55_9, Porphyromonadaceae bacteria_7, and Alistapes sp_2. Also, the administration of Probio-M9 increased the serum concentration of IL-9, IFN-7, IL-27, and IL-13 and a number of metabolites (e.g., pyridoxal, nicotinic acid, 3-hydroxybutyric acid, glutamine) and lowered IL-5. Such modifications may be linked to the protective action of Probio-M9 against cancer growth in the mammary gland. Therefore, anti-cancer action may be exploited by making use of the host gut microbiome with probiotics (Barcheloui NK et al.,2025).

There are numerous established risk factors of breast cancer related to dysbiosis (an aberrant microbiome). The mechanism by which bacterial products suppress cancer is, however, not well understood. The impact of an exopolysaccharide (EPS)-producing commensal bacterium, Bacillus subtilis, on breast cancer phenotypes was examined in a study. Though B. subtilis has traditionally been used as a probiotic preparation and its EPS prevents inflammatory diseases, it has been practically unheard whether B. subtilis-derived EPS influences cancer or not. The effects of EPS on breast cancer cells' phenotypes were studied as a cancer model. The findings reveal that an EPS molecule secreted by the probiotic bacterium B. subtilis has a multidimensional role on the breast cancer cell phenotypes (Jakubauskas M et al., 2022).

In vivo animal studies from global research settings assessing probiotic effects on tumor initiation, growth, progression, and metastasis

Breast cancer is a common malignancy in women across the entire world, and recurrence and side effects of treatment are posing serious challenges. Immunotherapy has demonstrated to be a promising strategy, though an immunosuppressive microenvironment in the tumor can inhibit its effect. The evidence that is emerging suggests that probiotics, particularly those of the Lactobacillus species, may have a positive influence on the immune response and tumor development with regard to cancer treatment. One of the studies measured the impacts of Lactobacillus reuteri PTCC1058 on tumor progression and immune response on a mouse model of breast cancer induced using 4T1 mouse breast carcinoma cells. The study states that the microenvironment of cancer is regulated by L. reuteri PTCC1058 and alters immune responses in breast cancer (Duan D et al.,2022).

A study compared probiotic supplementation and antitumorigenic effects on an experimental model of liver metastasis of CRC. Male Wistar rats at the age of six weeks were given a multispecies probiotic (1.2 x 109 CFU/kg/day) or placebo mixture. On the 14th day of the experiment, rat CRC cells (CC531) were transplanted under the liver capsule, which would be later treated with FOLFOX CTx (FOL (leucovorin/folinic acid), F (5-fluorouracil), and OX (oxaliplatin). The abbreviation CTx denotes chemotherapy). The tumor volume change was quantified by carrying out a micro-computed tomography (micro-CT) scan on days 28 and 34 of the experiment. There was no probiotic supplementation and FOLFOX CTx

observations. The angiogenesis was inhibited, resulting in reduced tumor volume, since the microvascular density in tumors was significantly reduced in rats fed on probiotic supplements. The study indicates that a multispecies probiotic mixture is very helpful in angiogenesis inhibition and impeding the growth of the CRC liver metastasis in an experimental rat model (Pellegrini M et al.,2020).

These in vivo findings are all consistent, mechanically, in their implication of immune activation (activation of cytotoxic T cells, cytokine modulation), antiangiogenic action, and inhibition of the metastatic growth. Although the majority of studies analyzed the growth and progression of tumors and not the early onset, the overall evidence reveals the involvement of probiotics in the regulation of systemic and local host reactions that limit the growth and invasion of tumors in animal models (Duan D et al.,2022).

Clinical evidence, including observational studies and interventional trials assessing probiotics in breast cancer prevention, treatment, and survivorship

Despite the lack of large prospective studies that specifically focus on probiotic supplements and cancer risk, evidence of reduced risk of cancer with regular use of probiotics (ex: yogurt and fermented foods) is provided in case-control and cohort studies, potentially because of effects on systemic inflammation or estrogen metabolism. Other epidemiological studies have shown that a regular probiotic intake since adolescence has a negative relationship with breast cancer occurrence, which underlines the hypothesis that a more balanced gut microbiome could decrease the risk of cancer in the long term (Seyyedi Z et al.,2025).

A study assessed the efficacy of probiotics combined with the Mediterranean diet (MD) compared to diet alone in the regulation of gut microbiota and metabolic profile of survivors of the overweight BC. Probiotics together with MD have a beneficial effect on the gut microbiota, and are better than MD alone to improve the metabolic and anthropometric parameters (Śliżewska K et al.,2020).

A systematic review was conducted to assess the possible impact of probiotics among breast cancer patients and breast cancer survivors in order to enable additional clinical research. The probiotics supplements that were used were Lactobacillus species, which included Lacto, Lacto plus estriol, Lacto plus prebiotics FOS (fructo-oligosaccharides), Lacto plus Streptococcus, FOS, Lacto plus Enterococcus as ProLB, ProLBS + FOS, and ProLB, respectively. The results indicated that FOS is potentially beneficial in counteracting obesity and dyslipidemia when used by breast cancer patients via ProLBS and by breast cancer survivors via ProLBE. ProLBS with FOS use reduces pro-inflammatory TNF-α in survivors of breast cancer and enhances the quality of life in breast-cancer-induced lymphedema. The combination of probiotics capsule (109 CFU) with a prebiotic and a 10-week intake period may be a more effective solution as compared to probiotics itself (Zhao LY et al.,2023).

ROLE OF PROBIOTICS AS ADJUNCTIVE THERAPY IN BREAST CANCER MANAGEMENT ACROSS DIFFERENT TREATMENT MODALITIES, FOCUSING ON EFFICACY, TOLERABILITY, AND PATIENT-REPORTED OUTCOMES

Probiotics and cancer

The application of probiotics in the treatment and prevention of neoplastic diseases such as cancer has also exhibited great promise, mainly due to the generation of bioactive metabolites and essential nutrients. Change of the composition of gut microbiota has been linked to the risk of cancer, and the substitution of pathogenic microbes with certain specific probiotic strains has been beneficial in the prevention of cancer (Górska A et al.,2019). The probiotics can reduce the side effects of chemotherapy and have the anti-cancer effect in a variety of ways, including by modulating the microbial enzymes and intestinal metabolism, and by lowering β-glucuronidase, azoreductase, and nitroreductase, which are pro-carcinogen compounds. Also, probiotics may attach or ferment dietary carcinogens such as heterocyclic aromatic amines (HCAs) and N-nitroso compounds, and outcompete pathogenic bacteria to inhibit tumor-promoting action. LABs, in particular, Bifidobacterium and Lactobacillus, have been indicated to decrease the populations of Clostridium perfringens in colorectal cancer and polyps of patients (Colella M et al.,2023).

Probiotics also regulate important cellular functions like proliferation and apoptosis, which are important in tumor suppression. As an example, the Lactobacillus reuteri is capable of suppressing the activation of NF-KB by tumor necrosis

factor (TNF) and inducing immune cell apoptosis through the mitogen-activated protein kinase (MAPK) cascade and IkBa stabilization. In addition, probiotics have the potential to suppress tumor-progression-related tyrosine kinase signaling pathways, and Saccharomyces boulardii was reported as a safe probiotic to suppress MAPK activation in cancer models of the (Zhao LY et al.,2023).

Probiotics are also able to prevent carcinogenesis by preventing the proliferation of tumor cells directly and also by reversing the reversal of immunosuppressive actions that tumor cells have employed. Furthermore, host immune responses can be controlled by secondary metabolites, cell wall structures, and genomic DNA, which are probiotic-derived products. SCFA is mainly synthesized by the species of Bifidobacterium and Lactobacillus and has beneficial effects on the intestinal epithelial integrity and functionality. These metabolites also suppress T helper 17 (Th17) cell polarization and suppress the release of pro-inflammatory cytokines, hence adding to the inhibition of tumor growth. Moreover, probiotics have been demonstrated to prevent tumor angiogenesis and modulate cancer cell metabolism by increasing tumor hypoxia by disrupting the anaerobic metabolic pathway (Górska A et al.,2019). Different anti-carcinogenic mechanisms of the probiotics have been summarized in Table 3.

Table 3: Mechanism of probiotics in cancer

Mechanistic category	**Probiotic strains involved**	**Key molecular mechanisms**	**Anticancer effects**	**Reference(s)**
Modulation of gut microbiota composition	*Lactobacillus spp., Bifidobacterium spp.*	Replacement of pathogenic microbes; competitive exclusion	Reduction in cancer risk and tumor-promoting microbial activity	(Górska A et al.,2019)
Detoxification of pro-carcinogens	LABs (*Lactobacillus*, *Bifidobacterium*)	Reduction of β-glucuronidase, azoreductase, nitroreductase activities	Decreased activation of dietary and endogenous carcinogens	(Górska A et al.,2019)
Binding and metabolism of dietary carcinogens	LABs	Binding/fermentation of heterocyclic aromatic amines and N-nitroso compounds	Lower intestinal exposure to carcinogens	(Górska A et al.,2019)
Suppression of pathogenic bacteria	*Lactobacillus*, *Bifidobacterium*	Reduction of *Clostridium perfringens* populations	Decreased colorectal tumorigenesis	(Colella M et al.,2023)
Regulation of cell proliferation and apoptosis	*Lactobacillus reuteri*	Inhibition of TNF-induced NF-κB activation; MAPK-mediated apoptosis; IκBα stabilization	Suppression of tumor cell survival and proliferation	(Zhao LY et al.,2023)
Inhibition of oncogenic signaling pathways	*Saccharomyces boulardii*	Suppression of MAPK and tyrosine kinase signaling pathways	Inhibition of tumor progression	(Zhao LY et al.,2023)
Immune system modulation	*Lactobacillus*, *Bifidobacterium*	Regulation via metabolites, cell wall components, and probiotic DNA	Restoration of antitumor immune responses	(Górska A et al.,2019)
SCFA production	*Bifidobacterium spp., Lactobacillus spp.*	Increased short-chain fatty acid synthesis	Enhanced epithelial integrity and anti-inflammatory effects	(Górska A et al.,2019)
Inhibition of inflammatory	SCFA-producing probiotics	Suppression of Th17 polarization; reduced pro-	Reduced tumor-associated inflammation	(Górska A et al.,2019)

immune pathways		inflammatory cytokine release		
Anti-angiogenic and metabolic modulation	Multiple probiotic strains	Inhibition of tumor angiogenesis; increased tumor hypoxia via metabolic disruption	Reduced tumor growth and progression	(Górska A et al.,2019)
Reduction of chemotherapy side effects	Multiple probiotic strains	Restoration of gut microbial balance and metabolism	Improved treatment tolerance	(Górska A et al.,2019)

Mechanism of action of probiotics in cancer

The well-established gut health-promoting probiotics have become of interest due to the potential use in the treatment and prevention of cancer. The anticancer effects of probiotics occur via a multi-faceted range of complex mechanisms that are reflections of the complexity of interactions between the microenvironment of the tumor and the gut microbiota, on the one hand, and host physiology, on the other. Several significant processes through which probiotics can influence the occurrence, character, and reaction to the therapy of cancer (Iqbal H et al.,2024).Figure 3 illustrates the mechanisms of the effect of probiotics in prevention of cancer.

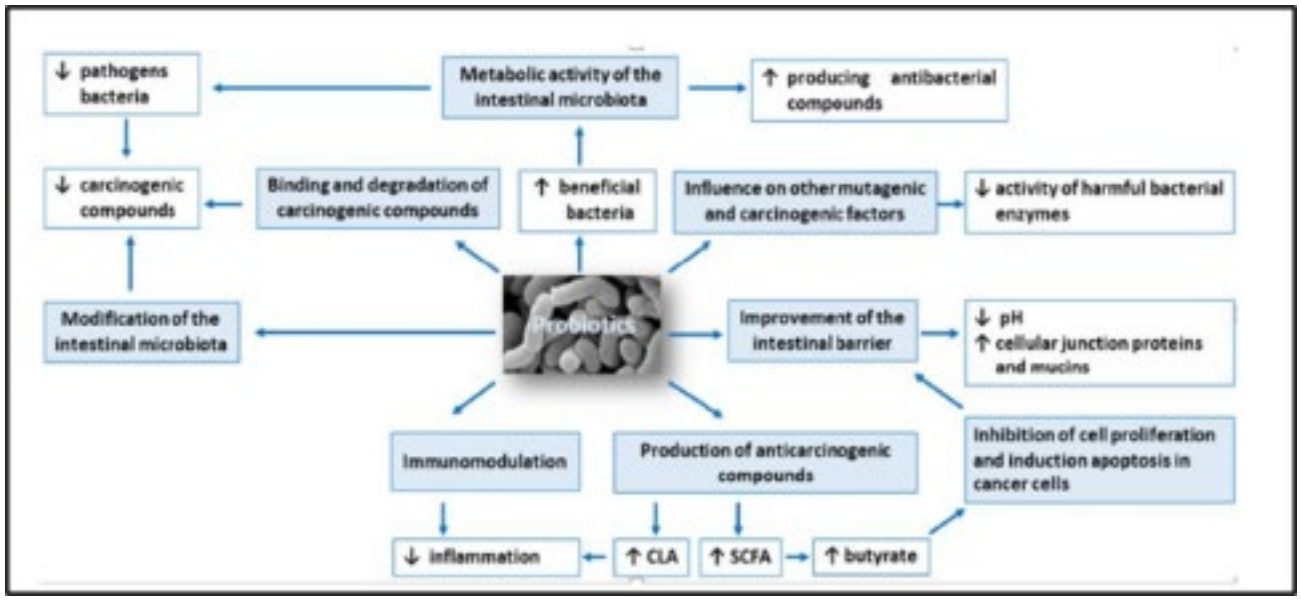

Figure 3. Mechanisms through which probiotics may act against cancer. From Śliżewska et al. (2021).

Probiotics in cancer prevention

The microbiome of the gut, which consists of trillions of microorganisms, is critical in keeping the gut in homeostasis, as well as controlling general human health. Analysis of this complex microbial ecosystem, which is referred to as dysbiosis, has been heavily linked to a heightened danger of malignancy. The probiotics will have a beneficial effect on the gut microbiota, as they can increase the growth of good bacteria and decrease the proliferation of bad microbes, thereby reestablishing the balance of microbes and limiting the pro-carcinogenic mechanisms (Colella M et al.,2023).

Exposure to carcinogens is one of the ways that probiotics help to prevent cancer. Probiotics have the potential to change the transit time in the gut, increase faecal elimination of carcinogens, and process what is consumed through the bowel like fiber and phytochemicals to bioactive compounds, which have anticancer capabilities. Probiotics also decrease the damage to DNA and mutagenesis caused by carcinogenic agents by keeping the gut healthy (Śliżewska K et al.,2020).

Probiotics are very important in immunodefensive mechanisms, both local and systemic. Probiotics increase immune surveillance, promote the use of anti-inflammatory cytokines, and augment the performance of immune effector cells such as natural killer cells by interacting with immune cells in the gut-associated lymphoid tissue. Chronic inflammation is one of the causes of numerous cancers; there is therefore some protective effect of probiotics, which inhibit the pro-inflammatory cytokines, the proinflammatory signaling pathways, which suppress inflammation-mediated carcinogenesis and tumor progression (Iqbal H et al.,2024; Colella M et al.,2023).

Cancer initiation and progression have been attributed to intestinal barrier dysfunction that is typified by elevated epithelial permeability. Probiotics also enhance the intestinal barrier by enhancing mucin secretions and the tight junction between epithelial cells. This minimizes the microbial products and inflammatory mediator translocation into the systemic circulation, thus decreasing systemic inflammation and the risk of cancer (Nagao-Kitamoto H et al.,2022).

Moreover, probiotics have antioxidant characteristics that aid in overcoming oxidative stress, which is one of the significant contributors to carcinogenesis. Probiotics have their effects on the prevention of oxidative DNA damage and mutagenesis through scavenging reactive oxygen species and stimulating the activity of antioxidant enzymes. Altogether, probiotics demonstrate a high cancer-preventive effect by the regulation of gut microbiota, decreased exposure to carcinogens, immunomodulation, anti-inflammatory effects, preservation of intestinal barrier integrity, and antioxidant properties (Masheghati F et al.,2024).

Probiotics chemopreventive effects

Chemoprevention is a significant approach that has been used to decrease the occurrence and occurrence of cancer by using natural or synthetic agents that can either delay, inhibit, or reverse cancer metastasis. Probiotics are chemopreventive agents that have received significant interest because they disrupt various cancer pathogenesis processes. A major process is the inhibition of the transformation of pro-carcinogens into their carcinogenic forms. Some probiotic strains, mostly Bifidobacterium and Lactobacillus species, have enzymatic activities that metabolize and detoxify carcinogenic compounds and, as a result, make them less bioavailable and genotoxic (Ma L et al.,2021).

Probiotics also increase cleansing and excretion of carcinogenic metabolites after exposure. Enzyme conversion then converts such metabolites into water-soluble ones, and they can be excreted efficiently through feces or urine. This minimizes carcinogen concentration and avoids the reaction of carcinogens with the cellular macromolecules. Besides this, probiotics have the ability to increase phase II enzymes involved in the conjugation and elimination of electrophilic and oxidized metabolites through the glutathione S-transferase (GSTs) and quinone reductase (QRs) enzymes. Increased phase II detoxification capacity is another way of decreasing genotoxicity and carcinogenic effects (Lokesh P et al.,2021).

The second significant chemopreventive effect of probiotics is their antimutagenic effect. Probiotics are capable of suppressing mutagenic microorganisms to inhibit the formation of DNA adducts and lower mutation rates. Probiotics produce bioactive metabolites, such as bacteriocins or short-chain fatty acids (SCFAs), which prevent the growth and metabolic activity of bacteria that produce genotoxic compounds (Liu H et al.,2021).

Probiotics also have a direct effect on cancer cell proliferation as they induce apoptosis and cell cycle arrest. Probiotics regulate intracellular signaling pathways of cell proliferation and survival via the synthesis of metabolites, including lactate and butyrate, that arrest at cell cycle checkpoints and are involved in the activation of apoptotic cascades. Moreover, probiotics activate immune-mediated anticancer functions through the stimulation of natural killer cells, macrophages, and dendritic cells and enhance antitumor cytokines like TNF-α and IFN-γ. Lastly, the probiotics can suppress the angiogenesis of tumors by suppressing the action of the pro-angiogenic factors, such as VEGF and MMPs, which limit tumor growth and metastasis (Iqbal H et al.,2024; Sankarapandian V et al.,2022).

Patient-related outcomes

In certain studies, probiotics supplementation increased fatigue and the capacity to carry out daily tasks, presumably related to fewer GI symptoms. Pro-inflammatory cytokines like TNF-α in survivors of breast cancer were reduced when prebiotics and probiotics were used, which increases the quality of life. The benefits of particular combinations of probiotics have been reported to improve the quality of life of survivors with lymphedema caused by breast cancer, suggesting that they have a positive impact on the disease even outside the scope of direct treatment (Thu MS et al.,2023).

Clinical studies

In recent clinical trials, probiotics have been considered as adjunctive therapies in cancer therapy with promising results in diverse contexts. For example, a study by Zheng et al. has shown that a specific probiotic substance significantly decreased inflammation and enhanced immune restoration in the gastrectomy patients undergoing gastric cancer. This paper indicates that the compound can be utilized as an adjuvant therapy for such a population (Zhao LY et ak.,2023).

The other interesting trial was that of the effect of Clostridium butyricum strain MIYAIRI 588 (CBM588) on metastatic renal cell carcinoma patients. The findings indicated that CBM588 has the potential to benefit progression-free survival when used with ipilimumab and nivolumab, which proves the idea that probiotics can be used to enhance the efficacy of immunotherapy. Researchers have found that probiotics can potentially be useful in preventing and treating oral mucositis (OM) caused by chemotherapy or radiotherapy (Zhao LY et ak.,2023).

After extensive review and meta-analyses of five trials involving a total of 435 patients made it was made known that probiotics have the potential to help in the management and prevention of oral mucositis (OM). The results suggest that there is a fairly high level of variability; however, in the case of the use of probiotics, the risk of OM was decreased in the case of the grade three or more, and overall grades. With respect to the proportion of patients who underwent their treatment fully with regard to cancer, no significant difference was detected between probiotics and placebo (Shu Z et al.,2020).

The findings of a general review of randomised controlled trials showed that, with the help of probiotics, especially the Lactobacillus and Bifidobacterium strains, patients troubled by colorectal cancer experienced less distress. They enhanced the gut microbiota productivity, minimized the complications, which were associated with postoperative infections, and prevented the production of pro-inflammatory cytokines. In addition, probiotics were also found to reduce the side effects of chemotherapy, enhance positive surgical outcomes, and reduce mortality risk (Dikeocha IJ et al.,2022).

SAFETY, REGULATORY CONSIDERATIONS, AND METHODOLOGICAL LIMITATIONS OF PROBIOTIC USE IN BREAST CANCER ACROSS DIVERSE CLINICAL CONTEXTS

Safety considerations

The use of probiotics in cancer patients is a serious issue in terms of safety, as their immune systems are frequently weakened by the disease or chemotherapy and radiotherapy. Although most probiotic strains are usually deemed to be safe, a few can cause bacteraemia or sepsis in people who are at risk, especially neutropenic individuals. Thus, probiotic use has to be carefully evaluated (Redman M et.,2014;Kothari D et al.,2019). Small pilot studies and randomized controlled trials have provided evidence that the chosen probiotic strains are safe and can be taken well even in neutropenic patients. An example is Enterococcus faecium M-74, which was not linked with infections and severe adverse outcomes in patients with solid or hematological malignancies (Mego M et al.,2005). Probiotic-related deaths and other major adverse events such as bacteraemia have not been observed in large systematic reviews and clinical trials of both adult and pediatric cancer patients (Wada M et al.,2010).

Regardless of these positive results, the process of safety assessment is complicated. Some of the aspects that are important include the strain selection, dosage, purity, stability, and quality of manufacturing, since poorly prepared probiotics can contain some dangerous contaminants. Another possible interaction of probiotics with cancer treatments is the change of gut microbiota and drug absorption. The gastrointestinal side effects are mild (bloating, diarrhea), and tolerability is affected by factors specific to individual patients (Ahmad MF et al.,2025).

In order to enhance the effectiveness and safety of probiotics, superior delivery systems have been advanced in order to provide survival and specific colonization of probiotics. Probiotics are coated by encapsulated microparticles and enteric-coated capsules that help them to overcome gastric acid and bile and increase their viability and colon delivery. The microparticle systems have a better protective capacity and a controlled release compared to conventional enteric-coated capsules (Yus C et al.,2019).

Future perspectives

Recent developments in high-throughput sequencing and bioinformatics have allowed the accurate characterization of the gut microbiota and its contribution to cancer. A combination of multi-omics data and clinical data can be applied to detect

microbial signatures linked to the risk, progression, and treatment response of cancer to aid the generation of specific probiotic therapy. The novel strategies are the use of genetically engineered probiotics with paramount anticancer and immunomodulatory capabilities and the combination of probiotics with diet, prebiotics, immunotherapy, and regular cancer therapies. New therapeutic approaches, such as microbial ecosystem therapy and fecal microbiota transplantation, are coming into the picture but require additional clinical research. The detection of microbiome-based biomarkers will enable accuracy in oncology and individualized probiotic treatment (Iqbal H et al.,2024).

CONCLUSION

In conclusion, probiotics are found to be a viable supplemental strategy for managing breast cancer, with possible advantages ranging from enhanced treatment tolerance, immunological regulation, metabolic balance, and gut microbiota modulation. Their importance in improving patient-reported outcomes, lowering therapy-related side effects, and potentially increasing the effectiveness of traditional treatments is supported by emerging research. The creation of customised probiotic interventions suited to specific patient profiles is made possible by developments in multi-omics, synthetic biology, and microbiome-based medicines. Large-scale, well-designed clinical trials are necessary to define standardised guidelines, ideal strains, dosing regimens, and long-term outcomes for incorporating probiotics into routine breast cancer care, despite encouraging safety and efficacy findings.

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