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Gut microbiota centered approaches for breast cancer intervention leveraging probiotics and postbiotics

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Abstract

Cancer is a leading cause of death globally, including breast cancer, the most commonly diagnosed cancer, which significantly affects women's mortality rates. Women exposed to hormones like estrogen from early menarche to delayed menopause may have a greater risk of breast cancer. The gut microbiota and its association with breast cancer are an emerging field of study. Any factors leading to dysbiosis of this gut microbiota could be a potential cause of breast cancer. Simultaneously, probiotics, postbiotics, and next-generation probiotics (NGPs) have emerged as promising supplements in cancer management due to their potential to modulate the gut microbiota and augment immune responses. Thus, these biotherapeutics contribute a greater insight into immunotherapies and the modulation of the tumor microenvironment. The ability to prevent dysbiosis and maintain a healthy gut microbial population can assist in treating breast cancer. Although they show promise, more holistic research is necessary to fully comprehend their mechanisms of action, safety, and clinical effectiveness in humans. This review highlights the crucial role of biotherapeutics in enhancing breast cancer treatments by examining the significance of gut microbiota in cancer progression and control, thus underscoring the necessity for continued research in this area.

Keywords Immunomodulation, Breast cancer, Probiotics, Gut microbiome, Postbiotics

1 Introduction

The Global Cancer Observatory (GLOBOCAN) reported 1.3 million new cases of cancer and around 850,000 cancer-related deaths in India by 2020. Breast cancer accounts for 13.5% of new cancer incidents and 10.6% of mortality [1]. Reports state that if the scenario proceeds in the current trend, the mortality might rise to 1 million deaths annually by 2040 [2]. The rising rates of breast cancer in both developed and developing countries are concerning, highlighting the urgent need for new and more effective anticancer treatments to address existing limitations. Breast cancer is a diverse disease, presenting various subtypes [3, 4]. Breast cancer, like any other type of cancer, is a multifactorial disease influenced by multiple factors. These include genetic and environmental elements

such as age, gender, early onset of menstruation (menarche), late onset of menopause, and personal or family history of breast cancer [3, 5]. As microbiota is a major factor influencing cancer progression and control, several researchers have emphasized the relevance of the complex relationship between microbiota and human health. Properly balancing gut microbes is essential, as any dysbiosis can lead to various diseases. The gut microbiota and their associated metabolites can have a strong impact on the inhibition of different types of cancers, including breast cancer [6]. The relative abundance of these microbes varies according to each type of cancer, aiding in improved therapeutic outcomes [3]. The bacterial abundance was analyzed using the BIC database, which focuses on the transcriptional landscape of bacteria in cancer. This analysis revealed a significantly higher diversity of bacteria associated with BRCA (breast invasive carcinoma) and OV (ovarian cancer) compared to other cancer types, the same is depicted in Fig. 1. Therefore, there is an emerging need to investigate the role of this microbiota in therapeutic approaches [7]. Breast cancer is mostly associated with hormones, and thus, the endocrine therapies are a main treatment method. But therapeutic resistance, being an emerging concern in the medical field, needs to be addressed properly [8]. The non-responsiveness of patients to the therapies often results in the recurrence and emergence of cancer. It becomes more challenging to understand the patient-to-patient response to various available therapies [9]. The gastrointestinal microbiota composition varies among individuals, and it is evident that these microbes play an important role in influencing various therapies. And thus, targeting these, potentially with probiotics and/or postbiotics, could be a promising method for effective therapeutic interventions [10].

The FAO/ WHO defines probiotics as live microorganisms that, when administered in adequate amounts, confer health benefits on the host [11]. The global probiotics market was valued at USD 58.17 billion in 2021. Due to increased acceptance and demand, it is projected to grow at a compound annual growth rate (CAGR) of 7.5% by 2030 [12]. Probiotics are effective in increasing the population of beneficial bacteria in the gut, thereby enhancing the overall health of the individual [13]. Once orally administered, probiotics

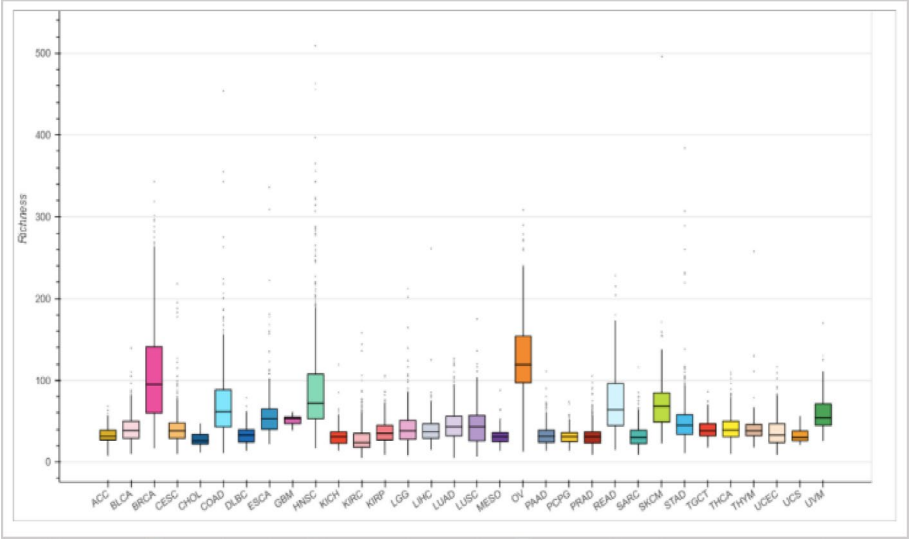

Fig. 1 Boxplot of the bacterial diversity of samples detected in cancer. It represents a visual analysis of bacterial diversity in terms of richness across different cancer types [7]

reach the intestine, where they exert beneficial effects, including maintaining microbial balance and enhancing overall health [14]. They play important roles in immunomodulation, anticancer, antidiabetic, and antiobesity activities, which aid in treating various disorders [15]. Probiotics are also involved in the bio-transformation of mycotoxins, the synthesis of vitamin K, riboflavin, and folate, and the detoxification of xenobiotics and other environmental pollutants [16]. They are associated with the production of various metabolites and other related compounds like SCFAs. They also promote health benefits to the host by promoting the growth of beneficial microbes and inhibiting infectious bacteria [13, 17]. Some studies have also indicated the potential applications of probiotics in lactose tolerance, hypersensitivity reactions, or even regulating intestinal inflammation [18].

According to recent advancements in science, postbiotics have also gained much acceptance. The postbiotics often involve the heat-killed microorganisms and their metabolic components that provide some benefits to human health [19–21]. The International Scientific Association for Probiotics and Postbiotics (ISAPP) proposed the definition of postbiotics as "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host". The term postbiotics is derived from two terms- 'biotic', "relating to living organisms", and 'post', "after". So, the term postbiotics could be decoded as 'afterlife' [21].

Postbiotics are naturally obtained molecules produced by certain bacterial or fungal species, like *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, *Eubacterium*, *Faecalibacterium*, and *Saccharomyces* [22]. Postbiotics are classified into various classes based on their elemental composition. These groups include lipids (propionate and butyrate), organic acids (lactic acids, acetic acid, propionic acids, 3-phenyllactic acid), secreted proteins/ peptides (lactocepin, p40 molecules), carbohydrates (teichoic acids, galactose rich polysaccharides), bacteriocins (acidophilin, bifidin, and reuterin), vitamins and cofactors (B- group vitamins- riboflavin, ascorbic acids), other complex molecules including the peptidoglycan derived muropeptides and lipoteichoic acids [23, 24]. The potential sources of postbiotics could be either the extracellular or intracellular components of probiotics. These may include exopolysaccharides, teichoic acids, and even surface protruding filamentous structures like fimbriae, pili, and flagella [23]. The postbiotics can produce a great impact on the host microbiota by influencing the physiological, regulatory, metabolic, and behavioural responses. Their beneficial contributions include the inhibition of pathogens and anti-inflammatory and immunomodulatory activities. Further, they are also well known for their antimicrobial and antioxidant properties [24].

2 Microbiota

Microbiota refers to the live microorganisms associated with a specific environment, such as the oral, gut, and other related sites [25]. Although once they were poorly explored and considered the dark matter of the body, recent advances in microbiome research and multiomics have expanded our insights into their immense role in human health. These microbiotas are often known as an organ, due to their impact on the overall organ systems and their environment, or a second genome of the human body, due to their huge amount of genomic data, even outnumbering the total genomic composition of the human body [26]. Studies combining the data from MetaHit and the Human Microbiome Project have revealed the existence of about 2,172 species of

microorganisms associated with human beings. A relevant term that is often found associated with microbiota is the microbiome. The microbiome is a broad term that refers to the collection of genomes of all the resident organisms in an environment, along with the biotic and abiotic components [27]. Any imbalance in this microbial equilibrium can lead to a stage called dysbiosis. In modern life, health, environmental factors, and other abiotic factors like antibiotic medications could also influence bacterial composition and often contribute to dysbiosis [28]. The use of probiotics, prebiotics, and several other combinations of probiotics and prebiotics could also be utilised to overcome this condition [29, 30]. The various methods to modulate the microbiota and their relevant impact on human health are depicted in Fig. 2. Certain metabolites associated with these microbes can directly or indirectly take part in modifying or modulating different signaling pathways [31].

2.1 Gut microbiota

Gut microbiota is a broad term used to refer to the whole set of microorganisms inhabiting the human gut, including bacteria, fungi, parasites, and archaea. It may also constitute viruses to a certain extent [32]. The gut microbiome can be defined as the functional and genetic profile of gut microbiota [33]. In the average lifetime of an individual, about 60 tons of food particles, along with millions of organisms, pass through the gastrointestinal tract of the human [34]. Some studies have also highlighted that a ratio of 10:1 indicates the ratio of bacterial population and the number of human cells in the same order [35].

A mutualistic or commensal relationship exists between gut microbiota and the human host. The composition of these microbes varies in different regions, with the colon hosting a significant portion of this population. Most of these organisms are anaerobic [36]. The gut microbiota provides varying benefits to the host, including maintaining gut integrity, protecting against pathogens, and regulating immune balance [25, 34, 37, 38].

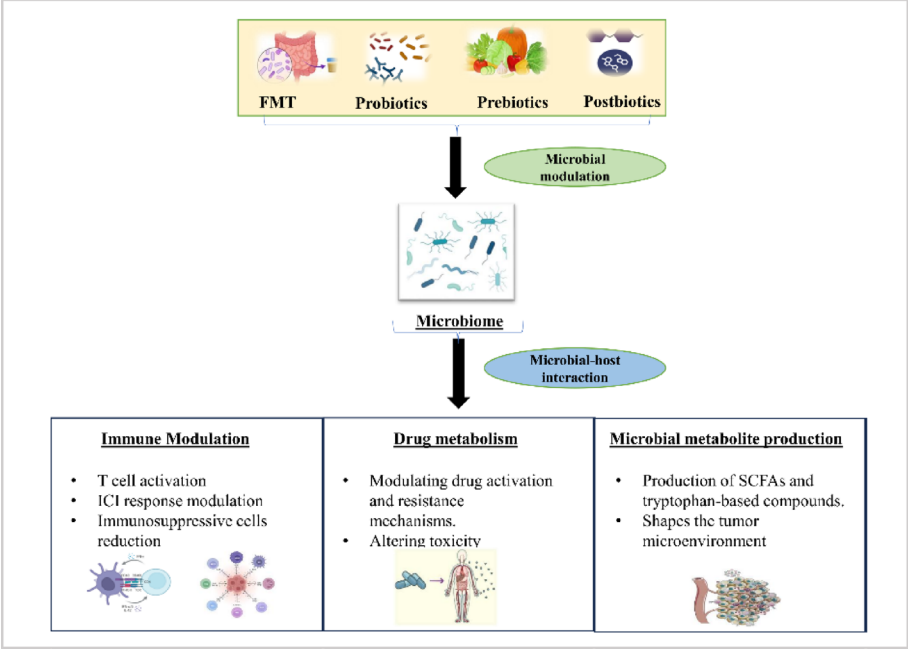

Fig. 2 Illustration of microbiota modulation and its relevance in human health

They support the normal functioning of the intestinal barrier and even exert anti-inflammatory effects [33]. They also perform some inevitable functions, such as synthesizing certain products like vitamins and short-chain fatty acids. Besides these functions, they boost the host's immune system and maintain the microbial flora in the body [39]. The colonization of microbiota usually starts during pregnancy and evolves throughout all life, with host (i.e., genetics) and external factors (i.e., diet, habits, hygiene, drugs, tobacco/alcohol consumption) being the main drivers of the gut microbial composition. To protect the established microbiota colony from the immune response, the GI tract has established a multifactorial and dynamic intestinal barrier- physical (epithelium and mucus), biochemical (secondary metabolites and enzymes), and immunological factors [40].

The gut microbiome plays a great role in maintaining the host's homeostasis and health. These microorganisms are often associated with the production and metabolism of various compounds like SCFAs, bile acids (BA), branched-chain amino acids (BCAAs), trimethylamine N-oxide, tryptophan, vitamins, neurotransmitters, and other antimicrobial peptides [41]. Some evidence suggests that a change in the composition of gut microbiota has been involved in various disease conditions like cancer, cardiovascular diseases, inflammatory intestinal diseases, psychiatric/neurological pathologies, type 2 diabetes mellitus, obesity, and even asthma [42]. Modulation of gut microbiota with certain probiotics co-adjuvanted the treatment of various diseases; a probiotic application of *Lactobacillus rhamnosus* is shown to have been effective in hyperlipidemia mouse models. Probiotics play an inevitable role in maintaining and altering the gut microbiota composition, promising potential therapeutic advancements [43, 44].

2.2 Mammary microbiota

Mammary microbiota involves the microbes inhabiting the mammary glands and breast milk. This microbiota is often constituted by the phyla Proteobacteria and Firmicutes [45]. The breast tissue was earlier considered to be sterile, but with further studies, it was found that breast tissue also harbors a good amount of microbial population similar to the gut [46]. The accumulation of microbiota in breast tissue is often established through various routes, including breastfeeding, intercourse, or bacterial translocation from the gut population [47]. Certain bacterial taxa associated with breast tissue can be either pathogenic, such as *Enterobacteriaceae or Staphylococcus epidermidis*, or probiotic, such as *Lactococcus lactis*, *Lactobacillus sps*, *Streptococcus thermophilus* [48]. These pathogenic and probiotic organisms can influence the host's health in several ways, such as immunomodulation, prevention, and even the progression of tumors [49]. According to recent research, it is evident that the microbes inhabiting normal breast tissue are associated with the incidence of breast cancer, whereas the composition of the microbes varies for both the normal breast tissue as well as the cancerous tissue [49]. The physiological and moist anatomical features of the human breast tissue during late pregnancy and the lactation period enhance the chances of microbial colonization, proliferation, etc. These conditions are good for meeting the nutritional and other abiotic factors necessary for their survival. Besides these factors, the well-established ductal system of the breast tissue favours the establishment of the microbial biofilm of organisms such as *Staphylococcus*. The bacterial composition of normal breast tissue differs from that of breast cancer tissue [45]. The healthy tissues often showed an abundance of *Actinobacteria* and

a decrease of *Proteobacteria*, and vice versa [50]. Studies conclude the dominance of families like Pseudomonadaceae and Enterobacteriaceae in tumor tissues. Besides this comparison between normal healthy and breast cancer tissues, the composition of the microbial community also varies among the cancer subtypes [51]. Therefore, the knowledge of these could be effectively utilized in probiotic-assisted therapies against breast cancer [52].

2.3 Milk microbiota

Breast milk microbiota and breast tissue microbiota are often connected. The breast milk microbiota contributes to a major portion of the commensal to the newborn [53]. Human Milk Microbiota (HMM) consists of a diverse community of microbes, and a wide range of nutritional and bioactive molecules [54]. Studies have shown the involvement of various microorganisms, including bacteria, fungi, and viruses, in HMM. The various significant microbial groups in HMM involve *Firmicutes*, *Bifidobacterium*, *Lactobacillus*, *Proteobacteria*, and *Actinobacteria* [54]. The HMM composition is often influenced by various factors, including lactation, maternal body mass index, age, diet, antibiotics, and prebiotics usage during delivery, and the type of delivery [55]. Culture-based methods have demonstrated a great array of populations of microbes associated with human milk, including various species of *Streptococcus*, *Corynebacterium*, *and Cutibacterium* [52].

The two main routes of sources of the milk microbiota include the retrograde flow and the entero-mammary pathway. In the retrograde pathway, the flow of microbes happens from the infant to the mother through the skin and saliva of the infant through the duct while suckling. This often could be proved by the presence of certain bacterial groups like *Veillonella*, *Leptotrichia*, and *Prevotella* from the infant's oral cavity and certain other groups like *Lactobacillus* from the vagina (often acquired by the baby at the time of delivery), in human breast milk [55]. Another pathway of bacterial entry into the mammary gland or human breast milk is the entero-mammary pathway. This pathway involves the immune cell-mediated bacterial translocation from the GI tract of the mother to the mammary gland, where they colonize [56].

3 Operational mechanism of action of pro and post-biotics

Probiotics and postbiotics are known to play vital roles in immunomodulation through several mechanisms, including the exclusion of pathogens by competing for receptors, nutrients and space, thereby decreasing the risk of infections [57]. They also reduce the pH and produce various metabolites, including bacteriocins and bacteriocin-like products, thus maintaining gut integrity [18]. The gut colonization and mucosal adhesion are the potential probiotic characteristics that help in maintaining microbiota homeostasis [58]. Certain probiotic groups of *Lactobacillus* present in the intestinal villi and enterocytes are known to block the pathogenic adhesion, thereby reducing the risk of infection [59, 60]. Probiotics also show certain anti-microbial activities by producing compounds like SCFAs, organic acids, hydrogen peroxide, lysozymes, proteases and bacteriocin [61, 62]. The probiotics can stimulate mucin production by the intestinal goblet cells, thereby strengthening the intestinal barrier [59]. For instance, the production of lactic acid by *Lactobacillus* is associated with the reduction of pH, or may bind directly to Gram-negative bacteria to inhibit their growth [60].

Thus, probiotics are known to maintain homeostasis and a balance between the microbiota and their metabolites. The normal microbes associated with the human body ecosystem may also have a significant contribution to controlling certain putrefactive bacteria, such as *E. coli* and *C. perfringens*. These putrefactive bacteria secrete specific molecules, including azoreductase, nitroreductase, and β-glucuronidase [63]. These molecules are involved in enhancing cancer progression and proliferation. The regular consumption of fermented milk products, a potential source of probiotics, plays a significant role in maintaining a decreased population of these putrefactive bacteria [64].

The anticarcinogenic activity of probiotic bacteria may also be associated with the binding and degradation of potential carcinogens. Many in vitro studies have revealed the significant role of certain probiotics in binding or metabolising mutagenic compounds such as heterocyclic aromatic amines (HAAs), nitrosamines, mycotoxins, polycyclic aromatic hydrocarbons (PAHs) and phthalic acid esters (PAEs) [65]. Postbiotics also aim to mimic the potential health and other therapeutic properties of probiotics. Due to the well-established molecular structure and storage stability, postbiotics have been proven to have various health benefits. These properties provide an elevated local effect duration on target tissues. Compared to probiotics, these inanimate molecules reduce the risks associated with the administration of live microorganisms [22]. Recent studies revealed the potential impact of dysbiosis on the gut and breast microbiota in breast cancer incidence. These gut microbiotas are associated with the metabolism of various steroid hormones such as estrogen. Estrogen has an inevitable role in increased breast cancer risk. Thus, regulating the incidence of breast cancer. Since the postbiotics have an immense impact on modulating the host immune system and the native microbiome, they show potent anticancer properties [66]. A list of postbiotics, their source organism, and the mechanism of immune modulation is given in Table 1. Postbiotics can introduce apoptosis to the target sites without killing the neighbouring cells, thus, they have gained great interest from the scientific community. They can induce apoptosis through both intrinsic and extrinsic pathways, which are often achieved by elevating the expression of Bad, Bax, caspase8, caspase 9, caspase 3, etc., whereas it is also associated with the suppression of Bcl-2 [67].

Table 1 List of postbiotics and their mechanism of action in human health

Postbiotics	Source organism	Mechanism of action	References
Exopolysaccharides (EPS)	*Peanibacillus mucilaginosus TKU032*	Potential antioxidant activity	(Liang et al., 2016)
Fermentative metabolites	*L. paracasei CNCM I-5220*	Antipathogenic, especially relevant in treating IEB integrity	(Algieri et al., 2023)
Cell-free supernatant	*Lactobacillus rhamnosus GG, L.reuteri*	Anticancer and cytotoxic effects against acute lymphoblastic leukemia.	(Banakar et al., 2021)
Cell-Free Filtrate	*Lactobacillus acidophilus*	Antibacterial, antibiofilm, and anti-inflammatory functions. It also regulates NF-κB activation.	(P. Wang et al., 2024)
SCFA	*Bifidobacteria*	Reduces the E.coli and Bacteriodetes load as well as reduces the level of ammonia and indole in stool of infants.	(Yeşilyurt et al., [111])
Mucin	*Bifidobacteria, Lactobacillus*	It enhances the antipathogenic activity and the antimicrobial activity of mucin	(Yeşilyurt et al., [111])
Heat killed cells	*Saccharomyces boulardii*	Maintenance of gut barrier and reduce the incidences of bacterial translocation and mucosal lesions.	(Egea et al., 2023)
Peptidoglycans	*Lactobacillus sps.*	It upregulates the production of cytokines through the LPS-induced TLR-4 pathway	(Kim et al., 2023)

4 Microbiome-based therapeutics

Since the use of antibiotics has drastically increased over the centuries, resistance to them has also emerged. This responsiveness to antibiotics has now questioned the efficacy of these chemotherapies. They are also a potential cause of the emergence of dysbiosis. The beneficial bacteria and their consortia are also explored for better therapeutic implications [68]. Recent advances in the knowledge and scientific evidence of microbiota in human health have inched towards the development of specific therapies to address microbial dysbiosis and thereby various diseases [68]. The current microbiome-based therapeutic strategies often involve fecal microbiota transplantation (FMT), probiotics, and postbiotics. As previously discussed, the microbial composition varies between normal and tumour tissues. Thus, the efficacy of each therapy may vary with various underlying factors, such as the variability in the microbiome among individuals, as well as the host-microbiome interactions [69]. An overview of the list of microbiome-based therapies and their positive impact in controlling the cases of dysbiosis by restoring the normal gut microbiota is picturized through Fig. 3. The potential of the microbiome to alter the immune response in individuals by influencing both the innate and adaptive immune systems has enhanced the relevance of immunotherapies. Thus, the development of personalized microbiome therapies utilizing the knowledge of individual microbial profiles could be effective as compared to the conventional methods [69].

FMT, being one of the promising and widely used microbiome-based therapies, often involves the administration of fecal matter from a healthy individual into the gastrointestinal tract of a patient for reestablishing the healthy microbial composition [70]. Biotherapeutics are also an inevitable component of microbiome-based therapeutics. The adequate administration of these is also considered an effective therapeutic method, which could effectively contribute to the immune modulation and maintenance of gut integrity [71]. The Next-generation probiotics identified by employing comparative microbiota analyses also promise to confer certain health benefits on the host organisms by enhancing gastrointestinal immunity and the efficacy of immunotherapy in cancer patients [72]. They could effectively contribute to the emerging areas of novel biotherapeutic strategies [73]. With the emergence of microbiome editing therapeutics

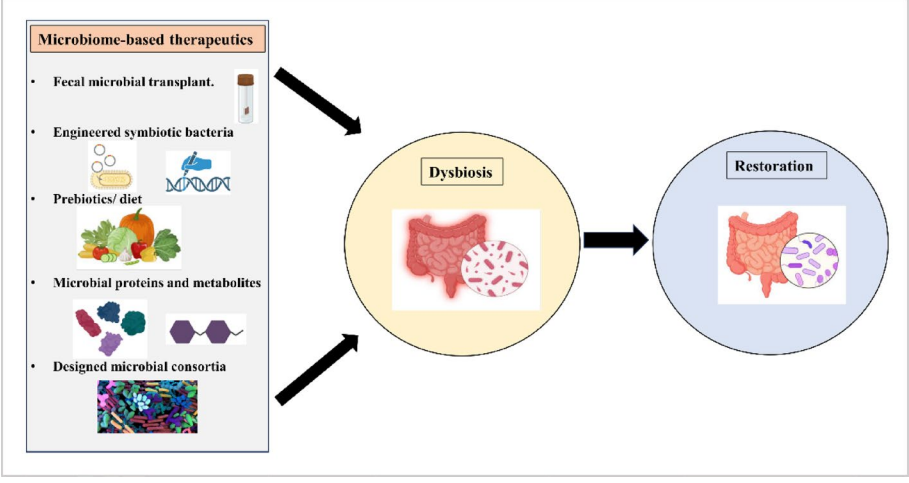

Fig. 3 Overview of microbiome-based therapeutic strategies in restoring gut microbial balance

like CRISPR and base editing, through gut microbial gene manipulation, a better therapeutic specificity is achieved in comparison to broad microbial transplants [74]. Besides these, engineered microbiomes and microbial consortia are also administered to alter the existing microbial communities and thus enhance the therapeutic outcomes. The gut microbiota is often described as the second human genome, and could effectively shape a tumor-promoting microenvironment, thus acting as a potential target for personalized therapeutic implications [69].

4.1 Probiotics' role in cancer

"Oncobiome" is a field of research concerned with the profound interaction of the human microbiome with cancer [75]. The human host body can also influence the microbiota, so any alterations can cause dysbiosis and may pave the way to many carcinomas [46].

The probiotic microorganisms are known to have a good number of therapeutic uses. These are often associated with the GI tract due to the influence of the Indigenous microbiota [76]. Colorectal cancer patients are found to be colonized by various populations like *Bacteroides*, *Prevotella*, etc., which are known to be responsible for producing certain carcinogens and other tumorogenetic compounds such as heterocyclic amines and bile salts. Some of the probiotic bacteria are known to have certain immunomodulatory and anticancer properties. These probiotic compounds not only help in the bioremediation of certain carcinogenic compounds but are also associated with the production of certain metabolites, such as short-chain fatty acids, responsible for the regulation of cell death and progression [63]. The prominent classes of LABs, *Lactobacillus* and *Bifidobacterium*, are also known to have efficient anticancer properties, due to the ability of these organisms to alter the enzyme activity of alpha-glucuronidase, azoreductase, and nitroreductase, which have an inevitable contribution in the development and progression of colon cancer [77]. The involvement of probiotics in cancer progression control is appreciable. Table 2 lists some of the probiotic organisms and their mechanism of cancer inhibition.

They are also involved in the production and upregulation of cytokines like IL-2 and IL-12, antioxidants (SOD, CAT, GSH), antiangiogenetic factors, mucin, defensins, IgA, etc. It is also associated in one way or the other in cytokine responses and inhibition of tyrosine kinases. The immunomodulation in the host body is often carried out by the secretion of various anti-inflammatory molecules and influencing the Th cell response and regulation, while the cancer proliferation is maintained by regulating cell differentiation and promoting apoptosis [78]. Several studies have revealed that the effective role of *certain Lacticaseibacillus rhamnosus GG* and *Bifidobacterium lactis Bb12*, along with oligofructose-enriched inulin, for 12 weeks of administration affects the gut microbiome, and a reduction in the levels of *Clostridium* perfringens, which may lower cancer risk through decreased toxic metabolite production, enhanced immune response and other anticancer effects [76].

4.2 Gut microbiota and breast cancer: probiotics intervention

Breast cancer is one of the most prominent malignant types of cancer associated with women worldwide (WHO, 2021). Being a multifactorial disease, breast cancer development and progression are often influenced by both internal and external environmental

Table 2 List of probiotics and their mechanism of action in cancer

Probiotics	Research model	Concentration	Mechanism	References
Bifidobacterium bifidum CGMCC	Rodent model	3*10^9 CFU/mL cells	B.bifidum is found to inhibit colorectal cancer and is also found to be potent for enhancing the intestinal microbiome.	(Garbacz, 2022)
Enterococcus faecalis, Staphylococcus hominis	MCF-7 cell line	25–200 µg/mL of cells	The cell cytotoxicity studies revealed the apoptotic activities of the probiotic organisms.	(Hassan et al., 2016)
Streptococcus salivarius BP8, S. salivarius BP156, S. salivarius BP160	MCF-7 cell line	Cell Free Supernatant	S. salivarius a potent probiotic is found to effectively inhibit both breast cancer, as well as liver cancer	(Srikham et al., 2021)
Lactobacillus rhamnosus	HT-29 cancer cells	30 mg/mL cells of 72 h incubation	These organisms are known to upregulate the pro-apoptotic genes like caspase-3, caspase-9, Bax, etc., thereby controlling the cancer progression.	(Dehghani et al., 2020)
Lactobacillus plantarum IIA-1A5	MCF-7	100 µg/mL of Intracellular protein	The intracellular and extracellular extracts showed both antiproliferative as well as cytotoxic effects.	(Adiyoga et al., 2024)
Lactobacillus acidophilus	Caco-2	7.5% of L.acidophilus extract gives 50% of Caco-2 cells to die.	L. acidophilus is found to have potential apoptotic and antiproliferative activities. It is also involved in the upregulation of SURVIVIN genes.	(Isazadeh et al., 2020)
Bifidobacterium sps.	SW480, Cac0-2, HT-29	Varying concentrations	These organisms often show anticancer activity utilizing the biotransformation process, which involves the transformation of a compound into a usable product by a certain biological process. These microbial products are potent in cancer treatment research.	(Wei et al., 2018)
Bacillus coagulans	MCF7	IC50 of the supernatant is 1 mg/mL at 72 h incubation in MTT assay	The organisms' supernatants exhibit effective anticancer activity, upregulating Bax, caspase 3, etc., while suppressing the expression of the anti-apoptotic gene bcl2.	(Dolati et al., 2021)
Bacillus polyfermenticus	HT-29, DLD-1, Caco-2	Varying concentrations, 95–99% inhibition on Caco-2 cell line	They are associated with the antiproliferative of colon cancer cells. They also inhibit ErbB2 and ErbB3, as well as under expression of E2F-1 and cyclin D1. Thus, a potential anticancer therapy.	(E. L. Ma et al., 2010)
Bifidobacterium bifidum	NSCLC cell lines	150 µg/mL of protein extract showed inhibition of cells.	The immune response is associated with the expression of apoptosis indicator molecules, cleaved caspase3, and PARP is increased. It is also associated with antiproliferation.	(Ahn et al., 2020)

factors. It is also influenced by genetic, hormonal, environmental and lifestyle factors [79]. A major histological type of breast cancer is adenocarcinoma, mostly associated with the breast ducts (75%) and lobular epithelium (15%). The ductal carcinomas have a great range, from either an in-situ localization or spread beyond the basement membrane to severely affect the breast parenchyma cells [80]. Rather than this, breast cancer has other broad types, such as triple-negative breast cancer (TNBC), breast Paget's disease, metaplastic carcinoma, and HER2-positive breast cancer. Besides these carcinogenic changes, the breast cells are highly prone to changes that may result in some lumps or cyst formation [79].

The impact of gut microbiota on breast cancer occurrence and development has gained greater attention over the past decade. This happens through various methods, like immune modulation, the release of various bacterial metabolites, and the alteration of estrogen levels [81]. The higher levels of circulating estrogen can increase breast

cancer risks [82]. The ability of microbial β-glucuronidase to bio-transform estrogen impacts breast cancer [83]. The estrogen, after conjugation and processing, enters the intestine and is often deconjugated by the β-glucuronidase and is marked for fecal excretion, thus reducing the risk [82]. The bacterial metabolites, such as SCFAs and bacteriocins like nisin, may also have potential anticancer effects on breast cancer [6]. There is also evidence that certain bioactive compounds, such as phytoestrogen, lithocholic acid (LCA), and cadaverine, to reduce the incidence and progression of breast cancer [84]. The gut microbes, including the *Lactobacillu*s and *Bifidobacterium* obtained through various fermented foods, are known to have various health benefits and could be considered an effective probiotic. The various external factors causing dysbiosis and the influence of biotherapeutics on human health are depicted in Fig. 4. While the availability of the proper strains, their survivability, and the adequate dosage are to be considered, there arises an emerging need for probiotics. Several recent studies have revealed a significant amount of correlation between cancer and probiotic bacteria [85].

The immunomodulatory and the potential ability to influence indigenous microbes give probiotics an immense capability to fight against breast cancer [86]. Some recent studies have shed light on the fact that the daily uptake of probiotics has a negative correlation with breast cancer incidence. The oral administration of *Lactobacillus acidophilus* has been shown to have a significant increase in survival time as compared to the control groups. These results demonstrated the ability of the organism to modulate the immune response [87]. The impact of probiotics on breast cancer is also supported by certain in-vitro cell experiments, which give shreds of evidence for the apoptotic activity or cytotoxic activity of these organisms on the breast cancer cells [88]. Besides these in vitro studies, several other studies have also been conducted using various animal models, which provide relevant insights into the evident role of probiotics in preventing and controlling breast cancer progression. So, Fig. 5 illustrates the suppression rate of breast cancer lumps on probiotic administration. Moreover, these organisms are also associated with reducing the adverse effects of the chemotherapies [89].

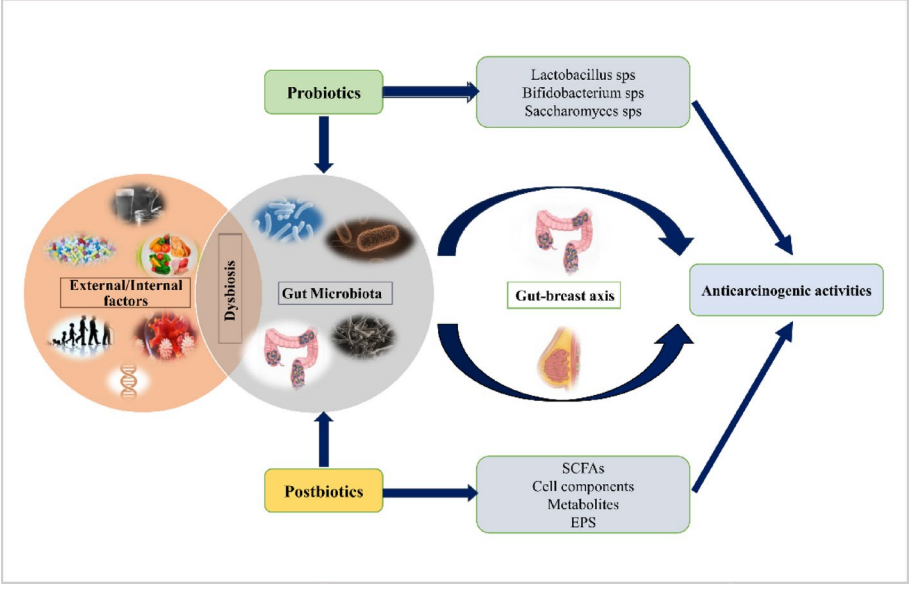

Fig. 4 Schematic illustration of the interaction between probiotics, postbiotics, and gut microbiota and their critical role in influencing the gut-breast axis and their anticarcinogenic activities

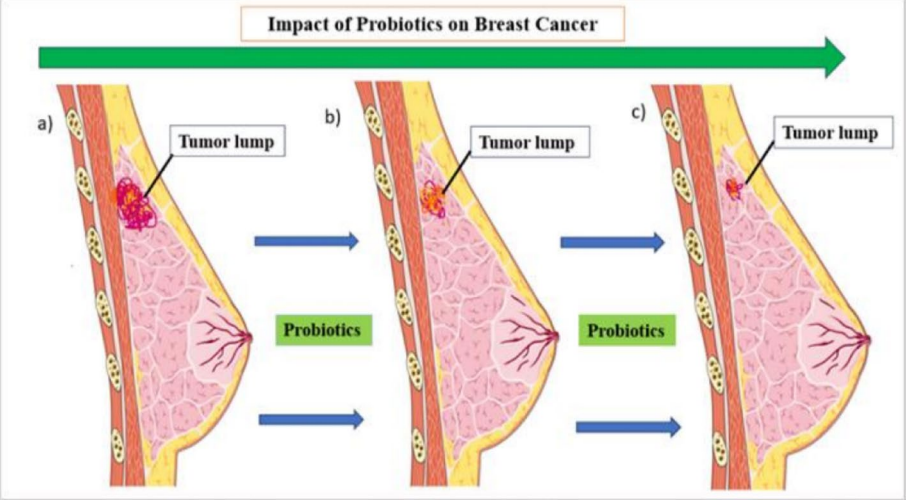

Fig. 5 Suppression of tumor lump on administration of probiotics-Illustration of the effects of probiotics on breast cancer progression through three stages (**a**, **b**, and **c**). Between each stage, probiotics are administered, resulting in a noticeable reduction in tumor size from stage a to stage c. This suggests that probiotics may offer a potential non-invasive treatment option for breast cancer

Probiotics maintain microbial homeostasis, thereby preventing dysbiosis. This happens usually through either increasing the population of beneficial bacteria or by eliminating the pathogenic microbes by competitive exclusion [90]. *Lactobacillus*, being one of the important groups of probiotic bacteria, has shown various health benefits. They could effectively improve the gastrointestinal barrier functions by limiting the proliferation of certain pathogenic organisms [43]. These *Lactobacillus* species, including *L. rhamnosus* GG and *Lactobacillus casei* are also known to restore homeostasis in intestinal disorders and could also be utilized for treating certain immune disorders [91, 92]. Besides *Lactobacillus*, certain species of *Bifidobacterium*, involving *B. pseudolongum and B. adolescentis*, *are* also known to alter the gut microbiota [93]. They are also involved in certain immunomodulatory activities [94]. They also have an important contribution in controlling various intestinal diseases, cancer, and certain allergies. The probiotic *Bifidobacterium* was found to be relevant in increasing the metabolic activity and composition of the gut microbes [42]. *Escherichia coli* is another probiotic bacterium with certain effects in maintaining the gut microbial composition. An *E. coli* strain, *Escherichia coli* Nissle 1917, is found to stimulate the production of human β-defensin 2, which provides a protective barrier that prevents the adhesion and invasion of various pathogenic bacteria [95]. Recent studies have revealed the potential effect of these strains against *Salmonella*, *Shigella*, and *Candida* [96]. *Enterococcus*, a Gram-positive probiotic bacterium, has important physiological and functional implications as a potential antitumor and anticancer agent, and could even modulate the immune system [97]. *Saccharomyces* is also a non-pathogenic probiotic yeast widely used in the production of probiotic foods. Among them, *S. cerevisiae* and *Saccharomyces boulardii* have been widely used in probiotic-based treatments. They also exhibit the potential effect of preventing inflammation by promoting the immune defenses and production of SCFAs [98, 99].

5 Probiotic and postbiotic molecules involved in host immune regulation

Probiotics act as immune system regulators, balancing protective responses with excessive inflammation. The interaction of these organisms with the immune system is primarily through the gut, where they engage with epithelial cells or are transported to interact with immune cells like dendritic cells and macrophages. This interplay leads to the activation of T and B lymphocytes, shaping the body's immune response. Probiotics exert their immunomodulatory effects by influencing gene activity and signalling within host cells [100, 101].

Recent studies have reported the role of probiotics in eliciting humoral, cellular, and other immune responses [44]. They also exhibit anti-inflammatory, antiallergic, and anticancer properties. Probiotics also regulate intestinal epithelial health through immunomodulation by enhanced IgA production, production of cytokines, antibacterial substances, etc. They also prevent pathogenic invasion by enhancing the tight junctions of the intestinal barrier. The probiotic antigenic fragments have the potential to bind to the epithelial cell membranes and the M cells of the Peyer's patches. This property also enhances the immunomodulatory effects of the probiotics [102]. The probiotics improve the immune response by improving the intestinal barrier integrity and preventing the effects of pathogenic bacteria by binding onto the mucosal epithelium, thereby reducing the chances of interaction between them [103]. Several studies involving probiotic Lactobacillus spp. have shown the immense capability to stimulate peripheral mononuclear cells producing interleukin 10 (IL-10) and interleukin 12 (IL-12) [101]. By various comparative genome hybridization studies and several other immune response studies on various species like *L. plantarum* WCFS1, several genes were identified that are involved in encoding the LamBDCA quorum-sensing system, an N-acetyl-glucosamine/galactosamine phosphotransferase system, components of bacteriocin biosynthesis, and transport pathways. Any alteration associated with these genes can affect the regulation of cytokine production [104].

Genetic engineering approaches facilitate the regulation of probiotics. Recent research has demonstrated that removing the phosphoglycerol transferase gene, which aids in the production of lipoteichoic acids, results in decreased levels of IL-12 and TNF, while increasing IL-10 production in dendritic cells. Thus, it reduces the ability to induce CD4 + T-cell activation [105]. In addition to the genes, certain probiotic components are also known to regulate the immune responses. MALDI-TOF analysis was done on probiotic proteins released by *Bifidobacterium animalis* subsp. *Lactis BB-12* revealed 74 distinct proteins; among these, eighteen proteins can interact with the host epithelial cells or extracellular matrix proteins. These proteins enhance the properties of the probiotic species for binding to plasminogen, fimbriae formation, adhesion to collagen, also the induction of immunomodulatory responses [106]. Several other studies also showed the various protein contributions of *Lactobacillus rhamnosus GG*, including p40, which reduced intestinal epithelial apoptosis and disruption of barrier functions in colitis. The p40 also plays an important role in the regulation of innate immunity and the Th1 immune response [107].

Probiotics play an inevitable role in regulating the host's immune system by activating toll-like receptors, which are responsible for recognizing and responding to microorganisms. This activation supports the immune cells, thereby contributing to a healthy and balanced immune system [108]. It can impact the immune system by stimulating

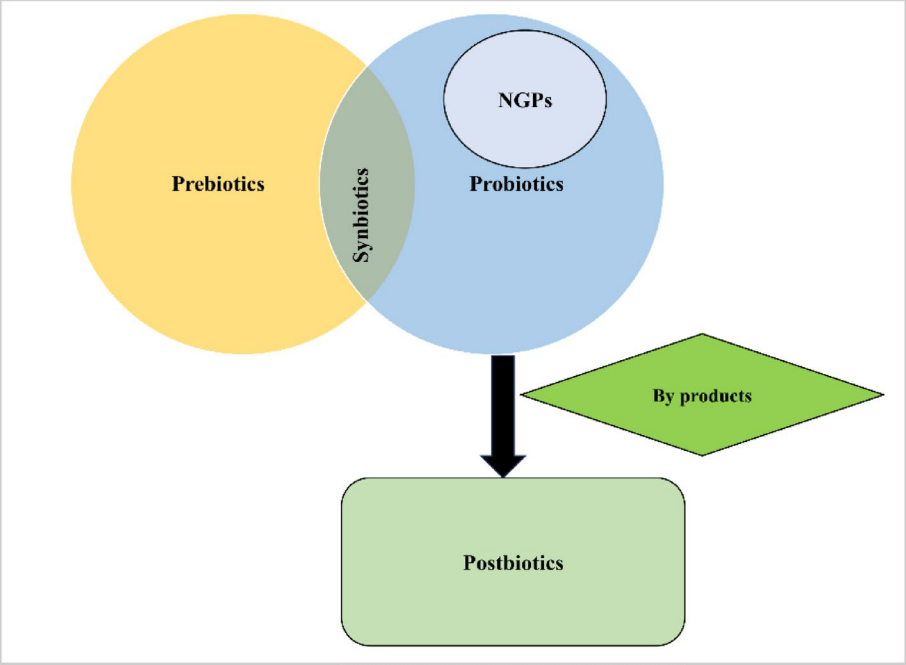

Fig. 6 The interplay between probiotics, prebiotics, synbiotics, and postbiotics within the human gut microbiota

regulatory dendritic cells, thereby promoting the development and proliferation of regulatory T cells (Tregs). Tregs help suppress excessive immune responses and reduce inflammation. Different probiotic strains and doses can have varying effects. For instance, high doses of *Lactobacillus rhamnosus* can trigger strong inflammation, while other strains, such as *Bifidobacterium breve*, have been found to increase Tregs and provide protection against allergies. It is noteworthy that certain probiotics indirectly support Tregs by creating a favourable environment, rather than directly influencing Treg numbers [109]. Overall, these findings suggest that probiotics have the potential to be used as therapeutic agents for inflammatory disorders by modulating immune responses [38]. Figure 6 implies the interrelationship between probiotics, postbiotics, and prebiotics.

The concept of postbiotics starts with pieces of evidence on the effect of inactivated microbes in immunomodulation [110]. Several clinical trials have also proven that the immune defense and immunomodulation of potential postbiotics have antiviral activities. The postbiotics can reduce pro-inflammatory cytokine production and stimulate anti-inflammatory cytokine production as well as stimulate the expression of TLR. They are known to involve in both innate and adaptive type of immune responses. Peptidoglycans produced by the *Lactobacillus species* (*L. acidophilus*, *L. Casei*, *and L. rhamnosus*) have increased the ability to release inflammatory cytokines via the LPS-induced TLR-4 pathway [111]. Following the term paraprobiotics, para-psychobiotics also came into the scenario [60].

6 Current clinical evidence and challenges

While preclinical studies provide supportive results on the potential therapeutic actions of biotherapeutics, influencing the gut microbiota, robust clinical trial data on humans remain limited. Only a few existing clinical trials have explored the relationships among

gut microbiota, probiotics and breast cancer. The inter-individual variability in the microbial composition is also a concern for the personalized immune responses and tumor biomarkers. A search conducted in clinicaltrials.gov (https://clinicaltrials.gov/) using the keywords "breast cancer", "probiotics" and "gut microbiome" yielded two studies, whereas that with "probiotics" and "breast cancer" returned twenty, and with the keyword "postbiotics" and "breast cancer", no such records were available. Whereas exploring WHO International Clinical Trials registry Platform (ICTRP) (https://trialsearch.who.int/) with the keywords "probiotics", "gut microbiota" and "breast cancer" gave no results and with "probiotics" and "breast cancer" alone gave 19 records. These highlight the limitations in terms of well-defined, large-scale clinical trials to address the therapeutic potential of these biotherapeutics in breast cancer management.

7 Future perspectives and conclusion on probiotics and postbiotics

The rise of antibiotic resistance to conventional drugs has made probiotics, postbiotics and Next Generation Probiotics significant areas of interest for the scientific community as effective alternatives to traditional treatments. The unique microbiota of individuals can enhance tailored therapeutic approaches, potentially improving treatment efficacy, especially for conditions like breast cancer, a leading cause of death among women. Advances in research on gut microbiota and probiotic strains, along with advancements in genomics, are paving the way for personalized medicine, which is gaining considerable attention. However, maintaining the viability of certain oxygen-sensitive microorganisms presents challenges that future research needs to address. The emergence of computational and synthetic biology could be exploited further for the development of novel probiotics through genetic engineering and the development of new targeted probiotic consortia. While postbiotics offer similar benefits to probiotics, their non-viability provides greater stability and safety. Ongoing studies aim to optimize production, dosages, and safety, along with utilizing the microbiota from breast tissue in therapeutic applications. In conclusion, probiotics, postbiotics, and next-generation probiotics are promising frontiers for managing immunomodulation, cancer immunology, and therapies. The influence of probiotics and postbiotics on holistic health transcends cancer therapy, contributing to maintaining a harmonized gut microbiota and boosting immune functionality and overall well-being. The administration of probiotics also plays a role in modulating the gut microbiome, while the production of postbiotics influences overall health. Thus, the combined administration of probiotics and postbiotics highlights an effective method to deal with breast cancer.

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Author contributions
Arya A S worked on conceptualization, data curation, writing – original draft, review, and editing. Mythili A supervised in writing and conceptualization.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
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