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# *Staphylococcus epidermidis* biofilm in inflammatory breast cancer and its treatment strategies

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A B S T R A C T

Bacterial biofilms represent a significant challenge in both clinical and industrial settings because of their robust nature and resistance to antimicrobials. Biofilms are formed by microorganisms that produce an exopolysaccharide matrix, protecting function and supporting for nutrients. Among the various bacterial species capable of forming biofilms, *Staphylococcus epidermidis*, a commensal organism found on human skin and mucous membranes, has emerged as a prominent opportunistic pathogen, when introduced into the body via medical devices, such as catheters, prosthetic joints, and heart valves. The formation of biofilms by *S. epidermidis* on these surfaces facilitates colonization and provides protection against host immune responses and antibiotic therapies, leading to persistent and difficult-to-treat infections.

The possible involvement of biofilms for breast oncogenesis has recently created the curiosity. This paper therefore delves into *S. epidermidis* biofilm involvement in breast cancer. *S. epidermidis* biofilms can create a sustained inflammatory environment through their metabolites and can break DNA in breast tissue, promoting cellular proliferation, angiogenesis, and genetic instability.

Preventing biofilm formation primarily involves preventing bacterial proliferation using prophylactic measures and sterilization of medical devices and equipment. In cancer treatment, common modalities include chemotherapy, surgery, immunotherapy, alkylating agents, and various anticancer drugs. Understanding the relationship between anticancer drugs and bacterial biofilms is crucial, especially for those undergoing cancer treatment who may be at increased risk of bacterial infections, for improving patient outcomes. By elucidating these interactions, strategies to prevent or disrupt biofilm formation, thereby reducing the incidence of infections associated with medical devices and implants, can be identified.

## 1. Introduction

### 1.1. Microbial biofilm

Biofilm is an aggregated form of microorganisms in an inducible protective barrier or a matrix comprising several extracellular polymeric substances (EPS), which are induced by the microorganisms, like proteins, carbohydrates, lipids, and extracellular DNA (eDNA), providing the infrastructure required to uphold a flexible and adaptable lifestyle and supporting them attach on a surface [1]. Different microbial species produce and use different variations of macromolecules, particularly proteins and polysaccharides, which contribute to the diversity of the development and composition of the biofilm [2]. EPS is essential to maintain and provide a complex chemical environment vital to microorganisms, besides its support for mechanical stability, adhesion and cohesion of a biofilm. The structure and composition of the biofilm vary depending on the species of the bacteria, the local environment, the bacterial stress state, the availability and accessibility of nutrients, and the host environment [3].

Biofilm formation, in response to stress, helps in the ability to withstand environmental challenges and enhances the chances of survival for the microbes under unfavorable conditions [4]. We have discussed the biofilm formation, types, characteristics and its control strategies in our previous paper [1].

Briefly, several factors, such as nutrient-rich environment, trigger biofilm formation since the cells will revert to a free-living state when nutrient is deprived [4]. We have previously discussed nicely about the factors associated with biofilm formation [1]. Nutrients which are

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responsible for the formation of adhesion proteins, EPS, receptors for quorum sensing and cyclic dinucleotide for extracellular matrix production etc. enhance transformation of free-living state of bacteria to a biofilm [1,5] However, the deficient in organic or inorganic chemicals for example, nitrogen, phosphate and magnesium can induce biofilm formation [6,7]. Hypoxia, a low state of oxygen level usually in the central of a biofilm or in a deep tissue, promotes the biofilm formation [8]. The human body has abundant amount of organic chemicals (e.g. carbohydrate, proteins, and lipids etc.) and trace amount of inorganic chemicals which favors the formation and establishment of a biofilm [9–11].

Several genes are often expressed during the process of initiating and propagating the EPS matrix, which promotes cell-to-cell adhesion [12]. Most biofilms start association with a certain surface using specific mechanisms and form microbial layers that increase immobilization, which is mediated by the adhesion of pili or flagella and then the growth of the microbial layer [13]. As the bacteria multiply, some microbes can even trigger quorum-sensing mechanisms that function in increasing the concentration of secreted signals from the bacteria to start profound regulatory changes that propagate to biofilm production [14]. Mature biofilms comprising microcolonies are held together by the complex layer of EPS on a variety of biotic and abiotic surfaces [1,15]. Because of the complex and protective nature of the biofilm, microbial cells are protected from many environmental and exogenous insults as antibiotics, UV damage, anaerobic conditions, pH gradients, desiccation, and bacteriophages [15].

Biofilm is emerging as a great threat in clinical field because of significantly increment of bacterial resistivity to many antibacterial drugs available in the market along with the higher concern on bacterial transmission to the patients through catheters, prosthetic heart valves, and orthopedic devices [15]. *S. epidermis*, a common microbial species, is highly associated with biofilm production on medical devices and responsible for certain nosocomial infections such as dental caries, otitis media, periodontitis, and endocarditis especially in neonates and immunocompromised individuals [15,16].

### 1.2. *S. epidermidis* biofilm and development

*S. epidermidis* is the most isolated coagulase-negative Staphylococci (CONS), a group of gram-positive, non-motile, non-spore-forming, facultative cocci that cannot produce the clotting-promoting enzyme, coagulase. It is typically a part of the normal flora of the skin and mucous membranes, protecting the host by preventing the proliferation of pathogenic microorganisms. In healthy individuals, it rarely causes any harm, as it does not produce many virulent factors. Its pathogenicity stems from its ability to adhere to surfaces and produce biofilm, and evade innate host defenses [17,18]. *S. epidermidis* has a power to produce thick multilayered biofilms on various polymer and metallic surfaces [19].

A commonly accepted mechanism of biofilm development is also applied in *S. epidermidis* biofilm formation, as we discussed earlier [1]. The operon and several genes, for example, the four-gene operon (e.g. icaADBC), have been identified to be vital to *S. epidermidis* biofilm formation and regulation in clinically significant isolates, however, most commensal isolates lack genes that are associated with this operon [19]. The *ica* operon comprises individual genes: *ica*A, *ica*D, *ica*B, and *ica*C and regulates those genes that code for an enzyme, polysaccharide intercellular adhesin (PIA) through the PIA-dependent mechanism. This mechanism is necessary for biofilm formation and bacterial aggregation on medical devices that lead to catheter-associated infections after implantation [19–22]. PIA-dependent biofilm production is also feasible with only two genes, *ica*A and *ica*D or bacteria can produce biofilms independent of PIA system [20,21].

While the detailed exact mechanism of biofilm development of *S. epidermidis* is unknown, it has been described as a four-step process: adherence, accumulation, maturation, and detachment [16]. Nonspecific and hydrophobic mechanisms mediate the initiation, and adherence of bacteria to a foreign surface or biomaterial is mediated through certain proteins, for example, bifunctional adhesins/autolysins AtlE and Aae [16]. Biomaterials or medical devices are usually coated in serum proteins like fibrinogen, collagen, and vitronectin to make them biocompatible before implantation. *S. epidermidis* has a power to bind serum proteins through its microbial surface components, recognizing adhesive matrix molecules (MSCRAMMs) [16]. Similar to MSCRAMMs, several other adessive proteins, for example, fibrinogen binding protein (Fbe) or serine-aspartate repeat-containing surface protein G and F (SdrG and SdrF) are present in bacterial cell surface [23]. SdrG and SdrF mediates binding to fibrinogen and collagen, respectively, are two of several surface proteins of *S. epidermidis* that are important to the initial adherence of the bacteria to surfaces, which is the start of biofilm production [23,24].

The next phase of biofilm formation in *S. epidermidis* is a bacterial accumulation on various biomaterials. The involvement of polysaccharide intercellular adhesin (PIA) as an essential component needed to adhere and accumulate *S. epidermidis* to surfaces is described well by Mack et al. [25]. PIA comprises structurally similar two polysaccharides, polysaccharide I and II [22]. The charged residues and unbranched structure of a polysaccharide enhance its ability to bind to surfaces and other proteins [25]. PIA is synthesized from the *ica* operon, which is described above. It is also an essential component in the architecture of a maturing biofilm [16]. Fey and Olson nicely described that *S. epidermidis* isolates expressing PIA have increased tower formation and greater 3D structures compared to isolates not expressing PIA at maturation stage [16]. This further shows how PIA can be advantageous to the pathogenesis of *S. epidermidis*. Other proteins, specifically synthesized from the *ica* operon or generally by *S. epidermidis,* also aid in the accumulation process [26].

Experiments have shown that bacteria growing in biofilm exist in four metabolic states: aerobic, anaerobic, dormant and dead cells. It is believed that these phases or growth states are one reason the bacteria evade exogenous attacks like antibiotics [16]. *S. epidermidis* bacteria within the biofilm can often shift their metabolic process from aerobic to anaerobic or micro-aerobic conditions with the support of arginine deiminase operon (ADI) though fully unknown mechanism, where arginine serves as a source of carbon in anoxic environment [16]. Phenotypic variation in biofilm maturation is frequently observed after tower formation [27]. Once the biofilm has been established on the biomaterial surfaces, *S. epidermidis* colonies inherently get certain intrinsic helpful traits like antimicrobial resistance that only perpetuate the persistence of the bacteria [1].

Part or intact sections of biofilm can be dispersed and metastasized to other organs through the little-known mechanisms, contact inhibition by surfactant (phenol-soluble modulins) and AIP-mediated detachment [28,29].

### 1.3. Antibiotic resistivity of *S. epidermidis* biofilm

Besides biofilm formation, there are other mechanisms that provide *S. epidermidis* the advantage of being resistant to antibiotics. The emergence of multidrug-resistant *S. epidermidis* (MDRSE) presents a challenge for physicians. Because of its prevalence as a commensal organism and a biofilm carrier, this makes *S. epidermidis* a troublesome pathogen. Staphylococcal mechanisms of resistance include gene recombination after acquiring different genetic information. Resistance to antibiotics is because of overuse and is conferred by genes found on mobile genetic elements (MGEs). The most frequent factor that confers antibiotic resistance for *S. epidermidis* is the *mec*A gene, which is located on an MGE called staphylococcal cassette chromosome *mec* (*SCCmec*). Horizontal transfer has been observed for this element between *S. epidermidis* and *S. aureus* [30]. Amongst hospital isolates, resistance against methicillin was observed for 75–90 % of cases [21]. Methicillin resistance is often associated with other antibiotics such as

aminoglycosides, rifampicin, erythromycin, and trimethoprim-sulfamethoxazole [31]. *S. epidermidis* antibiotic resistance has also been against fluoroquinolones, gentamicin, tetracycline, chloramphenicol, clindamycin, and sulfonamides [21].

### 1.4. Microbial biofilm in the oncogenesis

The interaction of microorganisms and cancer processes has received a lot of attention in recent years. Although formerly thought to be independent areas of studies, breakthroughs in technology and research have shown more and more effects of microbial populations on cancer biology and carcinogenesis. Investigating the complicated interactions between microbes and cancer may bring new insights into disease formation and therapy. Microbial oncology, an emerging field of research, seeks to better understand the various linkages and interactions that occur between microbial infections and various malignancies, including breast cancer.

The presence of the normal flora in breast tissue and its pathogenesis plays a significant role, establishing the diverse microbial environment. The bacterial profiles of normal tissue surrounded the breast cancer are significantly different compared to those of healthy breast controls [32]. Usually, patients with breast cancer have higher relative abundances of Bacillus, Enterobacteriaceae, and Staphylococcus [33]. *Escherichia coli* and *S. epidermidis* isolated from breast cancer patients have a capacity to breakdown the double-strand DNA of HeLa cells, pointing to a mechanism of genetic instability and accelerating to the development of breast cancer [34]. Further, a persistent inflammatory milieu in breast tissue by *S. epidermidis* biofilms encourages cellular proliferation, angiogenesis and genetic instability, which is thought to have a role in the initiation and the progression of breast cancer (Fig. 1) [35]. Some *S. epidermidis* strains have virulence factors, for example, toxins or enzymes, harming DNA directly or obstructing cellular signaling pathways that control cell division and proliferation. These pathogenic characteristics may raise the chance of developing breast cancer or increase tumor aggressiveness [36].

The tumor microenvironment comprises blood vessels, proteins, fibroblasts, immune cells, and different signaling chemicals, progressing the metastasis through modulating extracellular matrix and significantly effecting therapy response [37–39].

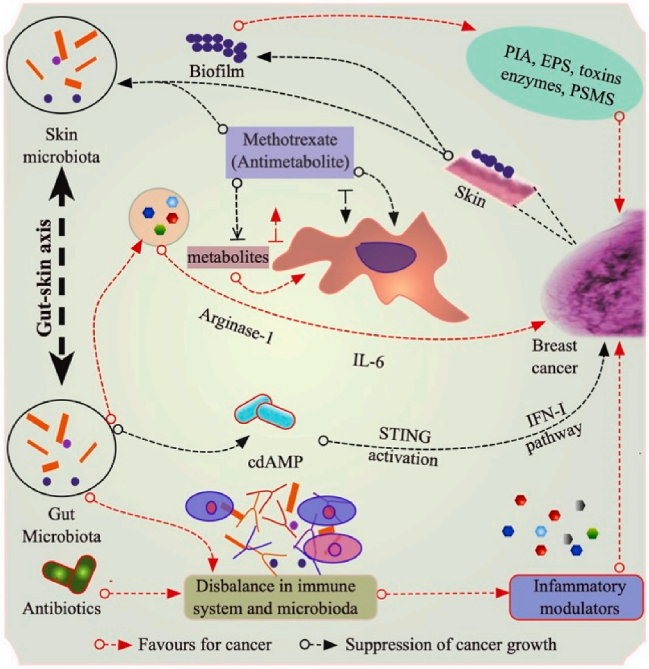


**Fig. 1. Gut-skin microbiome communication, and skin biofilm supports for cancer growth.** Biofilm releases various metabolites, e.g. PIA, EPS, toxins, enzymes, PSMS and supports for the further establishment of biofilm. Some metabolites are responsible for the initiation of signaling pathways for the arginase-1 release and activation that triggers to IL-6 production, involving for the inflammation & assisting for the breast cancer growth. Some, microdata in gut also secret good metabolites that help release cdAMP which ultimately stimulates IFN-I pathway through STING activation to reduce bacterial inflammation and inhibits the cancer proliferation. Antibiotics disturb the balance between microbiota and immune system, leading to the formation of inflammatory modulators that are responsible for biofilm resistivity and support for neoplastic changes in the cancer.

### 1.5. Hormonal influence in a biofilm and breast cancer

Steroid hormones significantly enhance the biofilm formation of certain bacteria, for example, *B. fragilis* and *E. coli*, and decrease the biofilm formation of B. *longum* [40]. Steroid derivatives of ethinyl estradiol and progesterone are usually detrimental to the gut bacteria, however, certain bacteria could substitute these derivatives with vitamin K that supports for the bacterial growth and biofilm development [40]. Effects of the sex steroid hormone estradiol on biofilm growth have been nicely described by Jiwar et al., where majority of bacteria isolates from cystic fibrosis patients had shown the biofilm formation under the influence of estradiol [41]. Hormonal imbalance can additionally be favorable for the growth of bacteria and tissue inflammation potentially by producing reactive oxygen species (ROS), which enhances inflammatory signaling pathways and damages to DNA, contributing to the growth and proliferation of cancerous cells (Fig. 2) [42,43]. Chronic inflammation in the breast microenvironment can promote a pro-tumorigenic environment that leads to increased angiogenesis, cell proliferation, and tissue remodeling, triggering cancer development [44]. Disruptions in the delicate balance of estrogen and progesterone hormones have also been linked to inflammation because of severe compromising in inflammatory pathways, and progression of breast tissue abnormalities and cancer (Fig. 2) [45,46]. Four molecular subtypes of breast cancer - luminal A, luminal B, HER2, and triple-negative breast cancer (TNBC)—can be differentiated based on the activity of the progesterone and estrogen receptors, as well as the excessive production of the human epidermal growth factor receptor 2 (HER2) [47]. Hormone therapy drugs, commonly used to treat symptoms of menopause and osteoporosis, have also been linked to an increased risk of breast cancer. These drugs contain estrogen and progesterone, which can stimulate the growth of abnormal cells in the breast. Studies have shown that their extended use can lead to higher circulating estrogen levels, increasing the risk of breast cancer compared to those who do not use these medications [45]. In addition, testosterone at higher level is also associated with the increased risk of biofilm formation and ER + breast cancer [48,49].

A microbiome in the intestine, estrobolome, is the aggregate of bacteria that is able to metabolize estrogens, and its dysregulation subsequently influences women's risk of developing postmenopausal estrogen receptor-positive breast cancer due to high level of circulating estrogens (Fig. 2) [50].

### 1.7. Age influence in an inflammatory biofilm and breast cancer

Understanding the demographic factors associated with breast cancer caused by *S. epidermidis* is essential to identify at-risk individuals and implement targeted prevention and treatment strategies [54]. Old age is a risk factor for skin infection and developing breast cancer [55,56]. Majority of the breast tissue is mammary gland, a composed of a fascial layer, fibroadipose pocket, and fibroglandular tissue, consisting of glandular lobes and ducts. During aging process, the lobules and ducts, collectively known as terminal duct lobular units (TDLUs), undergo gradual degeneration with the increment in the adipose tissue because of inadequate influence of the sex hormones, and decrement of

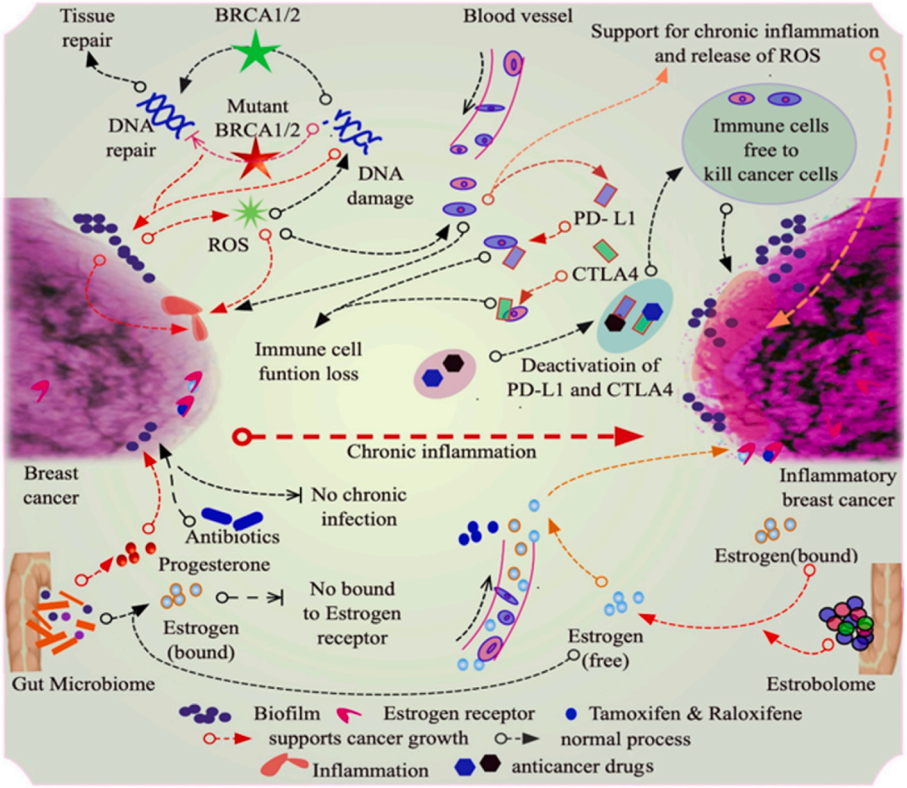


**Fig. 2. Biofilm plays the significant role for the conversion of breast cancer to inflammatory cancer along with other associated factors such as sex hormone, and their control strategy through antibiotic and anticancer drugs**. Free oxygen radicals (ROS) produced by the biofilm bacteria damages the cells and DNA that help recruit the inflammatory cells. These cells are deactivated by the PD-L1 and CTLA4 expressed by the cancer cells. Sex hormones, estrogen (E) and progesterone (P) will be transported to the breast tissue and bind with the respective receptors and increase the cellular activity and proliferation. Estrogen transported to the gut will be metabolized and converted them to bound form which is unable to bind with the hormone receptor in the breast tissue, however, there is no change in progesterone hormone. Some has estrobolome in the gut which has the capacity to free the estrogen hormone from bound form. Free estrogen hormone circulated back to the blood and breast, and binds to the ER. Because of more hormone, more ER will be induced, enhancing the breast tissue proliferation. Antibiotics help to eradicate the biofilm and prevent from chronic infection, however, antibiotic resistant biofilm release excess amount of ROS that further damage and mutate DNA of the breast tissue. DNA will be repaired by BRCA1/2, but they can be mutated with no further gene repairment, leading to the extension of the breast cancer. Anticancer drugs, for example, Tamoxifen and Raloxifene bind to the estrogen receptors and prevent estrogen-ER binding, limiting the breast tissue neoplasms. Overall, biofilm enhances the angiogenesis, proliferation and breast tissue necrosis, accelerating the breast tumor formation and growth.

myoepithelial and glandular epithelial cells [57]. Saturated fatty acid is predominant in the adipose tissue, and finding of the more percentage of saturated fatty acids in bacterial biofilm compared to free-state indicates that biofilm bacteria utilize them as the energy source to survive in adverse condition [58] As known, cancer cells engage in a metabolic symbiosis with adjacent adipose tissue, and inflammatory biofilm supports to transform the breast cancer to the inflammatory breast cancer (IBC) [59,60]. Though older women are more likely to get breast cancer, younger women—especially those under 40—may be more susceptible to aggressive forms of the disease that are linked to the production of bacterial biofilms [60]. Contrary to expectations, an established risk factor for breast cancer is mammographic density, which is more in younger age compared to old age. Women with high mammographic density have a one-to six-fold increased risk of developing breast cancer [61].

### 1.8. Breast cancer prognosis

Breast cancers with a 60–80 % survival rate are tubular mixed, mixed ductal with special type, atypical medullary, and alveolar lobular carcinoma. Breast cancers with invasive papillary, classic lobular, and medullary cancers typically have a worse prognosis with a 50 % 10-year survival rate. Inflammatory breast cancers have a poor prognosis, with only 30 % of patients surviving after 10 years [62]. Younger women have poorer outcomes with breast cancer as they are more likely to have a negative clinical presentation, such as being estrogen receptor-negative, having affected lymph nodes, having larger tumors with risk factors, and having a higher chance of developing a second cancer [47,62]. Estrogen receptor-negative patients have a worse prognosis compared to estrogen receptor-positive patients. Larger tumors and node-positive breast cancers have higher mortality [62,63]. Patients without concurrent health conditions or who are positive for LVI have higher mortality compared to those without comorbidities or who are LVI-negative. Recurrent or metastasized cancers are also poor prognostic indicators [62].

### 1.6. Genetic influence in a biofilm and breast cancer

The chance of developing breast cancer can be increased by inherited abnormalities in particular genes, including BRCA1 and BRCA2 [51]. Approximately 30 % of breast and ovarian cancer incidences are attributed to gene mutations in BRCA1 or BRCA2 [41]. BRCA1 or BRCA2 are most important genes to repair the damaged DNA, damage associated with bacterial ROS, and inhibition of cell proliferation, however their mutation leads to the breast cancer (Fig. 2) [52,53]. The role of biofilm in altering the BRCA1 and BRCA2 gene has not been studied yet.

## 2. Discussion

### 2.1. Bacteria and biofilm promote breast cancer

The microbiota results of breast tissues showed that patients with breast cancer had higher abundances of species from the Staphylococcus genus and Enterobacteriaceae group compared to that of the healthy controls [32]. By examining *S. epidermidis* and other bacteria isolated from the surrounding normal tissue of individuals with breast cancer revealed that all isolates can induce double-strand breaks in DNA (Fig. 1) [32]. The identification of skin-dwelling bacteria such as *S. epidermidis* and *Micrococcus luteus* within breast cancer tissues suggests a potential route of entry through the nipples, followed by migration through the mammary gland lobules and ducts [43].

Besides their presence in breast cancer tissue, *S. epidermidis* is noted for its ability to form biofilms (Fig. 1) [1]. Biofilm formation represents a critical aspect of microbial biology, contributing to their survival, persistence, and impact on the tumor microenvironment. Biofilms encourage persistent inflammation, offer a secure environment for bacterial colonization, and enhance their resistance to antibiotic agents [64]. The interaction between microbial and cancer-related factors at the molecular level is critical in biofilm-induced breast cancer. *S. epidermidis* is often found on human skin and mucosal surfaces. Though believed to be benign, its presence in breast tissue indicates that it may be associated with an increased risk of IBC. One prevalent bacteria linked to infections from medical devices and breast implants is *S. epidermidis* biofilm, a leading cause of breast implant-associated infection [65].

In the tumor microenvironment, *S. epidermidis* triggers significant inflammation, fostering tumor progression and immune suppression, thus promoting tumor growth. *S. epidermidis* produces a set of compounds that helps it defend itself against host defenses. Several proteins and exopolymers, particularly the exopolysaccharide PIA, which leads to biofilm formation, specifically block phagocytosis and human antimicrobial peptide action [21]. Recent research has identified a class of pro-inflammatory peptides in *S. epidermidis* known as phenol-soluble modulins (PSMs), which may be cytolytic and play a range of functions in immune evasion and biofilm formation [66].

Understanding the relationship between *S. epidermidis* biofilms and breast cancer is crucial for developing new treatment strategies and improving patient outcomes. By targeting both biofilm and cancer with specific antibiotics and anticancer drugs can lead to biofilm disruption and suppression of IBC [60]. Further research into this connection is needed to fully understand how *S. epidermidis* biofilms contribute to breast cancer progression and how they can be targeted for therapeutic intervention.

### 2.3. Anticancer regimens influence biofilm formation

Breast cancer treatment options depend on the age, tumor type, and cancer stage of the patient. There are different breast cancer treatments: surgery, adjuvant therapy, radiotherapy, and promising advancements in immunotherapy [72,73]. Surgeries for breast cancer include breast-conserving surgery (BCS) and mastectomy. Both methods are well-established local managements for early invasive breast cancer [73]. Breast-conserving therapy, followed by radiotherapy (RT), is the standard surgery for most breast cancer patients. Breast-conserving surgery can be preceded by neo-adjuvant therapy along with post-operation radiation to reduce recurrence [74]. Tumors that are greater than 5 cm can be treated with neo-adjuvant chemotherapy to reduce bulk size before surgery. However, a patient can still be ineligible for neo-adjuvant therapy due to tumor size, diffuse suspicious or malignant calcifications, pregnancy (especially in the first trimester), multicentric cancer, extensive ductal carcinoma in situ (DCIS), IBC, unclear margins for excision, and homozygous ATM mutations [75]. Mastectomies are surgical procedures that involve the removal of all or part of the breast [73,76].

Radiotherapy (RT) is typically given to patients post breast-conserving surgery, benefiting patients who have moderate or high-risk mortalities with breast cancer. Studies have shown that omitting radiation after breast-conserving surgery has negatively affected local recurrence and survival rates [77]. Determination of patient eligibility for radiation treatment depends upon prior chest wall irradiation, pregnancy status, and a connective tissue/collagen vascular disorder [73]. Administration of radiotherapy must be done within 121 weeks after surgery and cannot be given during all trimesters of pregnancy [77]. Depending on the individual case and the severity of the cancer, radiotherapy could be a viable option. Radiotherapy has anti-biofilm activity and disturbs the biofilm and kills the microorganisms [78].

Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has showed robust anti-tumor activity, especially against triple negative breast cancers (TNBC) [79]. Impairment of T-cell activity against breast tumor cells is because of interactions between inhibitory factors, such as programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), cytotoxic T-lymphocyte–associated protein 4 (CTLA4), and their ligands on cancer cells. Their interaction prevents therapy success and promotes T-cell exhaustion (Fig. 2). Targeting these immunosuppressive receptors is the basis of immunotherapy for breast cancer. Immune checkpoint inhibitors (ICIs) block immunosuppressive receptors on cancer cells and promote antitumor activity. Atezolizumab and pembrolizumab have the most robust data against triple-negative breast cancer (TNBC), and these ICI modalities have better disease outcomes and progression-free survival when combined with chemotherapy [72,80].

The combination of chemotherapy and immunotherapy based on PD-1/PD-L1 immune checkpoint inhibitors is effective for TNBC in both early and advanced stages (Fig. 2) [79]. The targeting of the PD-1/PD-L1 immune checkpoint could be considered a suitable checkpoint to suppress the biofilm formation in the IBC as in the chronic periodontitis [81].

Adjuvant therapy is the therapy using anticancer drugs for malignant growth, reducing their likelihood of returning. Several major classes of anticancer drugs exist including, alkalizing agents, antimetabolites, hormones, and natural products. Alkalizing drugs, for example mechlorethamine, a most common, are usually cytotoxic by targeting DNA, harvesting both monofunctional and bifunctional disruption through the binding to N7 (common) position of guanine creating a cross-bridge that halts DNA replication and leads to cell apoptosis [82].

Hormones can act as anticancer drugs, particularly in hormone-sensitive cancers such as breast cancer and prostate cancer. Hormone-sensitive cancers often depend on specific hormones, such as estrogen in breast cancer and testosterone in prostate cancer for growth and survival. As soon as a tumor has been identified as having an estrogen or progesterone receptor expression, there are many strategies developed to target the hormonal pathway that can be classified using mode of action. Selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene are drugs that both have estrogen agonist and antagonist properties, depending on the targeted tissue [31]. The main mode of action is blocking the estrogen receptor in breast tissue, halting cancer proliferation in breast tissue. However, the receptor modulator, tamoxifen, increases the inflammation in the breast cancer (Fig. 2) [83].

Chemotherapy is a widely accepted treatment plan to combat cancer, as it functions as a cytotoxic drug to destroy cancer cells. The drugs, for example, methotrexate, are a type of antimetabolite chemotherapy [84]. The mode of action of antimetabolites arises from their ability to establish agonistic relationships with metabolites that are structurally similar. This action leads to a lack of associated metabolite, disrupting normal cellular processes. To interfere with the synthesis of the DNA constituents, the most common antimetabolites should be structural analogs of purine and pyrimidine bases/nucleosides, or folate cofactors [85]. Taxol has a mode of mechanism by binding to microtubules (structural component) and preventing their depolymerization, leading

to the formation of unstable microtubule bundles. This disruption of normal microtubule dynamics interferes with cell division, causing mitotic arrest and ultimately leading to cell death (Fig. 2) [86]. Surprisingly, methotrexate promotes biofilm formation, whereas Taxol reduces the biofilm formation [87].

### 2.2. Prevention of S. epidermidis infection inhibits inflammatory breast cancer (IBC)

The best way to manage *S. epidermidis* infections is through preventative measures, such as maintaining hand hygiene and a sterile environment, sterilizing devices and equipment, using antibiotics with invasive medical devices, catheter care bundles, regular changes of temporary devices, and early detection of infection for rapid treatment [67,68]. Antibiotic prophylaxis is the main treatment for biomaterial-associated infections involving *S. epidermidis*.

Choosing antibiotic therapy for a patient depends upon multiple factors: drug pharmacokinetics and pharmacodynamics, antibiotic resistance of the germ, drug interactions, and patient conditions. For indwelling device infections, the device should be removed with the administration of antibiotics. Methicillin was the drug of choice for staphylococcal infections. However, with the emergence of methicillin-resistant *S. aureus* (MRSA), the use of the drug has subsided for staphylococcus infections. Vancomycin has become the preferred drug for suspected S. *epidermidis* infections and MRSA [30]. It is used to treat gram-positive bacterial infections as the antimicrobial works by inhibiting cell wall synthesis by preventing the polymerization of complex polymers, and this results in bacteria with weak cell walls. The microorganisms eventually do not survive as the weakened cell walls lead to the leakage of intracellular components. Vancomycin, in addition, inhibits the infiltration of neutrophils to inflamed organ, reducing the carcinogenesis, however, the bacteria which are sensitive to the vancomycin attract the pro-inflammatory neutrophils to start the inflammation, supporting for the cancer [69]. Daptomycin is an alternative to vancomycin, and it is also used to treat gram-positive bacteria that disrupts cell membrane functions. It is also useful for the angiogenesis and cancer suppression via inhibition of VEGF by binding to ribosomal protein S19 [70].

However, S. epidermidis biofilm is resistant to most of the drugs and can avoid the host immune system, leading to chronic inflammation and tissue remodeling [35]. It has been demonstrated that *S. epidermidis* biofilm within the breast microenvironment promotes angiogenesis, induce the epithelial-to-mesenchymal transition (EMT), and increase epithelial cell proliferation - all of which are factors in the development and progression of tumors (Fig. 2) [71].

### 2.4. Antibiotics function as anti-cancer drugs

Although the treatment of the cancers by using anticancer drugs is considered as the gold standard method, antineoplastic, pro-apoptotic, anti-epithelial-mesenchymal-transition (EMT) and antitumor activities of certain antibiotics are useful to prevent the cancer and control of bacterial biofilm formation, thereby reducing the incidence of secondary bacterial infections while patients under chemotherapy [88,89]. Most of the antibiotics are used as the bactericidal or bacteriostatic anti-pathogenic drugs that can impede the growth of other living cells [90]. Bernado et al. treated mouse mammary tumors with oral antibiotics; the results showed a reduction in population of *S. epidermidis* bacteria in the tumor, allowing other beneficial bacteria to thrive. These under-represented bacteria likely stimulate an antitumor immune response, leading to alterations in the tumor microenvironment that hinder tumor growth processes. These changes induced by oral antibiotics enhance the efficacy of paclitaxel, a chemotherapy drug commonly used in breast cancer treatment [43].

Chemicals produced by microorganisms that have anticancer properties are known as anticancer antibiotics. With a clear and potent inhibitory effect on the unchecked proliferation, aggressive growth, and spread of malignant tumors, they are mostly composed of peptides and anthraquinones [91]. The primary group of antibiotics classified as anticancer drugs are enediyne, mitomycin, bleomycin, actinomycin, guanorycin, and anthracyclines, disrupting the nucleic acid synthesis [92]. Anticancer antibiotics that are anthracyclines mostly consist of daunorubicin, doxorubicin, epirubicin, and mitoxantrone. Doxorubicin has a broad spectrum of activity and its main use is for solid tumors; it can also be effective in breast cancer, malignant lymphomas, liver cancer, gastric cancer, and many more (Fig. 3) [93]. Doxorubicin and daunorubicin both share anthracycline characteristics and involve a unique mechanism of DNA intercalations and inhibitions of topoisomerase II (Fig. 3) [94–97]. This becomes problematic to the spatial structure of DNA, preventing the creation of DNA and DNA-dependent RNA, and having the ability to function only on purine nucleosides [98]. Doxorubicin also can produce reactive oxygen species (ROS). Prolonged activation of the ROS is hallmarked to lead to oxidative stress, cellular damage, and contribute to the development of cancer (Fig. 3) [99].

Mitomycin has a broad anticancer effect, however, the therapeutic index is low with high toxicity. Mitomycin only affects one strand of DNA when they attach to it, and some of them create a cross-link to prevent the DNA double-strand from disassembling, partially disrupting the stable double helix shape of DNA (Fig. 3) [100]. Other antimicrobial classified as the anticancer drug include bleomycin isolated from *Streptomyces rotundus* [101]. Actinomycin D is a class of antibiotics inhibiting the operation of RNA polymerase and, eventually, RNA production and has been widely used as an anticancer drug. They contain cyclic peptides that can be buried in the groove of the DNA double helix and form a complex with DNA [102]. Another anticancer antibiotic is defuminomycin which can selectively impede RNA production by forming persistent complexes with DNA and interfering with the DNA template (Fig. 3) [91]. Antibiotics with an enzyme-like effect are comparable to those with an actinomycin-like impact [103]. While anticancer antibiotics have demonstrated their effectiveness in certain cases, complications can arise due to their ability to indirectly target commensal microorganisms of the gastrointestinal tract or cause unintended DNA damage [78].

Ciprofloxacin has the anti-proliferative properties through the decrease the expression of cycline B1 and Cdc2 and DNA damage through the increase the P53 and P21, similar to Adrianamycin. Gemifloxacin, however, has anti-EMT function by decreasing the expression of NF-kB and TNF-α, in addition to the anti-proliferative properties by lowering the activity of topoisomerase IV as seen in Epirubicin and DNA gyrase (Fig. 3) [91,104]. Salinomycin is a widely used anticancer antibiotic which has anti-apoptic, anti-EMT and anti-proliferative properties. Anti-apoptic properties are through increasing the expression of Caspase-3,8 & 9, Bax, DR5, FADD, anti-EMT properties by decreasing the Wnt signaling pathway and ZEB expression (Fig. 3) [91,105]. Anti-proliferative properties of salinomycin are through the decrease expression of cancer stem cells (CSCs), OCT3, and SOX2 gene. Interestingly, it supports for the proliferation of normal stem cells, opposite to CSCs and boosts the stem cells for self-renewal [105]. Mitoxantrone, Dactinomycin and Plicamycin have similar role to damage the DNA through DNA binding. However, Plicamycin can also inhibit the nucleic acid (DNA or RNA) synthesis (Fig. 3) [91,102].

### 2.5. Some anticancer antibiotics provoke cancer

The studies on the effect of antibiotic use on breast cancer treatment have suggested more adverse effect than a beneficial one [91]. Infections by antibiotic resistance bacterial is the second leading cause of death in patients with cancer [106]. The balance of bacteria in our intestines is essential which plays a crucial role in breaking down certain plant chemicals into compounds that might help protect against cancer [91]. However, antibiotic use can disrupt this process, reducing the

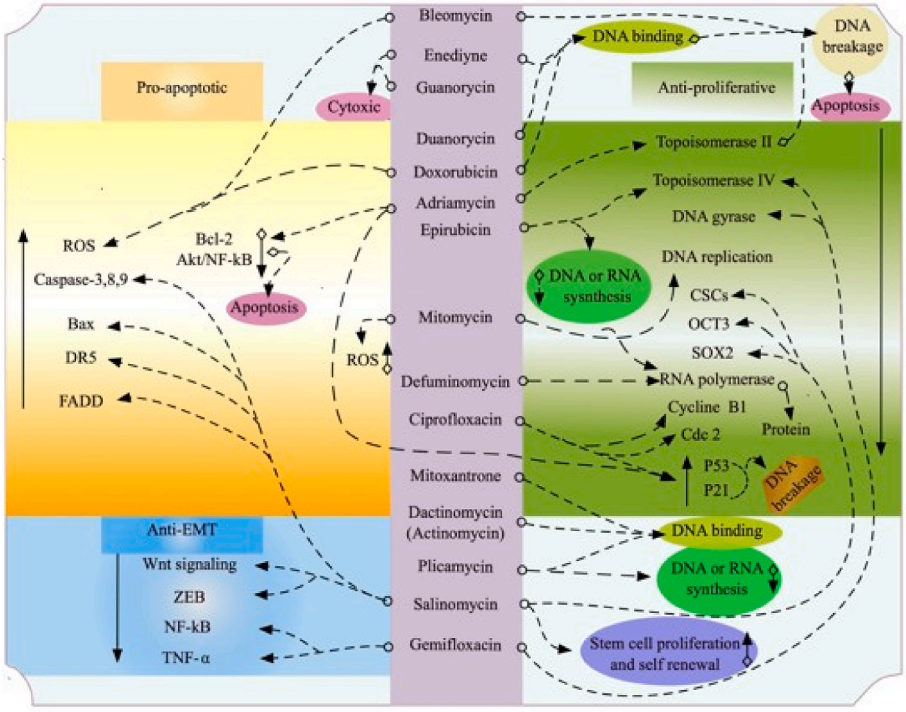


**Fig. 3. Antibiotics as anticancer drugs (anticancer antibiotic drugs) with their pro-apoptotic, anti-proliferative and Anti-EMT functions.** Bleomycin, Doxorubicin & Mitomycin increase the ROS in tumor microenvironment, enhancing the apoptosis of the cancer cells. Enediyne and Guanorycin are cytotoxic and damage the breast cancer cells, preventing from proliferation. Enediyne, similar to Bleomycin, Duanorycin, Doxorubicin, can bind the DNA and leads the cell death through DNA breakage. Adrianamycin, instead, decreases the Bcl-2 and Akt/NF-kB pathway that ultimately leads to the program cell death and also inhibits the DNA replication through inactivating topoisomerase II, leading to the DNA breakage and cell death. Epirubicin inhibits the DNA replication by inactivating topoisomerase IV as well as by blocking the DNA or RNA synthesis. Mitomycin further inhibits the DNA replication and inactivates the RNA polymerase for the formation of protein, similar to Defuminomycin. Ciprofloxacin and Gemifloxacin are fluoroquinolones used as the broad-spectrum antibiotics, they have inhibitory function to breast cancer. Ciprofloxacin has the anti-proliferative properties through the decrease the expression of Cycline B1 and Cdc2 and DNA damage through the increase the P53 and P21, similar to Adrianamycin. Gemifloxacin, however, has anti-EMT function by decreasing the expression of NF-kB and TNF-α, in addition to the anti-proliferative properties by lowering the activity of topoisomerases IV as seen in Epirubicin and DNA gyrase. Mitoxantrone, Dactinomycin and Plicamycin have similar role to damage the DNA through DNA binding. However, Plicamycin can also inhibit the nucleic acid (DNA or RNA) synthesis. Salinomycin is widely used anticancer antibiotics which has anti-apoptic, anti-EMT and anti-proliferative properties. Anti-apoptic properties is through increase the expression of Caspase-3,8 & 9, Bax, DR5, FADD, anti-EMT properties by decreasing the Wnt signaling pathway and ZEB expression. Anti-proliferative properties of Salinomycin are through the decrease expression of cancer stem cells (CSCs), OCT3, and SOX2 gene. Interestingly, it supports for the proliferation of normal stem cells, opposite to CSCs and boosts the stem cells for self-renewal.

production of these protective compounds and supporting for regulating the tumor microenvironment [107]. On the flip side, antibiotics can also alter how our bodies metabolize hormones, for example, estrogen, leading to lower hormone level in the bloodstream. While this might lower the risk of certain hormone-related cancers, the overall impact of antibiotics on cancer risk is complex and not fully understood. Antibiotics might also influence cancer risk by affecting immune function and inflammation [108]. The absence of a correlation between initial bacteriuria and subsequent breast cancer incidence suggests that antibiotic use itself, rather than the underlying infection, may be the true risk factor [109]. It was found that increased duration of antibiotic use and a higher number of prescriptions correlate with elevated risk of developing breast cancer [110]. This heightened risk by long-term use of all classes of antibiotics also increases the mortality from breast cancer [91].

### 2.6. Treatment strategies

As we discussed in detail above that bacteria and biofilm promote cancer. Inhibition of the *S. epidermidis* biofilm formation by various antibiotics inhibits the IBC. Certain anticancer drugs, however, influence biofilm formation, transforming the breast tumor to the IBC. In addition, some anticancer antibiotics could provoke the cancer. This is therefore very challenging to appropriately apply of the treatment strategies for the positive prognosis.

Screening and confirmation of the breast cancer are the first important steps before the start of treatment. As shown in Fig. 4, palpable breast mass and/or axillary swelling lymph node are certain indicators of possibly of breast tumor that suggest to get-go initial work through mammography and ultrasound without any delay. Biopsy of breast tissue collected from percutaneous and nodal area is highly recommended to histologically confirm the tissue abnormality. Any positive immunostaining result of ER, PR and HER2 is the alarm of most likely the breast tumor. Immediate attention should be given to classify the tumor stage [111]. Epithelial thickening and trabecular distortion can be a suggestive for IBC that can be further confirmed through histology, MRI and PET-CT. Multidisciplinary team that usually include oncologist, radiologist and pathologist defines the tumor stage and discusses for the treatment plan. Once IBC is ruled out, preoperative systemic therapy (chemotherapy, radiotherapy, and/or immunotherapy) based on the breast tumor stages, diagnostic results and availability of treatments is applied [73,91]. IBC if responses to the treatment, it is suggestive for the mastectomy without reconstruction along with adjuvant therapy to prevent the cancer reoccurrence. IBC could not response to the therapy, surgery is the alternative. However, it might not be possible for the surgery in certain cases, radiotherapy is the option. It is suggestive for the mastectomy if the IBC responses to the radiotherapy for the possibly recovery from the IBC. If not responsive to

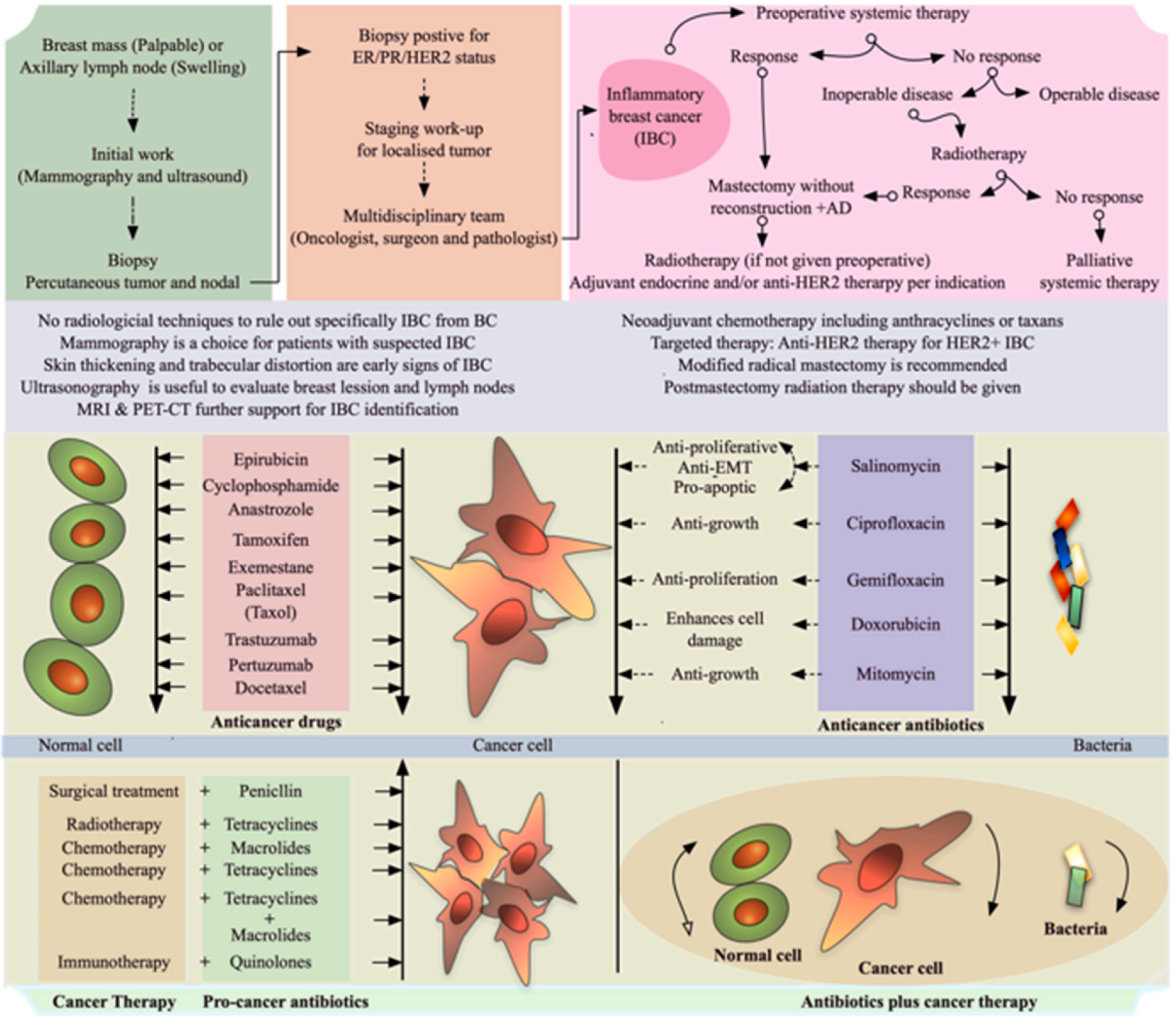


**Fig. 4. Overview of the inflammatory breast cancer (IBC) screening, diagnostic methods, effects of anticancer therapeutics and treatment strategies.** Identification criteria of IBC, diagnostic methods, effects of the anticancer, anticancer antibiotics and antibiotics to the normal cells and cancer cells and treatment strategies (radiotherapy plus antibiotics, chemotherapy plus antibiotics and immunotherapy plus antibiotics) are illustrated). Not all the strategies are of positive prognosis, some synergistic roles of cancer therapy together with antibiotics have adverse effects, enhancing the IBC. Effective plan should be established to target the cancer cells and infective bacteria for their lysis, while maintaining the normal physiology of the host cells and accelerating the activity of inflammatory and immune cells to cure the IBC and to prevent it from no response state to cancer therapy.

radiotherapy, palliative systemic therapy is the option to relieve the symptoms and to reduce suffering until the survival period of the patient [112].

Any strategy that inhibits cancer growth has adverse effects on the normal cells, tissues and organs. For example, doxorubicin causes alopecia, pruritus, dehydration, abdominal pain and photosensitivity. Some anticancer drugs such as pertuzumab causes pancytopenia, and tamoxifen causes the hot flashes and weight loss [91]. It is, therefore, very important to strictly monitor the patient's response to the therapy. Anticancer antibiotics are preferred for IBC treatment. Salinomycin, ciprofloxacin, gemifloxacin, doxorubicin and mitomycin are commonly used therapeutic drugs for the IBC treatment. Synergistic methods (e.g. radiotherapy plus chemotherapy or radiotherapy plus immunotherapy or surgery plus chemo-/immuno-therapy etc.) have been applied to treat the IBC with the maximum percentage of the positive prognosis [91]. Conventional anticancer drug-delivery systems are in transformative forms to deliver drugs for maximum effectivity with minimum adverse effects through the use of nanoparticles and nano-injection systems [113]. Tetracycline antibiotic is usually recommended with radiotherapy for IBC, however, intestinal microbiota disbalance by tetracyclines leads to the decrease in the formation of biologically immune active agents from glucosinolates, isoflavone and glycoside that favors for the cancer growth [114,115]. Further, tetracycline with chemotherapy suppresses the immune cells and their proliferation [116]. Another pro-cancer antibiotic, macrolides, induce chronic inflammation as the adverse effect when provided together with chemotherapeutics [116]. Quinolones has also cytotoxicity effect to both immune cells and normal cells and its effect increases when applying together with immunotherapy [117,118]. The effective therapeutic strategies to inhibit and cure the IBC are therefore in demand. The ideal cancer therapy without adverse effects and biofilm-cancer inner-supportive roles in micro-vicinity has not been achieved yet. The formulated cancer drugs and antibiotics should be designed to target specifically cancer cells and bacteria that are localized and participated in the IBC formation without disturbing the normal host and immune cells and intestinal microbiota. In addition, various in-vivo micro-imaging systems to detect early stage of cancer and advance drug delivery systems (e.g. nanoparticles and nano-vaccines) are supportive tools to monitor the IBC prognosis [119–121].

## 3. Conclusion

Breast cancer continues to pose substantial challenges despite the continuous improvements in detection and therapeutic options,

demanding for a deeper comprehension of the disease's complex etiology and pathophysiology. The potential impact of bacteria and the development of bacterial biofilms—especially those involving *S. epidermidis*—represents a fresh and fascinating facet of the pathophysiology of breast cancer that should not be overlooked. Recognizing the complex interactions between bacterial communities and breast tissue could provide additional insights into disease processes, risk assessment, and treatment approaches.

Moreover, bacteria linked to biofilms can interact directly with host cells, eliciting inflammatory reactions, damaging DNA, and initiating pro-tumorigenic signaling pathways. The development of biofilms in breast tissue may contribute to tumor growth, metastasis, and resistance to therapy, so clarifying the role of bacteria in breast cancer is therefore crucial for the improvement of patient outcomes.

Comprehending the function of *S. epidermidis* biofilm in the progression of breast cancer, as well as the demographic elements linked to this association, presents opportunities for the creation of focused preventative and therapeutic approaches. In order to reduce the risk of breast cancer and enhance patient outcomes, more research is required to clarify the mechanisms behind biofilm-mediated breast carcinogenesis and investigate novel therapies targeted at disturbing these microbial communities. Understanding the interplay between anticancer drugs and bacterial biofilms is important for improving patient outcomes, particularly for individuals undergoing cancer treatment who may be at an increased risk of bacterial infections. Explaining the interactions between anticancer drugs and bacteria may help identify strategies to prevent or disrupt biofilm formation, thereby reducing the incidence of infections associated with medical devices and implants. The potential impact of antibacterial drugs on breast cancer could have important implications for patient care and treatment decisions. It may inform discussions between healthcare providers and patients regarding the selection and duration of antibiotic therapy, particularly in individuals with a history of breast cancer or those at increased risk of developing the disease.

## Ethical declarations

The authors declare no competing interests.

## Declaration of AI use

No AI was used to generate the scientific writing.

## Conflicts of interest

We, all the authors, declare that there are not any conflicts of interest or no competing interest.

## CRediT authorship contribution statement

**D. Allen-Taylor:** Writing – original draft. **G. Boro:** Writing – original draft. **P.M. Cabato:** Writing – original draft. **C. Mai:** Writing – original draft. **K. Nguyen:** Writing – original draft. **G. Rijal:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Conceptualization.

## Data availability

No data was used for the research described in the article.

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