Bacterial metabolites: Effects on the development of breast cancer and therapeutic efficacy (Review)

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Abstract. Evidence suggests that various gut metabolites significantly impact breast cancer (BC) and its treatment. However, the underlying mechanisms remain poorly understood and require further investigation. In the present study, the current literature was reviewed to evaluate the roles of microbial metabolites in the development of BC and its response to treatment. Microbial metabolites, including secondary bile acids, short-chain fatty acids, amino acid metabolites, lipopolysaccharide, nisin and pyocyanin, serve crucial roles in the BC microenvironment. Microbial metabolites promote BC invasion, metastasis and recurrence by facilitating cellular movement, epithelial-mesenchymal transition, cancer stem cell function and diapedesis. Furthermore, certain metabolites, such as trimethylamine N-oxide and L-norvaline, can alter the pharmacokinetics of chemotherapeutic drugs. The present review highlights the possible involvement of microbial metabolites and bacteriocins in BC carcinogenesis, development and metastasis. These metabolites could provide new insights for BC treatment strategies and are considered potential therapeutic targets.

Contents

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1. Introduction

Breast cancer (BC) stands as one of the most commonly diagnosed malignancies worldwide. Mortality rates persist at a high level, ranking BC as the second leading cause of cancer-related deaths among females, with ~~290,000 fatalities annually globally (1). BC is associated with the disruption of several microbiome compartments, such as the gut microbiome, breast tissue microbiome and tumor microbiome, which has been termed oncobiosis (2). The human body harbors diverse communities of commensal and pathogenic bacteria in both the body cavity and the body surface, with >90% of the microbes residing in the gastrointestinal tract. Each individual has a distinct gut microbial composition, and dysbiosis of the gut microbiota has been demonstrated to contribute to the pathogenesis of several diseases, including BC, pancreatic adenocarcinoma, colorectal cancer (CRC), gastric cancer and hepatocellular carcinoma (3-7). The notable role of oncobiosis in the pathogenesis of BC is highlighted by the discovery that antibiotic usage increases susceptibility of mice to BC (8). Additionally, risk factors associated with BC, such as high breast density (9), early onset of menstruation, low levels of physical activity (10), increased body mass index (11), advanced age (12) and high alcohol consumption (10), have also been associated with alterations in the gut microbiome that contribute to the oncobiosis associated with BC.

Numerous bacterial metabolites are either products of microbial metabolism, such as bacteriocins, or compounds derived from the host that have been modified, such as secondary bile acids (BAs), short-chain fatty acids (SCFAs) and amino acid metabolites (13). These metabolites serve as crucial links in the reciprocal interactions between cancer cells and their surrounding microenvironment. The disruption of gut microbial communities, known as dysbiosis, can produce systemic immune responses due to the breakdown of mucosal barriers and the translocation of gut microbiome components

to breast tissue via the bloodstream (Fig. 1). Moreover, microbial metabolites are not solely derived from the gut microbiota. Human breast tissue also harbors symbiotic bacterial communities, and these communities and their metabolic products may influence the occurrence and progression of BC (14). Patients with triple-negative breast cancer (TNBC) have the least complex microbial signature, whereas those with luminal BC subtypes have the most complex microbial signature (15). The microbiota can influence cancer progression through several mechanisms, including modulating inflammation, inducing DNA damage and producing metabolites involved in tumorigenesis or tumor suppression (16). In summary, both gut-derived and breast tissue-derived microbiota and metabolites are considered to influence the development, progression and metastasis of BC, and its response to treatment.

In particular, previous studies (17-20) have reported that the efficacy of standard chemotherapeutic, targeted and immunotherapy drugs is influenced by gut microbial metabolites, and these metabolites may be implemented as combination therapies for BC. The impact of different taxa on the immune checkpoint inhibitor (ICI) response is mediated primarily through the release of various bacterial metabolites (21); however, there has been limited research on how these distinct metabolites affect the response to ICIs. The interaction between these metabolites and the host immune system is crucial for understanding how the microbiome can affect ICI efficacy. This also implies that certain metabolites could be used to predict the response to ICIs (22). Although evidence supports various gut metabolites having important effects on BC and its drug treatments, the underlying mechanisms are poorly understood and warrant further investigation.

Research has shown that the gut microbiota composition can impact the effectiveness of and adverse reactions to BC immunotherapy (23,24). However, little is known about the importance of the interactions between microbiota-induced metabolites and drug metabolites. In the present review, the mechanisms and therapeutic potential of several microbial metabolites in BC are reported and discussed.

2. Effects of microbial metabolites on BC development

Secondary BAs. BAs are synthesized from cholesterol in the liver and released into the small intestine. BAs interfere with glucose, fatty acid and lipid metabolism mainly by activating the farnesoid X receptor and the G protein-coupled bile acid receptor (TGR5), which are crucial for maintaining a healthy gut microbiota, regulating lipid and carbohydrate metabolism, enhancing insulin sensitivity and supporting innate immunity (25). Bacteria ultimately mediate the conversion of BAs into secondary BAs, including deoxycholic acid (DCA) and lithocholic acid (LCA) (26). A small population of intestinal species in the genus *Clostridium*, including *Clostridium scindens, Clostridium hiranonis, Clostridium hylemonae and Clostridium sordelli*, are capable of producing secondary bile acids (26). Tang *et al* (27) and Zhu *et al* (28) demonstrated that BAs and their metabolites can enter breast tumors through BA transporters, reduce BC aggressiveness and improve BC prognosis. The studies also showed that BAs may interfere with hormonal pathways in the breast tissue. The presence of secondary BAs can promote carcinogenesis through several mechanisms, such as inducing DNA damage, activating β-catenin signaling and increasing cyclooxygenase-2 activity (29). Secondary BAs can also influence tumor development and progression through their immunosuppressive effects (30), and have been shown to have anticancer effects and reduce cancer risk in clinical studies (31).

The contradictory effects of secondary BAs on carcinogenesis are context-dependent and may arise from the following factors. Low concentrations of secondary BAs may exert anticancer effects by activating FXR/TGR5 receptors (25,27,28). Conversely, chronic or high-dose exposure to secondary BAs can promote carcinogenesis (29). The balance between pro- and anti-carcinogenic BAs also depends on microbial composition. Specific *Clostridium* species (e.g., *C. scindens*) convert primary BAs to secondary BAs (26). Finaly, receptor signaling dynamics also contribute to the contradictory actions. For example, TGR5 activation in intestinal L cells stimulates GLP-1 secretion, improving insulin sensitivity (anticancer), but in macrophages, chronic TGR5 signaling may drive immunosuppressive M2 polarization (pro-cancer) (25,30).

DCA is formed by the de-hydroxylation of BAs and previous studies have shown that DCA increases the number of metastases generated from 4T1 cell tumors grafted into mouse fat pads by elevating the expression of vascular endothelial growth factor receptor 2 (Flk-1) and reducing the ceramide-mediated apoptosis of BC cells (32). In a previous *in vitro* study, physiological levels of DCA promoted cell proliferation by inducing AKT phosphorylation and cyclin D1 expression in MCF-7 BC cells, and was cytotoxic at supraphysiological concentrations; the mechanism of DCA involved the induction of apoptosis (33). Cong *et al* (34) screened a library of gut microbiota-derived metabolites and identified DCA as a negative regulator for $CD8^+$ T cell effector function. The study demonstrated a causal relationship between microbial DCA metabolism and impaired antitumor $CD8^+$ T cell responses in CRC, highlighting the immunosuppressive role of DCA in tumor progression. The dual roles of DCA have important implications for their therapeutic targeting. On one hand, strategies to inhibit the production or activity of DCA could restore antitumor immunity and reduce tumor progression, as suggested by Cong *et al* (34). On the other hand, modulating BA receptor signaling (e.g., FXR/TGR5 agonists) may offer additional therapeutic avenues (25,27,28). Furthermore, microbiome-directed interventions, such as probiotics or dietary modifications, could reshape the BA pool to favor antitumor effects. However, the precise balance between pro- and anticancer BAs must be carefully considered, as their effects are highly context-dependent.

Clostridium in the large intestine is mainly responsible for the production of LCA (2). In a previous study, patients with early stage BC had reduced serum levels of LCA, which may be associated with a decline in the biosynthetic capacity of LCA within the microbial community (35). Furthermore, serum LCA levels are negatively associated with the Ki67 labelling index in BC cells (36). Therefore, promoting the production of these protective metabolites by the gut microbiota in women with BC may improve their health (37). Moreover, LCA can reduce BC cell proliferation by 10-20%, inhibit tumor infiltration and metastasis, reduce epithelial-mesenchymal transition (EMT) and enhance antitumor immune responses (35). Another

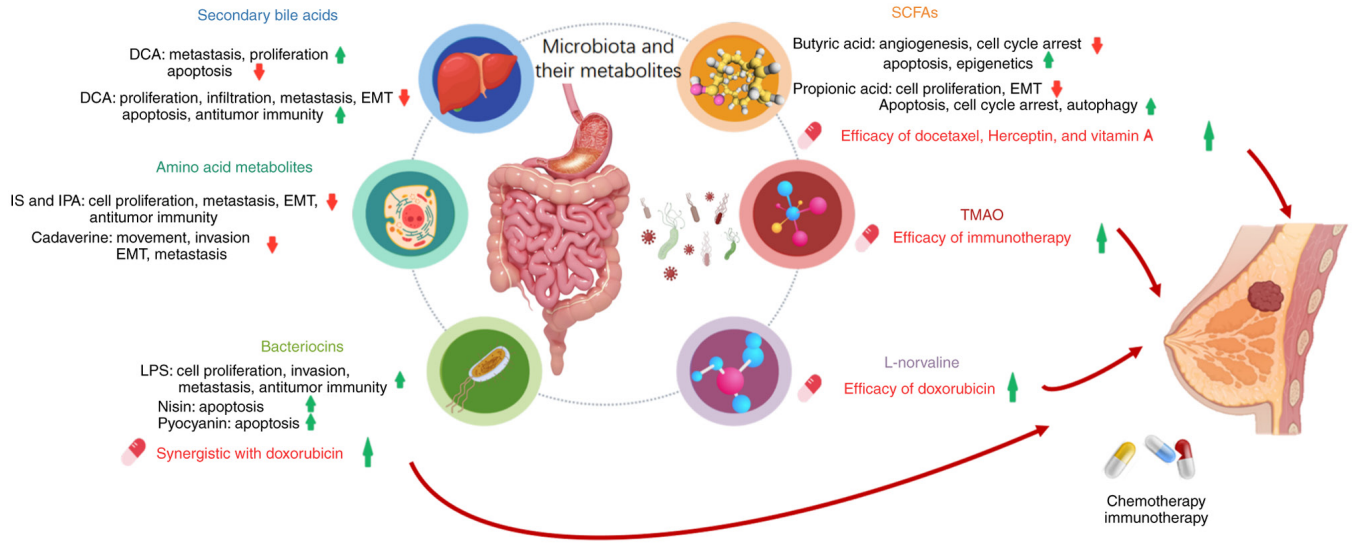

Figure 1. Bacterial metabolites influence the progression of breast cancer and the efficacy of breast cancer treatments via their translocation to breast tissue through the blood. DCA, deoxycholic acid; LCA, lithocholic acid; IS, indoxyl sulfate; IPA, indole propionic acid; EMT, epthelial-mesenchymal transition; LPS, lipopolysaccharide; SCFA, short-chain fatty acid; TMAO, trimethylamine N-oxide.

study revealed a potential therapeutic role of LCA in BC cells due to its reversal of lipid metabolism dysregulation (38); LCA induced TGR5 expression in MCF-7 and MDA-MB-231 BC cells, and had antiproliferative and proapoptotic effects. Moreover, the expression of the proapoptotic p53 protein increased and the expression of the antiapoptotic protein Bcl-2 decreased in MCF-7 cells after LCA treatment. Furthermore, LCA supplementation reduced vascular endothelial growth factor (VEGF) production by BC cells in an animal model of BC (2). In conclusion, LCA may have a therapeutic effect on BC cells and can be used as an antiproliferative and proapoptotic drug that targets lipid metabolism in these cells (38).

SCFAs. Gut microbes influence cancer growth through the production of SCFAs, such as acetate, butyrate and propionate (39). SCFAs can directly activate G protein-coupled receptors (GPCR) and inhibit histone deacetylases (HDACs) (40), resulting in cell attachment and differentiation, immune cell migration, cytokine production, chemotaxis and programmed cell death (41,42). Although the suppressive function of SCFAs in the development of CRC has been demonstrated (43), SCFAs can also affect various organs through the systemic circulation (29). However, their role in BC needs further study.

Among the SCFAs, propionic acid (SP), which can be produced from succinic acid, inhibits tumor growth and EMT, induces apoptosis in BC cells by binding to the GPCRs, GPR43 and GPR41, and inhibits BC cell proliferation and apoptosis in a dose-dependent manner (30). SP also suppresses the invasion of BC cells overexpressing GPR41 and GPR43 by activating large tumor suppressor kinase 1 and inhibiting extracellular signal-regulated kinase 1/2 (44). A previous study demonstrated the anticancer effects of SP on BC cell growth, programmed cell death, self-digestion processes and the production of substances that prevent oxidative damage (45). SP was shown to inhibit BC cell proliferation and induce apoptosis by inhibiting STAT3, increasing reactive oxygen species (ROS) levels and activating p38; however, these effects were not mediated by the SCFA receptors GPR41 or GPR43. Furthermore, SP suppressed the proliferation of BC cells by inhibiting the expression or activity of cell cycle checkpoint proteins, causing G_0/G_1 phase arrest and inhibiting DNA synthesis (45). Collectively, these results suggest that SP is a candidate therapeutic drug for BC.

The intestinal concentration of butyrate, the major protective SCFA, serves a crucial role in cell cycle regulation, cell proliferation and apoptosis (29). Owing to its anti-inflammatory properties and ability to induce cell differentiation, trigger cancer cell apoptosis and promote protective histone hyperacetylation, butyrate has shown strong antitumor effects in BC cell lines, including MCF-7, MDA-MB-231 and MDA-MB-453 (42,46), revealing its potential as an anticancer metabolite. Therefore, promoting butyrate production may have beneficial implications for patients with BC or for those at risk of developing BC (37). Previous studies evaluated the effects of butyrate on the proliferation and ultrastructure of BC cells (47,48). The study confirmed that the administration of butyrate resulted in morphological changes to the ultrastructure of MCF-7 cells, suppressed cell proliferation and triggered apoptotic cell death; however, the underlying mechanism of action remains unknown (47,49). Moreover, butyrate can induce calcium influx into MCF-7 cells (42), which activates caspases and other pro-apoptotic pathways, leading to cell death.

Compared with healthy premenopausal women, premenopausal patients with BC were determined to have markedly lower levels of SCFA-producing bacteria in the gut, as well as lower levels of key SCFA-producing enzymes; therefore, these SCFA receptors may be new targets for the treatment of premenopausal patients with BC (50). Overall, SCFAs are promising for BC treatment. Future studies should evaluate the effects of SCFAs on BC to understand their molecular mechanisms of action, as well as how SCFAs affect the efficacy and safety of standard BC drug therapies and BC prognosis.

Amino acid metabolites. Similar to SCFAs and LCA, certain amino acid metabolites play important roles in BC. Several bacterial taxa, such as *Clostridium*, *Bacillus*, *Lactobacillus*, *Streptococcus* and Proteobacteria species, efficiently metabolize proteins (51). Tryptophan catabolism is inhibited in BC cells and reduced tryptophan catabolism is associated with decreased survival in patients with BC, whereas elevated levels of extracellular tryptophan are linked to worse BC prognosis (52). Tryptophan metabolites may stimulate the immune system by interacting with the aryl hydrocarbon receptor (AHR) to impact human health and disease (52,53).

The microbiome contributes to 4-6% of the overall tryptophan catabolism and generates indole derivatives, including indole propionic acid (IPA) and indoxyl sulfate (IS), both of which have cytostatic effects on BC (54,55). Similar to other indole derivatives, IPA and IS act through the pregnane-X receptor and AHR. The expression of these receptors decreases as BC progresses, and in patients with a poor prognosis, the expression of these receptors is lower. In addition, indole derivatives have strong immunostimulatory effects, and can stimulate an antitumor immune response in BC and alter the microbiome composition (54,55).

The enzyme lysine decarboxylase catalyzes the decarboxylation of lysine to produce cadaverine (CAD), which is also produced by numerous bacterial species (e.g. *E. coli*, *Vibrio sp.* and *Lactobacillus sp.*) in the human microbiome (56). Reduced CAD biosynthesis in the gut has been reported in patients with early BC, leading to reduced production of anticancer bacterial metabolites and resulting in increased BC invasion (39). Kovács *et al* (56) reported that CAD inhibited BC metastasis and reduced the aggressiveness of the primary tumor. Moreover, CAD amine treatment of BC cell lines reversed EMT, inhibited cell motility and invasion, and rendered cells less stem cell-like by reducing mitochondrial oxidation over the range of serum concentrations tested (100-800 nM). CAD is thus expected to contribute to the development of tumor therapies; however, the mechanism of CAD in BC requires further investigation.

Lipopolysaccharide (LPS). Metabolites such as LPS, glycans and endotoxins are present in the outer membranes of gram-negative bacteria. The inherent microbiome of the breast and the gut is enriched in gram-negative bacteria. Bacterial LPS was found in $CD45^+/CD68^-$ cells of a highly inflamed breast tumor, indicating that the colonizing bacteria tune and activate the immune system (57). LPS is closely linked to human immunity. Toll-like receptors (TLRs), which respond to LPS stimulation, have gained significant attention in cancer research due to their role in tumor progression (58). TLRs serve essential roles in the initiation of inflammation and the activation of host innate immune responses against invading microorganisms through their recognition of pathogen-associated molecular patterns (PAMPs). LPS is a type of PAMP that has been reported to enhance the invasiveness of BC cells (2) and stimulate BC cell proliferation (59). The metastatic potential of BC cells is enhanced upon TLR4 and NF-κB activation, making these proteins promising therapeutic targets for metastasis prevention (60). In a previous study, the LPS-mediated activation of TLR4 markedly increased the mRNA expression of matrix metalloproteinases, MMP-2 and MMP-9, and VEGF. The subsequent triggering of the TLR4 downstream protein, myeloid differentiation factor 88, resulting in increased production of interleukins, IL-6 and IL-10, in human BC cells. TLR4 was demonstrated to be overexpressed in human BC tissues and has been associated with lymph node metastasis (61). A study by Li *et al* (59) revealed that in MCF-7 and MDA-MB-231 BC cells, LPS-stimulated TLR4 pathway activation triggered β-catenin signaling via PI3K/Akt/GSK3β to promote downstream β-catenin target gene transcription during BC metastasis. These findings suggest that TLR4 may be involved in the progression and metastasis of human BC and may be a new therapeutic target.

Nisin. Nisin, the most abundantly produced bacteriocin in the gut, also has important effects on BC and has been demonstrated to be capable of modulating the innate immune system by inducing chemokine secretion and inhibiting LPS-stimulated cytokines *in vitro* and *in vivo* (62). The precise mechanism of the anticancer effect of nisin remains unclear. However, it is hypothesized that nisin induces apoptotic cell death by initiating cell cycle arrest and altering intracellular ion levels (e.g., calcium) through membrane disruption and pore formation. This alters the transmembrane potential (42,62) and increases the permeability of the phospholipid bilayer (63).

Previous studies have demonstrated the antitumor potential of nisin in head and neck squamous cell carcinoma *in vitro* and *in vivo* (64). In addition, Ahmadi *et al* (65) demonstrated that nisin induced the intrinsic apoptosis pathway in colon cancer cells. While there is less research on nisin in BC, the *in vitro* experiments of Avand *et al* (62) reported for the first time the potent toxicity of nisin to MCF-7 BC cells. Compared with that in normal human umbilical vein endothelial cells (HUVECs), nisin exhibited selective toxicity to cancer cells (62). Overall, nisin is expected to be an anticancer agent; however, its precise anticancer mechanism needs further study.

Pyocyanin. Pyocyanin is a unique extracellular secondary metabolite pigment produced by *Pseudomonas aeruginosa* that exhibits redox activity and is toxic to mammalian cells (66). Previous research has demonstrated the apoptotic effects of pyocyanin on cancer cell lines, including rhabdomyosarcoma, hepatocellular carcinoma (HepG2) and human pancreatic cancer cell lines (67,68). Abdelaziz *et al* (69) were the first to report the toxic effects of pyocyanin to MCF-7 human breast adenocarcinoma cells. The study demonstrates that purified pyocyanin may be used in treatment strategies of human breast adenocarcinoma (MCF-7), which results in decreasing the viability of cells by the induction of necrosis and accelerating apoptosis via caspase-3 activation. Pyocyanin has a low molecular weight (210 Da) and exists as a zwitterion that readily diffuses across cell membranes under aerobic conditions, increasing the intracellular ROS levels (66). Excessive ROS leads to caspase-3 activation, which promotes cancer cell death via apoptosis. Therefore, pyocyanin is considered to have potential to be a new and effective alternative treatment for cancer.

3. Effects of microbial metabolites on BC therapy

There is growing evidence that the gut microbiota influences the effectiveness of cancer therapies and their associated

side effects. In the present section, the roles and underlying mechanisms of gut microbial metabolites on the efficacy and side effects of several anticancer treatments are summarized. Understanding these interactions may lead to the development of effective adjuvant therapies to improve the efficacy of anticancer treatments.

SCFAs. Although butyrate has shown notable anticancer effects as a stand-alone therapy, the synergistic effects of this compound combined with conventional anticancer medications have been documented in previous years (70-72). By inhibiting HDACs, butyrate has the potential to enhance the clinical efficacy and mitigate the toxicity associated with standard chemotherapeutic agents (42). A previous study evaluated the antitumor potential of Herceptin in combination with butyrate against HER2-overexpressing BC cells (73). The combination of butyrate and Herceptin markedly increased the growth-inhibitory effect on SKBR3 BC cells compared with the effects of butyrate and Herceptin alone (73). The potential synergistic effect of butyrate with vitamin A on MCF-7 BC cells was investigated in another *in vitro* study, which revealed that vitamin A enhanced the anti-proliferative effects of butyrate. Cell proliferation inhibition was 34, 10 and 46% following treatment with butyrate, vitamin A and their combination, respectively, suggesting that vitamin A potentiated the inhibitory activities of butyrate (74). Thus, the available evidence suggests that butyrate may offer notable benefits as an adjuvant therapy alongside standard anticancer drugs and has potential far-reaching clinical implications for the management of BC (42).

A clinical cohort study was performed to assess the fecal and plasma concentrations of SCFAs in patients with primary cancer undergoing treatment with the ICIs nivolumab or pembrolizumab. The results indicated that there may be an association between fecal SCFA levels and ICI efficacy. High concentrations of fecal or plasma SCFAs were associated with a response to ICI treatment and longer progression-free survival, suggesting that SCFAs could act as mediators between the gut microbiome and immunotherapy (75). Another study indicated that gut microbiota diversity was notably associated with the response to ICIs therapy in patients with non-small cell lung cancer. Responders (Rs) presented with a marked increase in the abundance of *Faecalibacterium* in their gut microbiota, along with increased levels of SCFAs, particularly butyrate, acetate and hexanoate. Furthermore, fecal microbiota transplantation from Rs to non-responders enhanced the anticancer effects of ICIs in mice and reduced Ki-67 expression in tumor cells (76). These studies provide evidence regarding how SCFAs affect ICIs therapy efficacy. SCFAs may modulate the response to ICIs by affecting the functions of immune cells and the tumor microenvironment (77). High blood SCFAs levels are associated with resistance to CTLA-4 blockade and a higher proportion of Treg cells (78). SCFAs, particularly butyrate, enhance the differentiation and function of cytotoxic $CD8^+$ T cells by inhibiting HDACs, leading to increased expression of effector molecules such as IFN-γ and granzyme B (42). This promotes antitumor immunity and synergizes with ICIs. The specific mechanism of action needs further investigation.

Trimethylamine N-oxide (TMAO). TMAO, a gut microbiota metabolite, is derived from phosphatidylcholine, choline, betaine, and L-carnitine. In previous years, TMAO has received increasing attention due to its possible carcinogenic effects (79,80). However, a recent study (81) revealed that TMAO triggers endoplasmic reticulum stress via eukaryotic translation initiation factor 2α kinase 3, which activates caspase 3 and gasdermin E, leading to pyroptosis in tumor cells and enhancing $CD8^+$ T-cell-mediated immunity against TNBC. In addition, high plasma TMAO levels are associated with improved immunotherapy outcomes in patients with advanced TNBC, indicating that TMAO is a potential biomarker for the response to immunotherapy (81). In mice, TMAO combined with anti-programmed cell death protein 1 antibodies inhibited tumor growth to a markedly greater extent than antibody treatment alone, suggesting that TMAO can increase the efficacy of immunotherapy (81). Therefore, as a driver of antitumor immunity, TMAO may enhance the antitumor immune response in BC. However, the effect of TMAO on BC therapy needs further investigation.

Zhou *et al* (79) demonstrated that TMAO promotes the proliferation and migration of hepatocellular carcinoma cells through the MAPK pathway, which is involved in regulating cell proliferation, differentiation and apoptosis. Given the role of the MAPK pathway in EMT, it is possible that TMAO may also influence EMT in hepatocellular carcinoma cells, but further research is needed to confirm this. Another study revealed that TMAO serves a carcinogenic role in CRC by promoting cell proliferation and angiogenesis (82). Although some studies have reported its carcinogenic effects, a growing body of research has recently focused on its role as a driver of antitumor immunity. TMAO is a significant inducer of inflammatory effects, reconfiguring tumor immune infiltrates to an immune-activated phenotype. Jalandra *et al* (80) also discussed the possible anticancer mechanisms of TMAO, which include inflammation, oxidative stress, DNA damage and protein misfolding. These studies provide evidence of the potential role of TMAO in immunotherapy efficacy.

The dual role of TMAO in cancer development suggests that its effects are context-dependent and may vary depending on the type of cancer and the specific microenvironment. Therefore, the use of TMAO as a BC treatment option requires careful consideration of its potential pro- and anticancer effects. Further research is needed to fully understand the mechanisms underlying these dual effects and to determine the most effective and safe ways to utilize TMAO in BC treatment.

Pyocyanin. Pyocyanin, a toxin produced and secreted by *P. aeruginosa*, can induce cancer cell apoptosis and suppress lymphocyte function. Pyocyanin is considered to promote cancer cell death (83) and enhance tumor proliferation inhibition by doxorubicin (84). Pyocyanin has redox activity and is toxic to mammalian cells, making it a potential new anticancer drug. A previous study reported that purified pyocyanin has marked toxicity to MCF-7 BC cells by inhibiting cell growth via the induction of necrosis and accelerating apoptosis induced by caspase-3 activation (69). When used in combination, pyocyanin can enhance the cytotoxic effects of doxorubicin

chemotherapy, especially in MDA-MB-231 and MCF-7 BC cells. Compared with the use of doxorubicin alone, the addition of 10% *P. aeruginosa* culture supernatant markedly increased doxorubicin-induced caspase-7 protein cleavage, indicating that pyocyanin enhances chemotherapy-induced apoptosis (85).

Additionally, since pyocyanin is a potent inducer of ROS, it is reasonable to hypothesize that pyocyanin enhances chemotherapy efficacy via a ROS-dependent mechanism. Compared with normal cells, cancer cells are more sensitive to increases in the ROS content, as cancer cells have a higher baseline level of ROS (86). The aforementioned studies have demonstrated that pyocyanin may be a promising anticancer drug candidate.

Nisin. Nisin has been reported to have specific anticancer activity against MCF-7 breast adenocarcinoma cells and potential synergy with doxorubicin (62). Nisin exhibits highly selective toxicity to MCF-7 cells, with an IC_{50} value of 5 μM, but is not toxic to noncancerous HUVECs. The combination of nisin and doxorubicin at subinhibitory concentrations resulted in increased cytotoxic activity compared with either agent alone, indicating potential synergistic effects (62). This observation was further supported by another *in vitro* study demonstrating that the coadministration of nisin and doxorubicin improved treatment outcomes in patients with skin cancer (87). The potential synergistic interactions between nisin and standard chemotherapeutics may lead to improved clinical outcomes for patients with cancer (88). Thus, nisin used alone or in combination with other chemotherapeutic agents could be a potential treatment option for patients with BC. Future research on nisin should prioritize *in vitro* studies, using multiple BC cell lines and animal studies to understand its potential synergy with standard anticancer therapies and provide more evidence for clinical trials.

L-norvaline. Metabolic profiling has revealed that L-norvaline, a gut-derived metabolite, is key in the diversity of the gut microbiota and has the capacity to modulate disease progression through interactions with the microbiome (89). Notably, *Lautropia*, *Rothia*, *Centipeda*, *Corynebacterium* and *Actinomyces* species have exhibited notable associations with L-norvaline biosynthesis (28). As an arginase 1 (ARG1) inhibitor, L-norvaline impedes cancer development by interacting with doxorubicin (28,90,91). ARG1 facilitates the conversion of L-arginine to L-ornithine and urea within M2-type macrophages (92,93). The generated L-ornithine is subsequently metabolized into polyamines by ornithine decarboxylase, a process that can increase cancer cell proliferation and differentiation. Recent research demonstrated that the coadministration of L-norvaline and doxorubicin in an M2 macrophage and BC cell coculture system markedly inhibited cancer cell proliferation (28). This combined therapy has shown superior efficacy over monotherapy with either agent alone, further reducing the proliferative activity of BC cells (28). The potential of bacteriocins to exert anticarcinogenic effects on BC cells highlights their utility as adjuvants in standard BC treatment regimens. Collectively, these discoveries provide novel perspectives for the development of innovative BC therapeutic strategies.

4. Conclusions and future perspectives

This review examines the types and sources of common metabolites from intestinal and tissue-resident microbiota, their impact on BC development, and their role in modulating tumor therapy responses. The potential roles of secondary BAs, SCFAs, amino acid metabolites and bacteriocins (such as LPS, nisin and pyocyanin) in BC carcinogenesis, progression and metastasis were explored. The impact of bacterial metabolites on the efficacy of BC drug treatments, including chemotherapy, targeted therapy and immunotherapy was also discussed.

Pretreatment analysis of the microbiota provides oncologists with insights into tumor aggressiveness and chemotherapy sensitivity to guide treatment modifications. Currently, breast microbiota research is primarily preclinical and has focused on comparing the microbiota of breast tumor tissue with that of healthy tissue to identify tumor-specific characteristics. Most studies have been performed *in vitro*, with limited *in vivo* data and no clinical trials documented. However, both *in vitro* and *in vivo* studies are crucial for understanding the complex interactions between the gut metabolites and cancer cells within the host.

Diet, probiotics and prebiotics may markedly impact BC, suggesting they have potential as adjuvants in standard BC treatments (94). Certain *Lactobacillus* strains have been shown to have effects against BC (95). Prebiotics, which are indigestible fibers, foster the growth of beneficial bacterial in the gut, which can metabolize the conversion of these fibers into phytoestrogens and SCFAs (96). These metabolites, along with others, possess tumor suppressive properties, and exhibit antiestrogenic and antiproliferative effects, which reduce the risk of BC. Investigating the synergistic effects of gut metabolites combined with chemotherapies and immunotherapies could enhance their clinical efficacy and safety.

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YG and WD wrote the first draft of the manuscript. YG contributed to the study conception, and reviewing and editing of the manuscript. YG, WD, DS, XZ, ZH, CL and YS contributed to manuscript revision. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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