BBA - Gene Regulatory Mechanisms 1865 (2022) 194873

Contents lists available at ScienceDirect

BBA - Gene Regulatory Mechanisms

journal homepage: www.elsevier.com/locate/bbagrm

# Epigenetic oncogenesis, biomarkers and emerging chemotherapeutics for breast cancer☆

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ARTICLE INFO

*Keywords:*
Breast cancer
Epigenetic oncogenesis and oncotherapy
DNA methylation
Histone deacetylase
Transcription factors
Estrogen receptor

ABSTRACT

Breast cancer remains one of the leading causes of cancer-related deaths globally and the most prominent among females, yet with limited effective therapeutic options. Most of the current medications are challenged by various factors including low efficacy, incessant resistance, immune evasion and frequent recurrence of the disease. Further understanding of the prognosis and identification of plausible therapeutic channels thus requires multimodal approaches. In this review, epigenetics studies of several pathways to BC oncogenesis *via* the inducement of oncogenic changes on relevant markers have been overviewed. Similarly, the counter-epigenetic mechanisms to reverse such changes as effective therapeutic strategies were surveyed. The epigenetic oncogenesis occurs through several pathways, notably, DNMT-mediated hypermethylation of DNA, dysregulated expression for ERα, HER2/ERBB and PR, histone modification, overexpression of transcription factors including the CDK9-cyclin T1 complex and suppression of tumour suppressor genes. Scientifically, the regulatory reversal of the mechanisms constitutes effective epigenetic approaches for mitigating BC initiation, progression and metastasis. These were exhibited at various experimental levels by classical chemotherapeutic agents including some repurposable drugs, endocrine inhibitors, monoclonal antibodies and miRNAs, natural products, metal complexes and nanoparticles. Dozens of the potential candidates are currently in clinical trials while others are still at preclinical experimental stages showing promising anti-BC efficacy. The review presents a model for a wider understanding of epigenetic oncogenic pathways to BC and reveals plausible channels for reversing the unpleasant changes through epigenetic modifications. It advances the science of therapeutic designs for ameliorating the global burden of BC upon further translational studies.

## 1. Breast cancer

Breast cancer (BC) remains the most common malignancy and constitutes about 11.6 % of the global burden of cancers [1]. It is highly prevalent among cancer diseases and associated with high rates of cancer-related deaths, mostly affecting women. In the U. S. for instance, in 2020, about 1,806,590 new cancer cases were recorded out of which BC alone accounted for ≈33.52 % with 605,520 cases [2]. In 2022, the total number of expected new cancer cases had risen to 1,918,030 out of which BC cases were forecasted as 290,560 with expected mortality of 43,780 [3]. In sub-Saharan Africa, half of all new cases of cancer were constituted by BC in 2018 with forecasted mortality of 112,000 in 2040, indicating its global epidemiology [4].

### 1.1. Symptoms of breast cancer

The basic general symptoms include the appearance of lump/thickening, changes in the shape and size of the breast; pain in areas of the breast; dimpling, irritation, redness or flaky breast skin, pitting and changes in the nipple area or breast skin; pulling in or pain in the nipple area; alterations in the areola and abnormal discharge from the nipple other than breast milk, such as blood. Although, some non-cancerous occurrences including benign masses, cysts and fibroadenomas could also cause lump formation, hence, necessitating adequate diagnosis [5–7].

☆ This article is part of a Special Issue entitled: Recent advances in epeginetics edited by Jinrong Min and Yong Xu.

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https://doi.org/10.1016/j.bbagrm.2022.194873
Received 30 April 2022; Received in revised form 20 August 2022; Accepted 28 August 2022
Available online 5 September 2022
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### 1.2. Risk factors associated with breast cancer

The risk factors associated with BC development are diverse with some controllable while others are uncontrollable. These include age, gender, personal/family relevant medical history, genetic mutations, history of exposure to radiation, reproductive factors, dense breast, histological factors, exogenous hormone, uncensored drug usage, alcoholism, lack of physical activities and post-menopause overweight/obesity (*e.g.* diethylstilbestrol), complicating its aetiology [8,9].

### 1.3. Diagnostic interventions for breast cancer

Early diagnosis and detection enhance effective treatment and survival outcomes generally. The applicable interventions for detecting BC include breast imaging (screening) and clinical examinations. The clinical laboratory and pathological devices/techniques commonly employed in the examination of BC include core needle biopsy, chest computed topography (CT), mammography, sentinel node mapping and tomosynthesis, and more relevantly, the biomarker analysis [10,11]. Other interventions for facilitating early detection include awareness education and training, physical examination, medical history and accurate tissue diagnosis to differentiate between benign and malignant. However, the process of early detection is hampered by economic, geographic, social and other interrelated factors. They represent stumbling blocks to affordable, timely, appropriate and effective health care facilities [12].

### 1.4. Prevention and treatment of breast cancer

The appropriate treatment strategies are determined by the type, stage, clinical conditions of patients and associated risk factors, indicating complications. Thus, focusing on preventive measures could effectively improve the survival of patients [4]. The common prevention strategies include behavioural routines such as regular physical exercise, prolonged breastfeeding, weight control, regulation of alcohol intake, tobacco smoke and exposure to radiation. These have been reported to reduce the risks of BC by ≈30 % [6,11]. The common treatment interventions include surgical removal methods (lumpectomy, biopsy, mastectomy, sentinel nodes and breast restructure), radiation therapy and medications (chemotherapy, hormone therapy and targeted biological therapy) as well as palliative and end-of-life care [10,11]. Raloxifene HCl and tamoxifen citrate are regular preventive chemotherapies for BC. Notably, the monotherapy medications for the treatment include abemaciclib, cyclophosphamide (C), doxorubicin HCl (A), paclitaxel (T), fluorouracil (F), gemcitabine HCl, methotrexate sodium, pertuzumab and trastuzumab. Depending on the condition, the drug combinations such as AC, AC-T, CAF *etc.* are oftentimes prescribed [13].

### 1.5. Limitations of the current medications for breast cancer

Failure of activity, lack of actionable target, loss of durability, inherent resistance, immune evasion, and high frequency of recurrence is associated with the degeneration of metastasis, genetic heterogeneity and systemic tumour recurrence characteristics of BC [14–18]. Late diagnosis and lack of early screening tools also weaken the efficacy and constitute failures of several prescription drugs, especially at critical clinical stages [19]. Specifically, the current chemotherapeutics for ameliorating triple-negative breast cancer (TNBC) are reported with indiscriminative toxicity, affecting normal cells and also inducing resistance in tumour cells [20]. Most other drugs also display various degrees of side effects such as joint pain, swollen limbs, flu-like syndromes, sweating, insomnia, dizziness, hair loss, diarrhoea, infertility, memory and urinary problem, and bleeding. Therefore, the search for improved alternatives to advance the effective prevention and treatment of BC, with minimal acute aftereffects remains crucial.

Epigenetic pathways contribute immensely to the risk factors and associated biological processes in the tumourigenesis of BC and its subtypes. As such, the prophylaxis/treatment strategies to reverse such prognostic events are effectively achieved *via* the counter-pathways, implicating major epigenetic biomarkers and therapeutic mechanisms.

Although, some literature surveys on epigenetic modifications for therapeutic interventions for cancer-related diseases were recently published. These include the overview of the clinicopathological significance of the astrocyte elevated gene 1 (AEG-1) gene for diverse cancer diseases [21], micro ribonucleic acids (miRNAs) as epigenetic modifiers against BC with less attention to other markers [22], epigenetic modification of histone mainly for gynaecological cancer [23], epigenetic modulation of immunotherapy response targeting specifically TNBC amidst other BC subtypes [24], epigenetic approach to diagnosis and treatment of lymphoma [25] and the survey of the efficacy of epitherapeutics for bone malignances and myeloid leukaemia [26,27]. However, a comprehensive review of the recent developments in the science of epigenetic oncogenesis, prevention and treatment of BC, implicating the connections between the epigenetic biomarkers, BC subtypes and potent anti-BC agents remains sparse. Thus, in this review, recent relevant literature was comprehensively surveyed to showcase the promising epigenetic targets for effective diagnosis, prevention and treatment of BC. Furthermore, some FDA-approved epigenetic medications currently in clinical applications for breast cancer treatment were highlighted along with their epigenetic targets and mechanisms of action as well as limitations. Progressively, some emerging epigenetic candidates in clinical trials and those from preclinical studies with therapeutic and safety advantages over the current medications were curated from recent relevant reports. The summary of the epigenetic oncogenesis and tumourigenesis of BC and the epigenetic reversal pathways for treatment herein captured is illustrated in Fig. 1.

## 2. Epigenetics of breast cancer development and emerging therapy

### 2.1. Epigenetic carcinogenesis and tumourigenesis of breast cancer

Epigenetic modifications of cellular apoptotic mechanisms in cancer cells, resulting in permanent genetic transformations and cell growth-regulating proto-oncogenes have been identified as a major route to BC initiation. Similarly, the modulation of tumour-suppressing activities in the host also constitutes a poor prognosis through atypical hyperplasia preceding the intermediate stages. The processes oftentimes induce rapid proliferation, acquired resistance and metastasis among various factors that contribute to the severity and stemness of BC [28–31]. The pathogenesis of onset development and progression of BC largely determines the subtypes [20], and the oncogenic pathways as enumerated below.

#### 2.1.1. Dysregulated expression of estrogen and progesterone receptors, and tyrosine-protein kinase

Estrogens are sex hormones importantly for regulating the reproductive systems and sexual features in females, and their signalling is significantly relevant to the carcinogenesis of TNBC. As such, a lack of expressions for estrogen receptor alpha (ERα), receptor tyrosine-protein kinase 2 (HER2/ERBB2) and progesterone receptor (PR) are earmarked in the course of TNBC. These inclusively engender immunity in TNBC cells against hormonal- and HER2-targeting therapeutics and constitute resistance challenges associated with TNBC [20]. Experimental evidence has shown that fractions of ER-beta (ERB) express suppressive effects on TNBC cells and improve the conditions of patients [20].

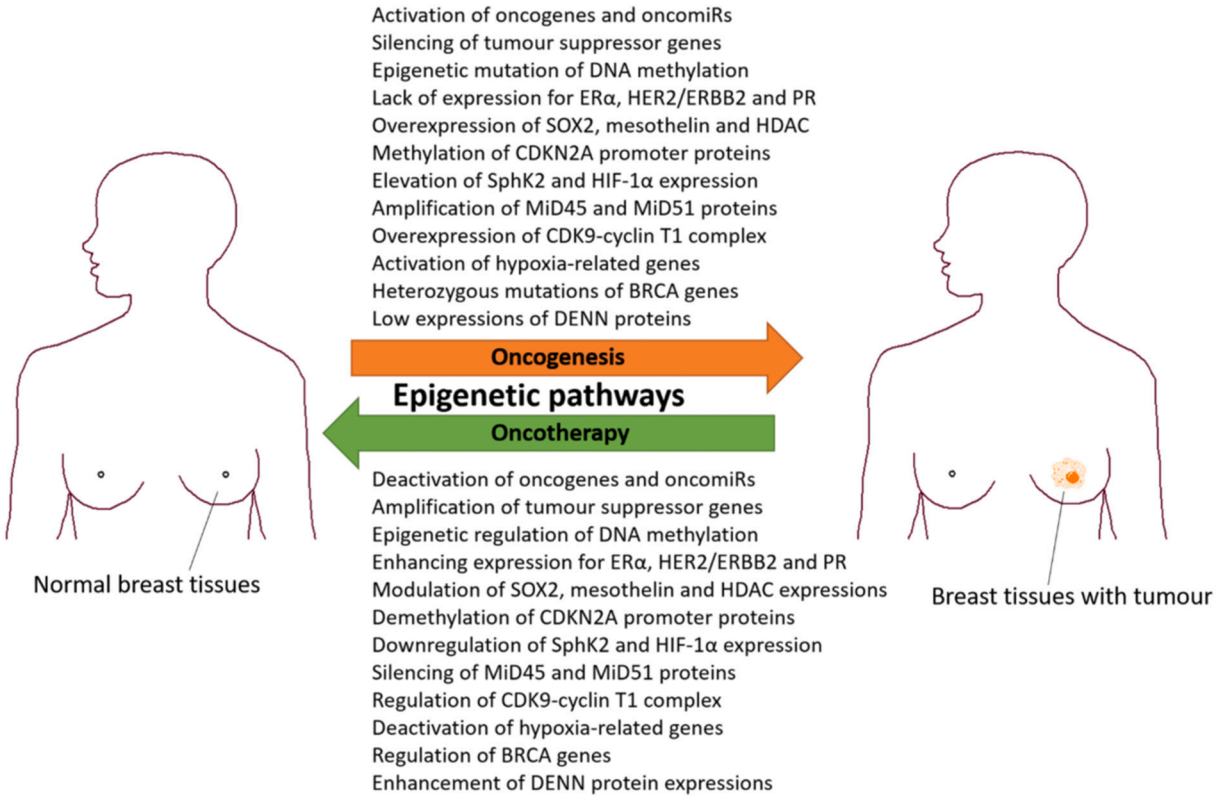



**Fig. 1.** Summary of epigenetic pathways to oncogenesis and oncotherapy of breast cancer.

*2.1.2. Overexpression of transcriptional and epidermal growth factors, and anchored proteins*

*2.1.2.1. Inhibitor of differentiation protein 4.* The inhibitor of differentiation protein 4 (ID4) is a predominant regulator of the helix-loop-like (HLH) family of transcription factors. The protein hypothetically plays bimodal roles as a tumour suppressor and oncogene in various tumour types [32]. For instance, overexpression of the protein is highly implicated in the phenotypic poor prognosis associated with the basal-like BC through its interactions with the mediator of DNA damage checkpoint 1 (MDC1) [33]. Macrophages are another renowned regulator of immune responses against pathogens and tumour initiation. In BC, they strongly suppress tumourigenesis by regulating the angiogenic switch and malignancy progression. However, their activities are reportedly modulated by ID4 through the promotion of pro-angiogenic cytokine IL-8, C-X-C motif chemokine ligand 1 (CXCL1) and vascular endothelial factor, thereby supporting BC angiogenesis [34]. It is also earmarked in TNBC initiation and progression [35]. The shreds of scientific evidence indicate the roles of the protein in BC oncogenesis, although, Nasif et al. reported its favourable tumour suppressing roles by frequently silencing the ER+ methylation, an oncogenic factor in BC episode [32].

*2.1.2.2. Cyclin-dependent kinase 9 and sphingosine kinase.* The cyclin-dependent kinase 9 (CDK) is a critical regulator of cell division and transcription. It is utilised by solid malignancies including BC for the generation of survival promoter genes, as such, several inhibitors of the kinase have been experimented to suppress BC progression [36]. It also regulates the transcription-polymerase II and is actively stabilized by the cyclin T1 protein (encoding for the CCNT1 gene in humans). Thus, overexpression of the CDK9-cyclin T1 complex also induces several oncogenic cellular processes that constitute serious conditions of TNBC [37]. Sphingosine kinase 2 (*SphK2*) is well recognised in the phosphorylation of the nuclear sphingolipid metabolite to produce sphingosine-1-phosphate (S1P), which in turn is involved in the epigenetic regulation of the expressions of the hypoxia-inducible factors (*HIF*) such as the *HIF-1α/2α* in BC. As such, elevated *SphK2* and *HIF-1α* expressions are reportedly implicated in the progression of the ER(+) and TNBC subtypes of BC [38].

*2.1.2.3. Y-box binding and bromodomain-containing proteins.* The Y-box binding (YB-1; nuclease-sensitive element-binding) protein is a highly conserved cold shock domain (CSD) multifunctional protein of the DNA- and RNA-binding family. The protein is localised in the cytoplasm and nucleus, functioning as a gene transcriptor, cell cycle and DNA damage regulator, RNA silencer and immune promoter, thereby implicated in several cancer prognoses [39]. As an oncoprotein, its high expression is earmarked in the epigenetic oncogenesis and poor prognosis of basal-like BCs [40,41]. Mechanistically, it also interactively promotes the Kruppel-like factor 5 (KLF5) and cell proliferation through the transcriptional activation and stabilization of the KLF5 mRNA, thereby enhancing the progression of BC [40]. Again, amplification of its mRNA enhances macrophage infiltration and T cell exhaustion, and its association with interleukin-6 (IL-6) has been identified as an oncogenic pathway to the poor prognosis of metastatic BC [42,43]. High expressions for bromodomain-containing protein 4 (BRD4), and Pellino proteins and low expression for lysine-specific demethylase 1 (LSD1) have been reported as epigenetic oncogenic pathways to BC. The interaction of BRD4 with LSD1/NuRD complex is strongly linked to an enhanced resistance of BC to chemotherapeutics and poor survival in patients [44].

*2.1.2.4. Sex-determining region Y and octamer-binding transcription factors.* High expression of the transcription factors, sex-determining region Y (SRY)-box 2 (SOX2), octamer-binding transcription factor 4 (OCT4) and homeobox protein, NANOG reportedly enhance the stemness of BC cells, thereby contributing to its progression and metastasis, especially in respect to the luminal B and HER2+ subtypes [45,46].

*2.1.2.5. Epidermal growth factor.* Oftentimes, overexpression of the human epidermal growth factor receptor (EGFR) commonly induces the development of various cancers including lung, ovarian, colorectal and BC [14]. Additionally, the release of steroid receptor hormones is also implicated in the initiation and growth of mammary glands in BC development through the ER [2].

*2.1.2.6. Mesothelin.* Overexpression of mesothelin (MSLN), an oncogenic glycophosphatidylinositol (GPI)-anchored protein encoded in the human MSLN gene has been implicated in various cancers including BC. Its success in early clinical trials as a plausible marker for targeted therapy facilitated the recent evaluation of epigenetic regulation with GPI by non-coding RNAs (ncRNAs) [47,48].

*2.1.3. Deoxyribonucleic acid methyltransferase methylation*

The deoxyribonucleic acid (DNA) methyltransferase 1 (DNMT1) is an epigenetic regulator enzyme primarily involved in the maintenance of DNA methylation patterns. As such, epigenetic mutation (epimutation) or remodelling of the DNA methylation pattern is usually associated with an upregulation of oncogene expressions including the transcription factors, cell cycle regulators and DNA repair genes, and down-regulation of tumour suppressor genes. The resultant effects of the processes usually manifest as the proliferation of BC [1]. Studies have shown that the epigenetic modifications including the DNA methylation

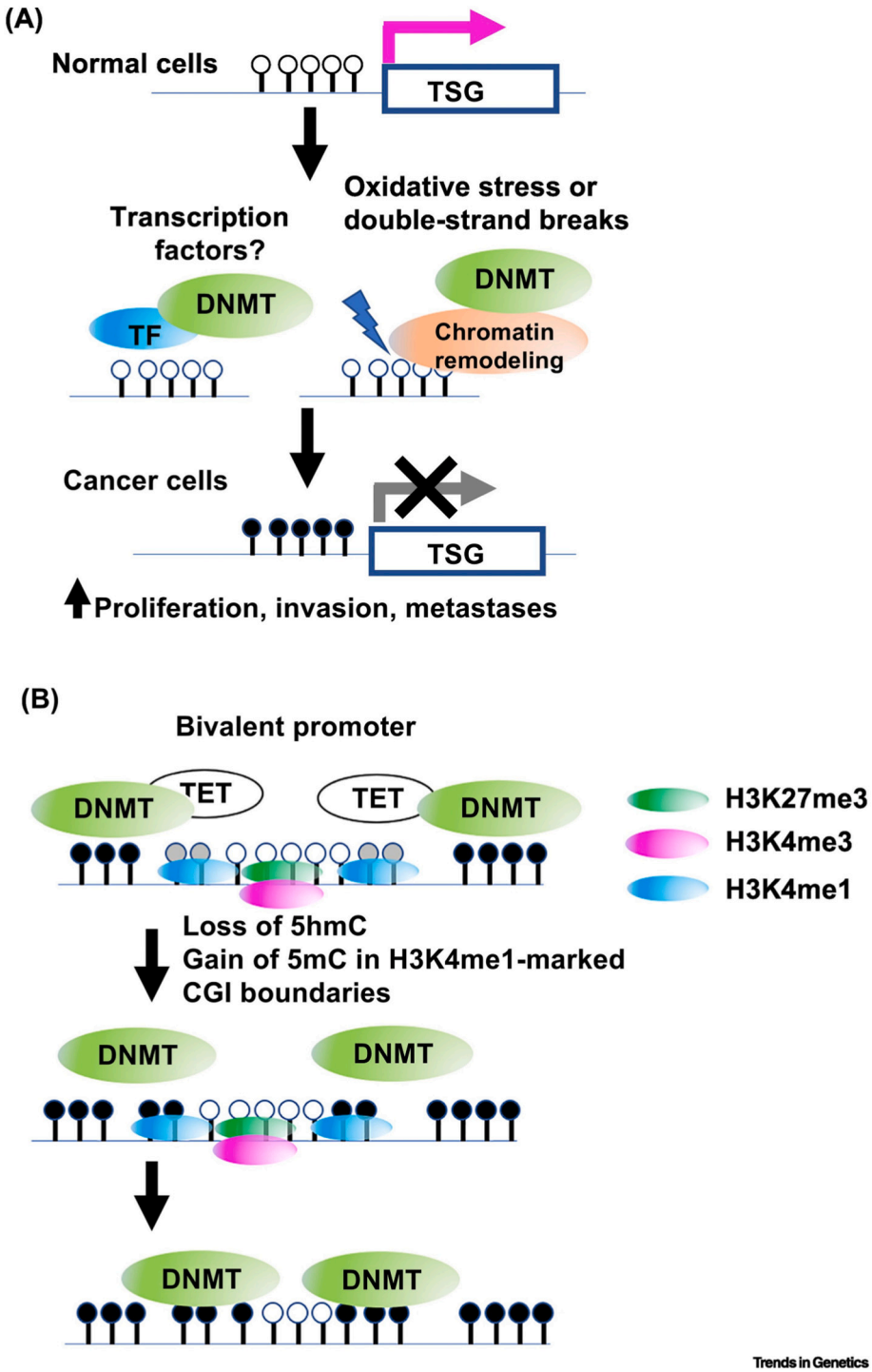



**Fig. 2.** Hypermethylation of promoter CpG islands in cancer cells. (A) Hypermethylation of CpG islands in TSG promoters is one of the key features of cancer cells. (B) Several promoter CpG islands that show DNA hypermethylation in cancer cells are characterized by bivalent chromatin marked by H3K27me3 and H4Kme3 in the boundary with the DNA methylation shore, where DNMT and TETs antagonize to prevent DNA methylation expansion. The resultant loss of TET activity is the DNA methylation invasion of CpG islands which induces the shortening and loss of unmethylated CpG islands.
(Reproduced from [49], Licensed under CC BY-4.0.)

region at the CpG islands of the gene promoters (specifically at the 5th carbon of cytosine in the DNA backbone) contribute to tumourigenesis of BC. Structurally, the chromodomain helicase DNA-binding protein 4 and Mi2-/nucleosome-remodelling and deacetylase (Chd4/NuRD) as remodelling factors are suggestively accumulated upon DNA damage possibly mediated by DNMT. The methylated DNA then represses the tumour suppressor gene (TSG) expression through its binding proteins, thereby promoting cell migration, invasion and metastasis. The DNMT antagonizes the Ten-eleven Translocations (TETs) and the cellular process resulting in the loss of TET activity which aids the DNA methylation, invasion of CpG islands and induces the shortening and loss of unmethylated CpG islands. The overall process presents a landscape for cancer proliferation, invasion and metastasis (Fig. 2) [49]. A recent study by Zhu and co-workers also revealed the facilitation of BC growth by DNMT1 through the induction of hyper-methylation on the maternally expressed gene 3 (MEG3), a long non-coding RNA gene, indicating significant contributions of the DNMT1 to the oncogenesis of BC [50].

#### 2.1.4. Downregulation of tumour suppressor genes and proteins

*2.1.4.1. Breast cancer genes 1/2.* Breast cancer genes (BRCA1/2) are tumour suppressor genes that play essential roles in DNA repair through several pathways including maintenance of genomic integrity, regulation of cell growth and division, homologous recombination and cell cycle control. Epigenetic germline heterozygous mutations to the BRCA genes in women hypothetically expose them to a high risk of BC [30].

*2.1.4.2. Cadherin.* A recent application of The Cancer Genomic Atlas (TCGA) BC dataset by Chiang and co-workers showed higher methylation of the protocadherin β15 (PCDHB15) promoters in BC samples than in normal tissues. Lower expression of the PCDHB15 was also observed to shorten the relapse-free survival time of BC, making the protein-coding gene an emerging epigenetic target in the prognosis of BC [19]. Furthermore, BC has been reportedly developed *via* the cadherin-1 (*CDH-1*) gene, encoding for epithelial CDH (*E-CDH*) and importantly for cellular processes including cell growth, proliferation and apoptosis. The pathomechanisms involve the methylation-mediated activation of oncogenes and silencing of TSGs. [31].

*2.1.4.3. DENN protein family.* The DENN family protein, suppression of tumorigenicity 5 (ST5/DENND2B) is considered a tumour suppressor gene due to its implications in the prognosis of BC. Low expression of the protein was experimentally observed in BC cells, more predominantly in the invasive and recurrent BCs relative to the non-invasive types [51].

*2.1.4.4. MicroRNA.* MicroRNAs are endogenously conserved, single-stranded, non-coding RNA molecules that mainly function in the post-transcriptional regulation of gene expression. They are tumour suppressors or oncogenes (oncomiRs). As such, their deregulation induces cell differentiation, proliferation and survival factors implicated in a wide range of cancers. For instance, in BC, the miRNAs encoded as miR-10b, miR-145, miR-520, miR-200 family and let-7 family are involved in a series of cellular processes pivotal for tumour suppression. Their dysregulation has been proven to be associated with BC tumourigenesis through the cell cycle and gene modifications [52,53]. On the other hand, enhancement of the dynamic-related protein 1- (Drp1)-mediated mitochondrial fission is a phenotypic indicator of highly proliferative and apoptosis-resistant cancers such as non-small cell lung cancer and BC. In an experiment by Dasgupta et al., an amplification of the Drp1-binding mitochondrial dynamic 49- and 51-kDa proteins (MiD49 and MiD51) was shown to be associated with epigenetic tumourigenic mechanisms of BC, involving the expression of miR-34a-3p [54]. As a continuous scientific innovation for new anticancer mechanisms and predictors for overcoming BC resistance, an epigenetic connection between a micro-RNA (miRNA), miR-181a-5p and ERα was studied by Benedetti and co-workers. The study demonstrated the induction of the miRNA for downregulating the ERα signalling as a checkpoint for ERα-mediated BC progression, thereby expanding the targeted therapeutic mechanisms [55].

*2.1.4.5. Leukaemia inhibitory factor receptor.* The downregulation of a renowned tumour suppressor gene, leukaemia inhibitory factor receptor (LIFR) significantly contributes to osteolysis and dormancy of BC cells when proliferated into the bone marrow. The resultant effects include the metastasis of BC and associated poor survival [56].

*2.1.4.6. Protein arginine methyltransferase 5 and ST5 protein.* The protein arginine methyltransferase 5 (PRMT5) is reportedly involved in the epigenetic methylation of several proteins for regulating gene expressions and its dysregulation is implicated in the oncogenesis of several cancers including the BC [57]. The **ST5 protein** has been identified as a tumour suppressor gene against BC. Its upregulation reportedly inhibited cell migration and proliferation, and induce cell cycle arrest *in vitro* BC cell lines [51].

#### 2.1.5. Histone modification

Histone deacetylases are Zn-dependent enzymes localised in the nucleus and overexpressed in several cancer types including BC through DNA modification [58]. Acetylation, a key epigenetic modification for the mechanistic regulation of chromatin and gene expression is modulated by the antagonistic effects of histone acetyltransferases (HATs) and histone deacetylases (HDACs). An impaired balancing of HAT and HDAC activities usually results in BC initiation and progression [59,60]. A decreased level of miR-646 was observed concurrently with an upregulated HDAC 2 in clinical patients with BC compared to the specimens from non-cancerous patients' tissues [61], indicating the contribution of histone modification to BC development. Hypoxia is a renowned initiator of the metastatic cascade, the condition in which G9a, a histone methyltransferase epigenetic modifier becomes accumulated. A recent study by Casciello and co-researchers has recognised the type-II cadherin, *CDH10* as a hypoxia-gated gene that enhances the motility/invasion of breast tumour cells, suppression of cell adhesion genes and silencing expressions for *CDH10*, thereby influencing poor survival [62]. The studies indicate the synergy between histone modification and other contributing factors to BC oncogenesis.

### 2.2. Epigenetic changes as indicators of breast cancer

Epigenetic changes induce reversible modifications of DNA integrity without alterations to the DNA sequence. Mechanistically, the changes occur through various pathways including the methylation of cytosine nucleotides of DNA bases, micro RNA-mediated RNA interference, and moderation of chromatin status through the post-translational modulation of histone proteins implying a transcriptional moderation of gene expression. The changes also occur through the influences of gene expression modulation on cellular reprogramming of the cancer micro-environmental conditions, thereby channelling various epigenetic pathways to BC development as previously enumerated [31,62–64]. From experimental investigation, epigenetic changes were observed in the early stages of BC through the comparison of methylation profiles of the cyclin-dependent kinase 2 inhibitor (CDKN2A) gene-encoding promoter proteins, *ATM*, $p14^{ARF}$ and $p16^{INK4a}$ in the blood and plasma cell-free DNA (cfDNA) of women with impalpable breast lesions and those without the lesions (control group). Methylation of 37.5 %, 27 % and 48 % were shown in the respective proteins from women with breast lesions while those without breast lesions were recorded with 7 %, 7 % and 9 % methylation respectively. The study strongly implicated the CDKN2A gene as a potential target for the diagnosis and treatment of early-stage BC through methylation-inclined epigenetic changes [65].

Carbonic anhydrases (CAs) are zinc-dependent ubiquitous catalysts

in several biological systems including pathogenic microorganisms and cancers, and oftentimes contribute to resistance to drugs [66]. However, the expression of CA12 is reportedly in direct variation with the ERα expression in BC, thereby influencing a milder prognosis and low risks of metastasis. A recent study has revealed the Transcription Factor Activator Protein 2γ (TFAP2C) as a determinant of luminal BC through a/an direct/indirect epigenetic modulation of the ERα and its associated genes [67]. Glycosylation, a fundamental post-translational modification is reportedly altered in cancer situations due to epigenetic modifications, as such, its epigenetic modulation was demonstratively achieved by a DNMT inhibitor, decitabine [68].

### 2.3. Epigenetic classification of breast cancer and prognosis

The determining factors for BC subtypes include the prognostic stages and histomorphologic factors such as size, grade, lymph node metastasis, estrogen/progesterone status and HER status [63].

#### 2.3.1. Subtypes of breast cancer and prognosis

Breast cancer is usually initiated in the lining cells (epithelia) of the lobule (15 %) and duct (85 %) of the breast glandular tissues. Depending on the stages, BC is broadly classified into *in situ* (stage 0), a commonly asymptomatic pre-cancer initiate, confined within the milk duct/lobule with low potential for spreading to tissues for metastasis. The second classified stage is invasive BC (IBC) in which (primary) cancer cells have spread/infiltrated the nearby lymph nodes (regional metastasis) or to other organs (distant metastasis) (Stages I-III). The non-invasive BC (NIBC) is mostly localised in the lobules and ducts, however, mortalities are mostly arising from widespread metastasis (Secondary cancer; Stage IV) (Fig. 3) [6,69,70]. Furthermore, BCs are sub-categorized according to molecular features, basically into four subtypes, luminal A, luminal B, HER2 (EGFR) and basal type [11,17,71].

*2.3.1.1. Luminal A.* Breast cancers of this class show luminal expression (low molecular weight), cytokeratins and strong signalling for relevant genes and hormone receptors such as the estrogen, ER(+) and PR(+), however, with negative receptor tyrosine-protein kinase 2 (HER3/neu). They constitute about 50 % of IBC and are characterized by various histological correlations including tubular, low-grade invasive ductal, cribriform, lobular and not otherwise specified (NOS) carcinoma. They have a good prognosis, high response to endocrine and chemotherapy, and most favourable long-term survival [2,11,71,72]. Although, the efficacious benefits of adjuvant and chemotherapy to the prognosis and survival of patients with ER/PR(+), HER2(−) and lymph node positive luminal A BC subtype remain strongly debated at scientific levels [73–76].

*2.3.1.2. Luminal B.* The luminal B type also exhibits luminal features and cytokeratins but moderate expressions for relevant genes and hormone receptors and forms about 20 % of IBC. They have ER(+)/PR(+), variable HER2/neu, and higher proliferation and histological grade than luminal A. They express histological correlation of micropapillary, NOS and invasive ductal carcinoma. Relative to the A counterpart, they are usually associated with mild prognosis, lower recurrent rates and response to endocrine therapy, but better response to chemotherapy. Endocrine therapy with mechanistic downregulation of estrogen levels and blockade of ER-signalling pathways is usually suitable for such [2,71,72]. Although, a recent prospective single-centre study also indicated high parity as an adverse factor for a poor prognostic outcome in the BC subtype [77]. A high expression of the transcription factor, SOX2 has also been recently reported in luminal B and HER2+ BC cells [45].

*2.3.1.3. HER2/neu breast cancer.* Receptor tyrosine-protein kinase 2 (HER2) is a member of the human EGFR family. Other similar members include HER3/ERBB3 and HER4/ERBB4. The amplification of HER2 is implicated in about 20 % of BC as a HER2-positive (HER2+) malignancy. As such, the BC developed through the pathway is termed HER+ (ER+) BC, and is significantly characterized by microenvironmental and tumour heterogeneity, producing intrinsic subtypes [15,71,72]. For instance, about 70 % of patients with BC and prostate cancer show bone metastasis upon diagnosis [78]. Connectively, the ER+ subtype of BC is known for spreading into bone marrow where it strongly induces osteolysis or bone metastasis. The bone microenvironmental osteogenic niche has recently been proved to enhance the phenotypic plasticity, stemness and endocrine resistance of ER+ BC through the enhancer of zeste homolog 2- (EZH2-)mediated epigenetic reprogramming [56,79].

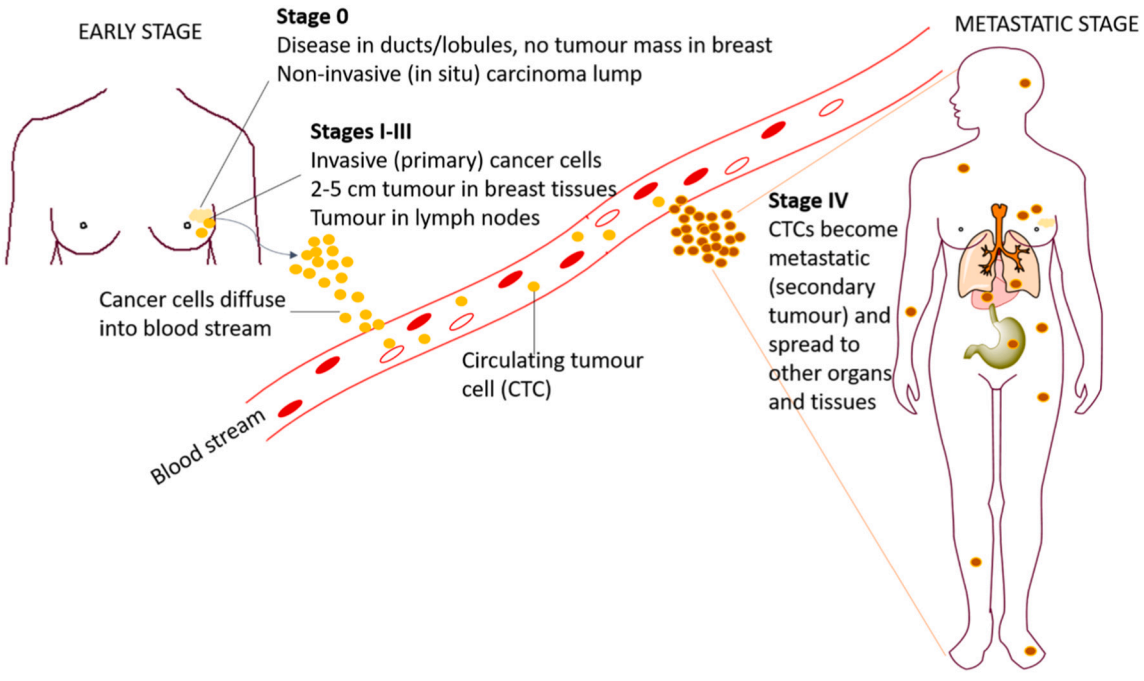



**Fig. 3.** Illustration of basic stages of breast cancer development.

Generally, BCs of this class show low expression for ER-related genes (i.e. ER(−)/PR(−)), high proliferation, histologic grade and diffused tumour protein 53 (TP53) genetic mutations. They feature as high-grade invasive ductal and NOS carcinoma in response to HER2-targeted therapy including a monoclonal antibody, trastuzumab [15,71,72].

*2.3.1.4. Basal type.* The basal type BCs highly feature basal epithelial genes and cytokeratins but lack expressions for ER, PR (i. e. ER(−)/PR(−)) and HER2/neu and related genes, making them more resistant to treatment. They partly constitute the multidrug-resistant (MDR) BC. Moreover, they proliferate rapidly with virulent factors such as the dysfunctional sporadic/germline breast cancer gene 1 (BRCA1), complicating the control strategies. They constitute ≈15 % of IBC mostly characterized by ER(−)/PR(−)/HER2/neu(−) genes in their cells, as such, often referred to as the triple-negative BC (TNBC). They appear as metaplastic, medullary, high-grade invasive ductal and NOS carcinoma. Other characteristics of this class include zero response to endocrine, but high sensitivity to platinum chemotherapy and inhibitors of poly adenosine diphosphate- (ADP-)ribose polymerase (PARP) [2,71,72,80].

*2.3.1.5. Special types of breast cancer*

*2.3.1.5.1. Triple-negative breast cancer.* Triple-negative breast cancer represents the most threatening and aggressive ER(−) subtype of BC. It lacks expressions for ER, PR and HER2. Its phenotypic characteristics include rapid prognosis, various intra-tumour genetic heterogeneity, high invasiveness, metastasis and relapse risks, poor response to treatment and high recurrence rates, yet with limited molecular targets for effective treatments [16,20,35,37,71,72,81,82]. TNBC mostly exists in epithelial-mesenchymal states and occasionally as non-mesenchymal [82]. The malignance induces virulent conditions implicating poor prognosis and survival rates, and resistance to chemotherapy and is reportedly responsible for 25 % of BC-related deaths [20,83]. Oftentimes, TNBC is reported to evoke growth suppression and senescence characteristics [84]. Late diagnosis and daunting aftereffects of chemo- and radiotherapies are among major setbacks in the successful treatment and constitute the lethality of TNBC in clinical situations [47].

*2.3.1.5.2. Inflammatory breast cancer.* These are aggressive types of IBC characterized by the blockade of the lymph vessels in the skin by BC cells thereby inducing inflammation in the breast. They constitute ≈15 % of all BCs [72].

*2.3.1.5.3. Rare types.* These are less common types of BC-related diseases that affect other cells of the breast, as such, require a dimensional diagnosis and treatment. Firstly, the **Paget disease** of the breast develops in the breast duct, then spread to the skin of the nipple and then to the areola. It accounts for 1–3 % of all BC cases. Secondly, **angiosarcoma**, the malignancy of endothelial tumour, represents the soft tissue sarcoma of the breast. Angiosarcoma develops in the lining cells of the blood and lymph vessels. It is very rare (<1 %) and sometimes, associated with radiation history. **Phyllodes** are fibroepithelial neoplasm which develop in the connecting tissues of the breast and accounts for 0.3–1 % of BCs. Unlike the conventional BCs, phyllodes mostly exhibit benign features and very rarely, appear as recurrent and malignant [72,85,86]. The invasive breast carcinoma with a glycogen-rich clear cell pattern represents another subtype of the rare IBCs, sensitive to epigenetic modulatory mechanisms [87].

## 2.4. Therapeutic targets, chemotherapeutics for breast cancer and mechanisms of action

The enzymes that are responsible for epigenetic modifications have been identified to include DNA methyltransferases, histone acetyltransferases/deacetylases, histone lysine, and cyclin-dependent kinases as well as histone demethylases. The epigenetic modifications aided by the associated markers were used to classify the epigenetic biomarkers as 'writers', 'readers' and 'erasers'. The 'writers' are specific enzymes/protein groups with the potential to modify the nucleotide bases and certain amino acid residues in histone. The 'readers' is a series of proteins that can potently recognise specific epigenetic changes/marks while the 'erasers' group consists of the removers of the epigenetic markers [88]. Other biological targets include the interleukins, EGFRs, miRNAs, mitochondrial DNA, cadherin genes, promyelocytic leukaemia (PML) nuclear protein and some specific micro/macro biomolecules as illustrated below. The treatment strategies can be broadly classified as surgery, radiotherapy, chemotherapy: endocrine therapy (*e.g.* tamoxifen and aromatase inhibitors), immune-targeted and combination therapy [63]. The major focus of this review is chemotherapy.

### 2.4.1. Histone deacetylase

Histone deacetylases are localised in the nucleus and implicated in several cancerous growths including BC through DNA modification, and as such, represent critical therapeutic targets. They are classified into class I comprising HDAC1, 2, 3 and 8; class II consisting of HDAC4, 5, 6, 7, 9 and 10 while HDAC11 belongs to class IV, all based on the presence of conserved deacetylase domain, homolog sequence and amidohydrolases [58,64].

*2.4.1.1. Inhibitors of HDAC.* Histone deacetylase inhibitors bind to the catalytic active sites of HDAC I and II, thereby chemosensitizing the BC cells to the cytotoxic microenvironment [64]. Vorinostat, an inhibitor of the enzymatic activities of HDAC I and II with epigenetic modulatory effects are used to treat lung cancer, cutaneous T cell lymphoma and metastatic BC [14]. Cysteine dependence is an emerging target for effective treatment of mesenchymal TNBC. Although, many TNBC cells are non-mesenchymal, as such, become resistant and non-responsive to the cysteine-deprivation strategy. However, the application of HDAC6 inhibitors, specifically tubacin, tubastatin A and CAY10603 is suggested to synergistically sensitize and induce apoptosis in the non-mesenchymal TNBC cells [82]. Due to their direct relationship, the expression of clone evolution, CXCL1 is sometimes a favourable factor in the survival of BC patients cumulating effective HDAC inhibition [83]. Valproic acid is a renowned inhibitor of HDAC and antiepileptic (anti-seizure) medication. Its pharmacological propensity against BC was evaluated on the MCF-7 cell line using LC-MS/MS metabolomics. The drug was shown to alter some key metabolic pathways such as the pentose phosphate pathway and 2′deoxy-α-D-ribose-1-phosphate degradation. The resultant effects involve the activation of metabolites for inhibiting cell growth and proliferation, interference with energy sources and elevation of ROS, thereby inducing cell death on BC. The suggested mechanism of anti-BC demonstrated by the drug is ferroptosis due to the associated L-cysteine deregulation, making the drug a promising repurposable epigenetic medication for BC upon further study [89].

Chidamide (CHI), an HDAC inhibitor in combination with doxorubicin (DOX) induced p53-mediated cell cycle arrest and apoptosis, and suppresses the MDR BC. In the study, relative to the CHI monotherapy, the combined therapy significantly enhanced the cytotoxicity of the drugs against MDR BC cells *in vitro* and *in vivo*. Regardless of the presence of DOX, the cell cycle distribution data revealed that CHI produced G0/G1 cell cycle arrest and strongly inhibited cell growth. It sensitized the p53, up-regulated p21 and pro-apoptotic protein Bax, Bcl-2 and activated the caspase cascade to induce apoptosis in the CHI-treated animal group and combined regimen groups. The study indicates an enhanced efficacy of CHI in combination with DOX for further combination anti-BC therapeutic design [90]. Belinostat, an HDAC inhibitor was evaluated by Han et al. 2021 on chemotherapeutic resistant TNBC. Significant alterations at the transcriptome level of a TNBC line (MDA-MB231) were observed after the treatment with the drug. The important biological processes were identified using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment studies. To screen prospective genes related to cancer prognosis, the

researchers built and analyzed a protein-protein interaction (PPI) network. A total of 465 DEGs were discovered, with 240 genes down-regulated and 225 genes upregulated. The cytokine-cytokine receptor pathway was significantly altered. Additionally, CXCL1 expression has been linked to a higher overall survival rate in breast cancer patients. Furthermore, the drug was observed to trigger apoptosis and promote the expression of CXCL1 in two more TNBC cell lines (BT-549 and HCC-1937) [83].

Tubacin, an HDAC inhibitor combined with Erastin, a voltage-gated anion channel ligand showed high cytotoxicity to MDA-MB-436 and HCC70 cells, compared to their respective low cytotoxicity as a single treatment agent. Significant action was also recorded for Erastin on TNBC when CAY10603 was combined with it. HDAC6 inhibitors showed capability for increasing the synthetic cytotoxicity of cysteine depletion in non-mesenchymal tumour cells. The combination therapy greatly induced the expression of apoptotic genes and ATF3, CHOP and HOMX1. The mechanism of action of the HDAC6 inhibitors is novel and in combination with Erastin enhanced cell death through PKCγ signalling and is independent of HDAC6, leaving room for further studies on the identification of the pathways [82].

An alkoxyamide-based methoxy-phenyl-substituted LMK235, an HDAC2 inhibitor showed high efficacy and increased ability to reverse cisplatin resistance in chemo-resistant cancer cells with an $IC_{50}$ value of 1.15/3.35 at 0.2 μM/0.8 μM in Cal27/Cal27 CisR cells respectively. The co-treatment was reported to result in ubiquitinylation of PCNA and its apoptosis [64], supporting the applicability of biologics as epigenetic modifying therapy against BC.

### 2.4.2. *Deoxyribonucleic acid methyltransferase*

Ari and co-workers recently demonstrated the plausibility of the combination of epigenetic modulators with conventional therapeutic regimens to suppress BC growth. The combination of the 5-fluorouracil-epirubicin-cyclophosphamide regimen with epigenetic modulators, decitabine and valproic acid was evaluated as adjuvants to suppress the survival of BC cells. The mechanisms involved an increment in the demethylation of BC-promoting uPA and PAI-1 genes and enhanced the pro-apoptotic DAPK gene [63]. The epigenetic regulation by catalytic activities of the DNMT1 significantly contributes to the onset initiation and progression of BC. As such, scientific evidence has revealed that small molecules with inhibitory potentials on DNMT1 could suppress the

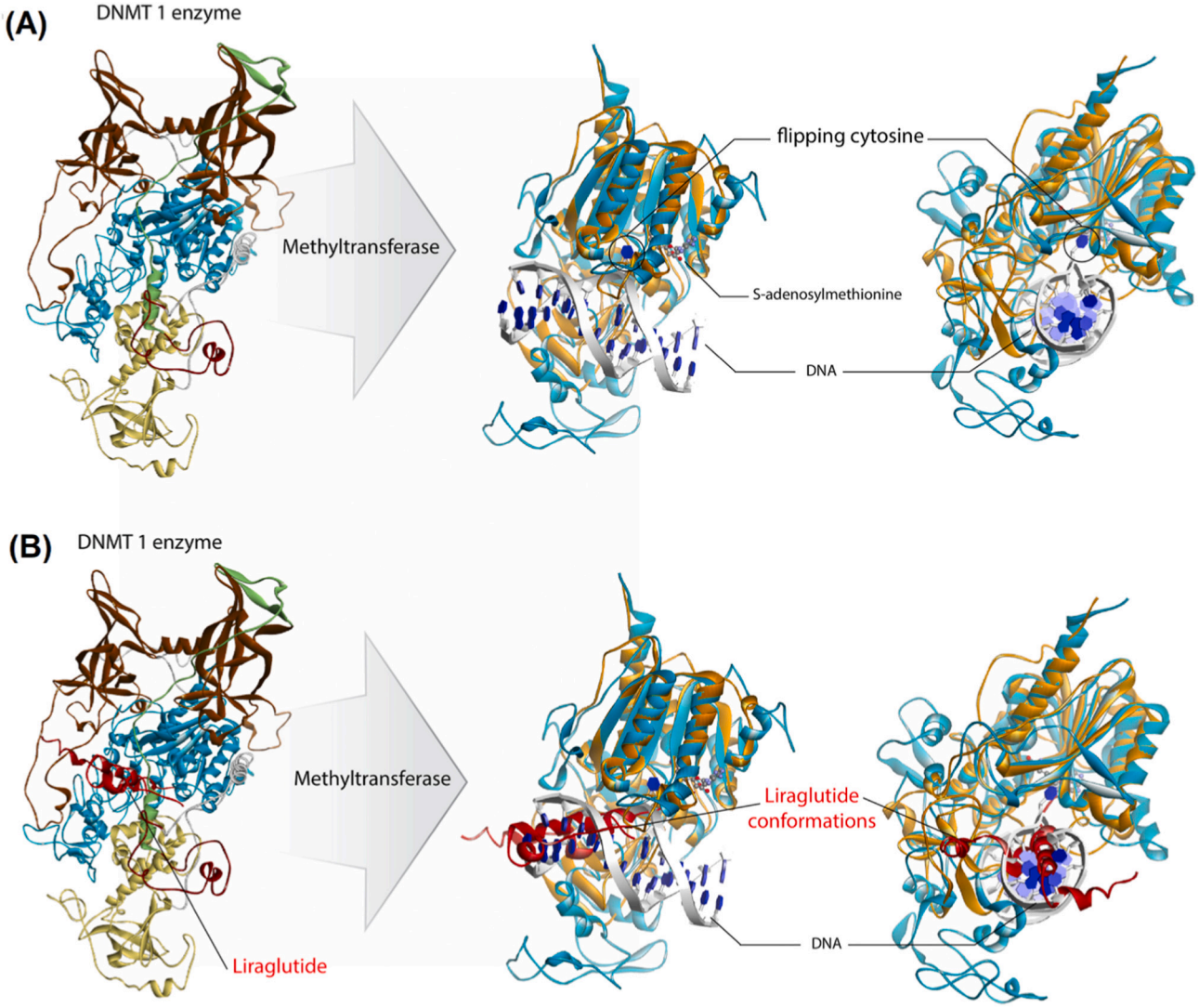



**Fig. 4.** *In silico* molecular analysis of human DNMT1 and liraglutide. (A) Structural overview of DNMT1 human enzyme (PDB ID: 4WXX) with enlargement of the methyltransferase domain representing two orthogonal views of DNMT1 from *Haemophilus parahaemolyticus* (PDB ID: 1MHT in light blue ribbons) complexed with DNA superposed with human DNMT1 (PDB ID: 4WXX in orange ribbons). (B) Structural representation of the most interacting conformations of liraglutide (red ribbon) that docks in a pocket that may disturb the DNA approach into the methyltransferase catalytic domain.
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resistance-inclined modifications and sensitize cancer cells to the cytotoxic environment [80,91]. In an experimental study by Greville et al., decitabine, a renowned inhibitor of DNMT was shown to induce epigenetic changes in the chemosensitive TNBC through the glycosylation of secreted glycoproteins, supporting DNMT as a marker for epigenetic management of TNBC [68].

*2.4.2.1. Inhibitors of DNMT1.* Supporting the correlation between the activation of CDH and inhibition of DNMT, liraglutide (Victoza), an antidiabetic medication was evaluated as a repurposable epigenetic modulator of BC, targeting the DNMT pathway. The *in vitro* study showed that the drug induces downregulation of the oncogenic pathways *via* the inhibition of cell proliferation and viability, and DNMT activity. Further evaluation *in vivo* mouse gene model indicated the upregulation of the CDH, ESR and ADAM 33 genes through the suppression of the DNMT activity by the drug in combination with paclitaxel or methotrexate. The *in silico* structural analysis revealed the electrostatic binding of the drug to the catalytic cleft through H-bonding and salt bridge formation with human DNMT1 (PDB ID: 4WXX). The interdomain contacts of the drug with the active pocket residues effectively disrupt the enzyme conformation for activity checkmate (Fig. 4) [17].

Decitabine, a renowned inhibitor of DNMT was also shown to induce epigenetic changes in chemosensitive TNBC through the glycosylation of secreted glycoproteins and enhanced the migration and EMT of the BC cells [68]. Alraouji et al., 2020 evaluated the anticancer effects of tocilizumab and its potential to sensitize TNCB cells to cisplatin cytotoxicity, targeting cancer stem cells. It was revealed that tocilizumab suppressed the IL-6/STAT3 signalling in various cell lines and also induced the suppression of the IL-6/STAT3/NF-κB-related cancer/inflammatory response loop that is pivotal for the alteration of cells and tumourigenesis *via* an epigenetic switch. Tocilizumab inhibited three critical epigenetic pathways implicated in BC tumourigenesis including STAT3, NF-κB, and PI3K/AKT, and the production of IL-6. Additionally, it also inhibited the growth and proliferation, along with EMT activity in TNBC cells. Moreover, it was equally observed that the drug repressed the paracrine activation of normal breast stromal fibroblasts to myofibroblasts and enhanced the cytotoxic effects of cisplatin *in vitro* TNBC cells, and EMT pathway in humanized orthotopic breast tumours in mice. The study indicates that tocilizumab can inhibit the pro-metastatic potential of TNBC cells and augment the cytotoxic efficacy of cisplatin against the cells [16]. A recent high throughput biochemical screening discovered a highly potent and selective inhibitor of ATPase family AAA domain-containing protein 2 (ATAD2) from the AstraZeneca screening collection, (2*R*)-11-(8-((1-(2-Fluoro-2-methylpropyl)piperidin-4-yl) amino)-3-methyl-[1,2,4]triazolo[4,3-*b*]pyridazine-6-carbonyl)-2-isopropyl-2,3,5,6-tetrahydro-1,5-epiminobenzo[*d*]azocin-4(1H)-one (AZ13824374) as an epigenetic inhibitor with cellular target interactions and adequate antiproliferative effects against BC models [92].

Similarly, some botanicals have been proven to demonstrate promising epigenetic modifying-based anti-BC activities inclusively *via* the regulation of mechanisms and proteins responsible for chromatin remodelling [93,94]. Brazilin, a heterotetracyclic compound present in *Caesalpinia sappan* reportedly reduced the growth of MCF-7 cells and expression of DNMT1 by decreasing the DNA methylation, and also by actuating p38 MAPK and raising p53 levels inside the cells. The amplified expression of p53 enhanced the inhabitancy at restricted locations inside the 200 bp upstream site in the DNMT1 promoter, leading to a decrease in DNMT1 gene expression [91]. Genistein (4′,5,7-trihydroxyisoflavone) is an isoflavone, naturally found in soybeans and soy products [95]. Genistein has been shown to induce cell cycle arrest at the G2/M phase in MDA-MB-231 cells. The mechanism of the cell cycle arrest was suggestively mediated by Ras/MAPK/activator protein-1 [96]. Epigallocatechin-3-gallate (EGCG) is a polyphenolic compound naturally found in green tea. It may impede carcinogenesis by targeting epigenetic alterations [97]. Current studies revealed that EGCG may inhibit breast cancer proliferation and migration by regulating different TSGs through effective inhibition of DNMT and HDAC enzymes [97,98]. Baski and co-researchers also reported potent chemopreventive effects demonstrated by quercetin and silibinin. The two bioflavonoids inhibited the TNBC cells, MDA-MB-468 in a dose-dependent manner mechanistically *via* the regulation of apoptotic signalling cascade, modulation of expressions for Bcl2 and p53 genes, and superoxide dismutase (SOD) activity [28].

Also, the combined therapy of vegetables, broccoli sprouts (BSp) and green tea polyphenols (GTPs) downregulated and induced hypermethylated changes in Rpl13, Ndufa1, and Get4 genes. The Ndufa1 was reported to be downregulated and hypermethylated with a methylated difference of 28.91, and Rpl13 was deregulated too. The regimen also induced an upregulation of the pancreatic and duodenal homeobox 1 (*Pdx1*) and activated a TSG, transmembrane protein 132d (*Tmem 132d*) gene, and regulated cell division. The results showed that combined therapy of BSp and GTPs could reverse the abnormalities in DNA structures induced by epigenetic carcinogenesis [2].

### 2.4.3. MicroRNAs

The miRNAs are renowned markers for the epigenetic modulatory networks due to their enormous contributions to cellular processes involving the epigenetic suppression/regulation of initiation, progression and metastasis of BC. Upregulation of the miR-646 was experimentally demonstrated to suppress the proliferation and progression of BC cells *via* the suppression of HDAC2 expression. Further studies using cell lines also implicate the dysregulation of miR-646 or HDAC 2 in the tumourigenesis and epigenetic modulatory prevention of BC, implicating the miRNA as a plausible therapeutic target for epigenetic modification [61].

*2.4.3.1. MicroRNA-targeting chemotherapeutic agents.* Some chemopreventive dietary supplements for influencing anticancer processes such as indole-3-carbinol (13C) and 3,3′-diindolylmethane (DIM) have been investigated as tumour suppressors with the potential for elevating the relevant miRNAs levels. The miRNAs with elevated expressions include the let-7a-e, miR-17-5p, miR-19a and miR-20a, while the expressions of the oncomiRs were decreased by the agents. The compounds also suppressed the CDK4 and CDK6 expressions, and the apoptotic markers, Bcl-2 and survivin. Mechanistically, these further support the miRNAs as critical epigenetic targets for strategic therapeutic developments including molecular mimicry and RNA regulations in BC management [53,99]. Metformin was also reported to reduce cell proliferation, enhance apoptosis and cause cell cycle arrest in a dose-dependent manner. Metformin therapy enhanced the acH3K9 abundance while decreasing acH3K18 levels. It also increased the expression of the long non-coding RNA (lncRNA) and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). The MALAT1 knockdown in turn boosted the Bax/Bcl-2 ratio and elevated p21 expression in metformin-treated cells, but decreased cyclin B1 expression. The drug suppressed cell proliferation, enhanced apoptosis, and caused cell cycle arrest in a dose-dependent manner. The findings support a promising repurposing strategy for metformin on BC treatment involving the epigenetic modifiers [100]. Studies have shown that some bioactive natural products can also invert the epigenetic aberrations by acting as modulators of miRNA expression associated with oncogenesis, tumour suppression and cancer-derived protein production [101].

### 2.4.4. Mitochondrial DNA

The mitochondrion has been strongly earmarked as an apoptosis-initiating organelle and in the reactive oxygen species (ROS) generation which induces oxidative stress usually in association with cancers including BC. Thus, epigenetic mutations and modifications of the mitochondrial DNA (mtDNA), and 'mitoepigenetic' were postulated as

an ideal marker for diagnosis and targeted therapy for regulating oxidative stress in BC conditions [102,103]. Epigenetic tumourigenic mechanisms of BC have also been shown to implicate the MiDs-mediated expression of miR-34a-3p, making both important biological targets for monitoring and controlling BC progression [54].

*2.4.4.1. Mitochondrial DNA modifiers.* Epigenetic regulation/modifications by targeting relevant biomolecules are regarded as an emerging method of action for metal complexes against cancer cells [104]. Copper complexes usually display the potential to act on single or numerous epigenetic targets/pathways, promoting their multifaceted anticancer effects. Mechanisms of their activities usually involve the induction of endoplasmic reticulum stress and cell death [105], dysregulation of mitochondrial function and triggering of apoptosis [106], epigenetic ROS-induced apoptosis [107], mitochondria-dependent apoptosis [108], DNA binding, cleavage, superoxide dismutase mimetic activity, cell cycle regulation and inhibition of topoisomerase I and II [109], proteasome inhibition [110] and chloride channel-3 activation [111]. For instance, anti-BC activities of some chiral and racemic ternary copper(II) complexes were evaluated by Chan et al. [104] *in vitro* MDA-MB-231 cell line. One of the metal complexes showed enhanced activities in multi-folds of the cisplatin effects. The study involved the apoptosis and cell cycle analysis, ROS assays, JC-1 mitochondrial membrane potential test and proteasome inhibition assay on MDA-MB-231 cells. Furthermore, the docking of the complexes at the 20S proteolytic sites revealed fresh information on their proteasome inhibitory mechanisms. An initial epigenetic evaluation on MDA-MB-231 and T47D breast cancer cells treated with the complexes to monitor their EZH1, EZH2 and H3K27me3 protein expression revealed a novel mode of action involving histone methylating enzymes. The outcome showed an unusual effect of EZH1 and EZH2 knockdown initially in the two cell lines on the apoptosis induced by copper(II) complexes, suggesting them to be cell subtype-sensitive [104].

Vorinostat is a known inhibitor of HDAC while erlotinib is an inhibitor of EGFR. Vorinostat and erlotinib were singly and doubly loaded in titanium oxide nanoparticles (NPs) and assessed for inhibitory potency on cell growth using MDA-MB-231, MCF-7 and WISH cell lines. A significant reduction ($p = 0.04$) was recorded for the first two cell lines with negligible reduction shown by WISH cells in response to all nanoparticles except the ERL+ SAHA-loaded $TiO_2$. ERL+ SAHA-loaded $TiO_2$ showed the highest potency followed by SAHA-loaded NPs. High cytotoxicity was shown by the NPs, especially the dual-loaded NPs. These could be linked to DNA damage and production of ROS, an indication of apoptosis through the mitochondrial pathway and cell cycle arrest at the G2/M phase [14].

As a natural mtDNA modifier, Shendge and co-workers isolated apigenin from the leaf extracts of *Clerodendrum viscosum* and evaluated its anticancer activity on the MCF-7 cell line using various relevant analyses. The results showed that the treatment with apigenin induced intracellular ROS on MCF-7 cells followed by G2/M phase cell cycle arrest and further apoptosis through the regulation of p53 and caspase-cascade signalling pathway [112].

### 2.4.5. Epigenetic growth factor receptor

Inhibitors of targeted antibodies and kinases are keystones in suppressing the HER2(+) malignancies, especially BC. These include the monoclonal antibodies such as pertuzumab and extracellular domain-targeting trastuzumab (Fig. 5), adenosine triphosphate (ATP) active site inhibitors of EGFR/HER2 dual-target kinase such as lapatinib, and pan erb-B inhibitors such as afatinib and neratinib. Due to the implication of the overexpressed EGFR in tumour development, erlotinib, an inhibitor of EGFR is commonly applied against several tumour progressions including BC [14,15]. For instance, Sheng and co-researchers investigated the effect of EGCG on signal peptide-CUB (complement protein C1r/C1s, Uegf, and Bmp1)-EGF (epidermal growth factor) domain-containing protein 2 (SCUBE2) methylation in BC cells. The findings indicate a significant decrease in SCUBE2 methylation by EGCG by downregulating the DNMT expression and activity [97].

*2.4.5.1. Regulators of HER2-positive.* FOXA1, a DNA-binding protein was evaluated for adaptive response determinants to HER2 targeted therapy, since the inhibition of the HER2/ERBB2 receptor is

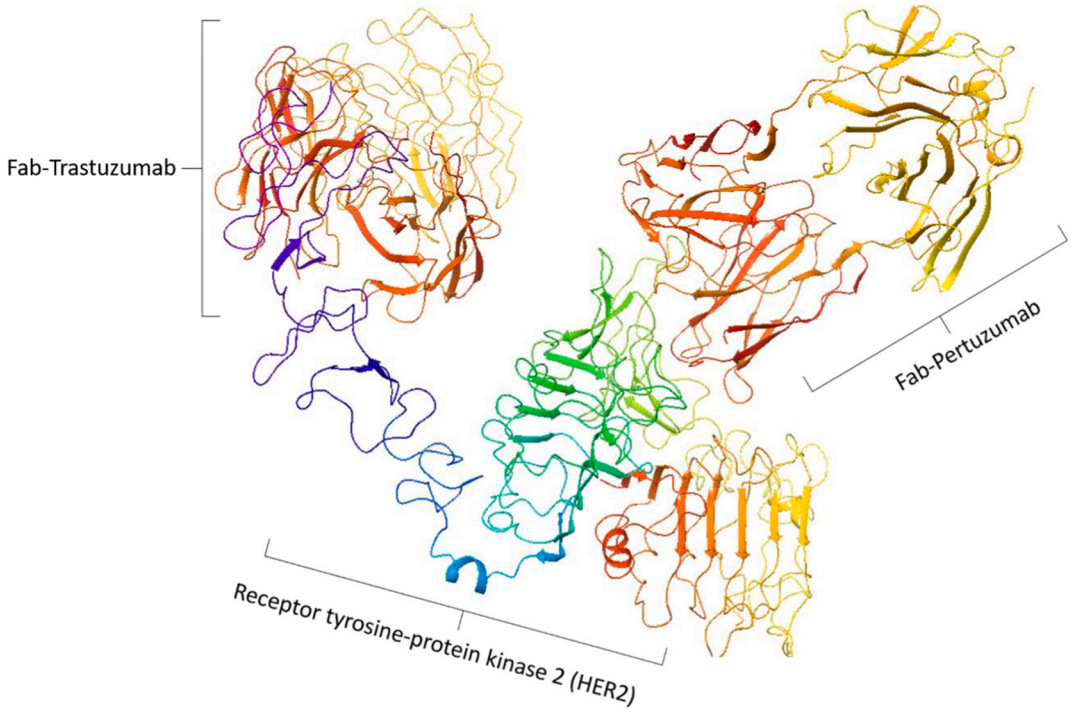



**Fig. 5.** Cryo-EM structure of HER2 in complex with extracellular domain-targeting Fab-pertuzumab and Fab-trastuzumab (PDB ID: 6OGE; image produced using Maestro 12.2, Schrodinger, LCC, New York, NY, 2019).

fundamental to reversing HER2(+) BC. However, a crucial fragment of HER2-positive BC failed to respond. The HER2+ cell lines' reaction to inhibition with lapatinib was assessed by RNAseq and ChiPseq to characterize transcriptional and epigenetic modification. Motif analysis of the lapatinib-responsive genomic areas reportedly compromised the ground breaker transcription factor FOXA1 as an intermediary of adaptive feedback. Additionally, the combination of lapatinib with FOXA1 impaired adaptive upregulation of HER2 and suppress proliferation. The expression of FOXA1 was downregulated in the presence of trastuzumab, supporting the anti-HER2(+) BC potential of the antibody for epigenetic HER2-targeted therapy [15].

#### 2.4.6. Protein arginine methyltransferase 5

The **PRMT** is another target for inhibition by small molecules to exert epigenetic modulatory antiproliferation of BC [57]. A novel inhibitor of PRMT5 currently in clinical trials for various solid tumours, JNJ-64619178 displayed potent antiproliferative activity against BC cell lines, thus, suggested for further studies and inclusion in clinical trials for BC [57].

#### 2.4.7. Y-box binding protein

A renowned transcription factor, YB-1 protein has been related to an upregulation of the **KLF5**, a transcription factor implicated in the tumourigenesis of basal-like BC. Phosphorylation of **YB-1** at Ser 102 by the ribosomal S6 kinase 2 (**RSK2**) has been proved to enhance the formation of the YB-1-KLF5 transcriptional complex. This in turn upregulated the basal-like BC-specific genes such as the *lymphocyte antigen 6* of the *D* family (**Ly6D**) and *keratin 16* (**KRT16**), thereby promoting cell proliferation. As such, the **RSK2-YB-1-Ly6D/KRT16** axis was suggested as a plausible epigenetic tumourigenesis of BC and a potent marker for diagnosis and treatment [40]. A complex epigenetic axis consisting of several biomarkers, RSK2-YB-1-KLF5-Ly6D/KRT16 has been demonstrated as a target for mitigating BC. A potent pan-RSK2 inhibitor, LJH685 was experimentally recorded with effective epigenetic suppressive activity against the basal-like BC tumourigenesis *via* an interruption with the YB-1-KLF5 complex pathway [40].

#### 2.4.8. Lysine demethylase

The SOX2 is a transcriptional regulating factor for the embryonic and pluripotent cell stemness associated with cancers. In BC, it is involved in the initiation, progression and metastatic processes *via* the induction of BC cell stemness, yet with undruggable features, complicating the treatment for sex-mediated cancer types such as BC. The LSD1 has been identified as an epigenetic target for regulating the SOX2 enhancers, making it a plausible target for mitigating cell stemness by selective epigenetic LSD1 inhibitors such as iadademstat (ORY-1001) [45]. The NuRD is a multisubunit protein host of chromatin-remodelling enzymes, ATPase, a BRD and HDAC for repressing transcription. Both ATPase, particularly, ATAD2 and BRD4 are reportedly overexpressed in many cancer microenvironments. An interaction of BRD4 with a complex of LSD1/NuRD has been proved to significantly promote resistance to chemotherapeutics and worse survival of BC patients, making the BRD4-LSD-NuRD pathway a potential marker for diagnosis and therapy [44,92]. Moreover, SOX2, OCT4 and Nanog are reported as markers for BC diagnosis and therapy [46]. An inflammation-related enzyme, phosphodiesterase 3A (PDE3A) was recently demonstrated to also induce the expression of OCT4 stem cell marker with associated mechanisms including the suppression of cAMP/PKA and the induction of the inflammatory nuclear factor, NFκB, making it a therapeutic target [113]. Biochemical screening of tumour organoids derived from mice and humans identified some tumour inhibitors annotatively, BML-210, CUDC-101 and GSK-LSD1 with potentials for promoting antigen presentation and T-cell-mediated tumour-specific cytotoxicity. They showed antitumour effects in orthotopic mouse mammary tumours, upregulation of antigen expression, sensitization of tumour cells to inhibitory checkpoint programmed death-1 and apoptosis through epigenetic tumour organoid-based T-cell cytotoxicity [18].

#### 2.4.9. Histone-lysine N-methyltransferase enzyme

The metastatic progression of BC has been understood to inclusively involve the expression of a histone-lysine *N*-methyltransferase enzyme, EZH2, as such, making it an emerging therapeutic target for epigenetic inhibitors of BC [104].

*2.4.9.1. Inhibitors of histone-lysine N-methyltransferase.* Some chiral and racemic Cu(II) complexes of some multidentate ligands, alanine, 4-methyl-oxazolidine-4-carboxylate and 1,10-phenanthroline were evaluated for cytotoxicity on metastatic and normal BC cells, MDA-MB-231 and T47D respectively. The metal complexes were observed to be more cytotoxic than cisplatin by up to 24-folds against the cells. Further biochemical and structural-activity relationship studies showed that the complexes have multi-target-directed potentials amenable to overcoming MDR BC. The mechanisms of their interesting activities were suggested to include the induction of apoptosis *via* the knockdown of the EXH1 and EZH2 [104].

#### 2.4.10. Interleukins

Triple-negative BC is associated with high secretion of pro-invasive (prometastatic) IL-6 cytokine, a pleiotropic inflammation-inducing cytokine. Thus, targeting the IL-6-signalling is an ideal chemotherapeutic strategy for BC.

Tocilizumab, an IL-6-targeting monoclonal immunosuppressive drug effectively inhibits/neutralizes the expression of IL-6/STAT3 signalling and suppresses cancer-related inflammation through the IL-6/STAT3/NF-κB pathway. The drug has been evaluated to potently inhibit the proliferation, epithelial-mesenchymal transition (EMT) process and metastasis in TNBC cells [16].

#### 2.4.11. Cadherin genes

Epigenetic CDH-1 genes are implicated in the onset and sporadic progression of BC, and dysfunction CDH-1s are commonly associated with BC cells, especially the lobular types. As such, the activation of CDH-1 through multifaceted genetic editing tools such as the clustered regularly interspaced short palindromic-repeats Cas9 (CRISPR/Cas9) has been proven to be a strategic suppressor of metastasis in BC [31]. A member of the CDH superfamily and calcium-dependent cell-to-cell adhesion molecule, PCDHB15 protein was implicated as a marker in BC prognosis through methylation. As such, treatment with DNMT inhibitors such as 5-azacytidine/5-aza-2-deoxycytidine (decitabine/5-aza-dc) reportedly silenced the promoter methylation and restored the PCDHB15 expression in BC cell lines. Although, its overexpression was also observed to suppress colony formation, indicating a negative correlation. Thus, PCDHB15 is suggested as an emerging tumour suppressor target gene for diagnostic and therapeutic designs [19].

#### 2.4.12. Cyclin-dependent kinase (CDK), CDK9-cyclin T1 complex and sphingosine kinase 2

The overexpression of CDK9 in complex with the cyclin T1 protein enhances various cellular tumourigeneses of BC inclusively through the mechanistic regulation of the RNA transcription-polymerase II elongation, amplification of the transcriptional myeloid cell leukaemia (Mcl-1) and cellular myelocytomatosis oncogene (*c-Myc*). Thus, the transcriptional CDK9-cyclin T1 protein-protein interactions have been identified as a plausible target for modulating the unpleasant cellular processes and improving the conditions of TNBC [37]. An iridium chelate containing 7-chloro-2-phenylquinoline CˆN ligand reportedly showed interesting anti-metastatic effects against TNBC allografts in mice comparably with cisplatin. The metal-based agent was observed to bind potently to the CDK9 thereby disrupting the corresponding CDK9-cyclin T1 complex, representing a promising epigenetic pathway for BC treatment [37]. In a recent study by Hait and co-researchers, S1P and

SphK2 have been shown to regulate the epigenetic functions of the HIF-1α/2α expressions in the progression of some BC subtypes, particularly, ER(+) and TNBC. As such, the **S1P**, **SphK2** and **HIF-1α/2α** are also regarded as potential targets for BC diagnosis and treatment [38].

#### 2.4.13. Promyelocytic leukaemia nuclear protein

Upregulation of PML nuclear protein expression is associated with TNBC development and regulates cancer-initiating cellular activities. As such, the protein, PML represents a plausible therapeutic target with PML-mediated stratification. Experimental evidence has shown that inhibition of PML significantly induces a decrease in proto-oncogenes, *c-Myc* and PIM1 kinase levels, resulting in growth arrest and senescence features triggered by the accumulation of CDK inhibitor 1B (CDKN1B; P27) [84]. Doxycycline and short hairpin RNAs (shRNAs) reportedly induced silencing of the PML protein which in turn triggered a significant morphological change on the MDA-MB-231due to its high expression of PML [84].

#### 2.4.14. Suppression of tumorigenicity 5 protein

The **ST5 protein** has been identified as a tumour suppressor gene against BC. Its upregulation reportedly inhibited cell migration and proliferation, and induce cell cycle arrest *in vitro* BC cell lines. Mechanistically, an amplification of the protein suppressed the phosphorylated extracellular signal-regulated kinases 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK) and the expression of *c-Myc* pathways. These make the protein an epigenetic target for consideration in the effective checkpoint, prophylaxis and treatment strategies for BC [51]. A specific MAP kinase (MEK1) inhibitor, PD98059 was experimentally shown to inhibit the ERK1 and subsequently nullified the modulatory effects of the ST5 depletion on the ERK1/2/*JNK*/*c-Myc* signalling pathway [51].

#### 2.4.15. Leukaemia inhibitory factor receptor

The **LIFR** is a renowned tumour suppressor gene. Its hypoxia-mediated downregulation is associated with aggressive osteolysis and metastasis of BC cells. Repressive effects on the BC cells have been experimentally demonstrated through effective stimulation of the LIFR within the hypoxic microenvironment by pan-HDAC inhibitors, entinostat and panobinostat. These support LIFR as a plausible target for the diagnosis and treatment of BC [56].

A summary of some current epigenetic medications in clinical applications for BC subtypes, and their targets, as well as epigenetic mechanisms of action, are presented in Table 1, and their chemical structures in Fig. 6.

However, despite the multimodal epigenetic mechanisms of actions of the current medications, implicating relevant targets, the limitations mentioned in Section 1.3 seriously beleaguered their continuous applicability in combating BC. This critically necessitates the search for newly designed candidates with potential for improved pharmacology and milder aftereffects. Sometimes, the resistance to treatment is developed through bypass signalling on the relevant targets, complicating the process [114]. Additionally, some of the currently available drugs including the CDK-inhibiting flavopiridol (alvocidib) exhibit off-target activities, thereby inducing dose-limiting systemic toxicities [37].

Analyses of gene expressions involving various markers and biological targets, and their epigenetic modulatory effects on reversing/suppressing the oncogenic processes reveal the network pharmacology amenable for conquering the resistance of BC cells. For instance, the study of HER2 inhibitor-resistant and –sensitive BC cells revealed the amplification of EMT and enhanced fibroblast growth factor receptor 1 (FGFR1) and transmembrane glycoproteins, neuropilins (NRPs). Due to the significant contributions of NRPs to growth factor signalling, the combination of epigenetic modulators with inhibitors that target the FGFR kinase could suppress the EMP-related resistance and metastasis in patients [114].

Progressively, some of the promising epigenetic inhibitors/modulators for BC from various chemical formulations are currently in various

**Table 1**
Some current epigenetic medications for breast cancer, their targets and mechanisms of action.

| Breast cancer subtype | Therapy | Target | Mechanism | Reference |
|---|---|---|---|---|
| Lobular BC | CRISPR/Cas9-therapy | CDH-1 | Activation of CDH-1 through CRISPR/Cas9-mediated genetic editing | [31] |
| Luminal B HER2+ | Iadademstat | LSD1 | Blockade of cancer stem cell-mediated mammosphere formation<br>Inhibition of the activation of LSD1-targeted SOX2 enhancer for cell stemness | [45] |
| HER2+ | Pertuzumab | HER2 | Monoclonal antibody | [14,29] |
| HER2+ | Trastuzumab | HER2 | Extracellular domain-targeting | |
| HER2+ | Afatinib and neratinib | ERBB | Inhibition of ERBB2 | |
| HER2+ | Trastuzumab-emtansine | ERBB2 | Monoclonal antibody | [29] |
| HER2+ | Trastuzumab-deruxtecan | | Inhibition of ERBB2 | |
| HER2+ | Pertuzumab-trastuzumab hyaluronidase | | | |
| HER2+ | Lapatinib | EGFR/HER2 | ATP active site inhibition of EGFR/HER2 | [14,15] |
| HER2+ | Erlotinib | EGFR | Inhibition of EGFR | [15] |
| HER2+ | Decitabine | DNMT | Inhibition of DNMT<br>Sensitization of BC cells to anthracycline, doxorubicin effects | [29] |
| HER2+ | Entinostat<br>Panobinostat | LIFR, HDAC | Stimulation of LIFR in BC cells within the hypoxic microenvironment.<br>Non-selective inhibition of HDAC | [56] |
| TNBC | Tocilizumab | IL-6 cytokines | Inhibition/neutralization of IL-6/STAT3 signalling.<br>Suppression of IL-6/STAT3/NF-κB pathway | [16] |
| TNBC | Tubacin, tubastatin A and CAY10603 | HDAC 6 | Inhibition of HDAC 6<br>Synergistic sensitization of non-mesenchymal TNBC cells | [82] |
| Metastatic BC | Decitabine | DNMT PCDHB15 | Inhibition of DNMT<br>Amplification of PCDHB15 protein | [19] |
| Metastatic BC | Vorinostat | HDAC 1 & 2 | Inhibition and epigenetic modulation of HDAC I & II | [14] |
| MDR BC | Chidamide-doxorubicin | HDAC, P53, Bcl-xL, Bcl-2, Bax | Inhibition of HDAC<br>Activation of P53, pro-apoptotic Bax and caspase cascade to induce G0/G1-mediated cell cycle arrest and apoptosis<br>Downregulation of Bcl-xL and Bcl-2<br>Inhibition of cell growth | [90] |

(*continued on next page*)

**Table 1** (*continued*)

| Breast cancer subtype | Therapy | Target | Mechanism | Reference |
|---|---|---|---|---|
| Unspecified BC | Doxorubicin | DNMT1 | Inhibition of DNMT1 expression and mtDNA methylation. | [102,103] |
| Unspecified BC | 13C DIM | miRNAs, CDK4, CDK9, Bcl-2 and survivin | Elevation of let-7a-e, miR-17-5p, miR-19a and miR-20a expressions Suppression of oncomiRs, CDK4 and CDK expressions Repression of apoptotic markers, Bcl-2 and survivin | [53] |

stages of clinical trials (Table 2) [115] and (https://clinicaltrials.gov/). The chemical structures of some epigenetic drugs currently in clinical trials for BC are provided in Fig. 7, except the monoclonal antibodies with complex protein structures.

In addition to the currently prescribed epigenetic drugs and those in clinical trials, several other bioactive agents of various chemical formulations have been reported with promising therapeutic effects against BC through epigenetic modifications as enumerated in Section 2.4. Interestingly, these include repurposable drugs (Table 3) with established pharmacokinetics and pharmacodynamics for immediate/speedy assessments, and some bioactive products from vast natural resources for easier accessibility (Table 4). The chemical structures of the enlisted active repurposable and natural product phytoconstituents are presented in Fig. 8.

## 3. Conclusion and perspectives

Breast cancer remains one of the leading causes of cancer-related

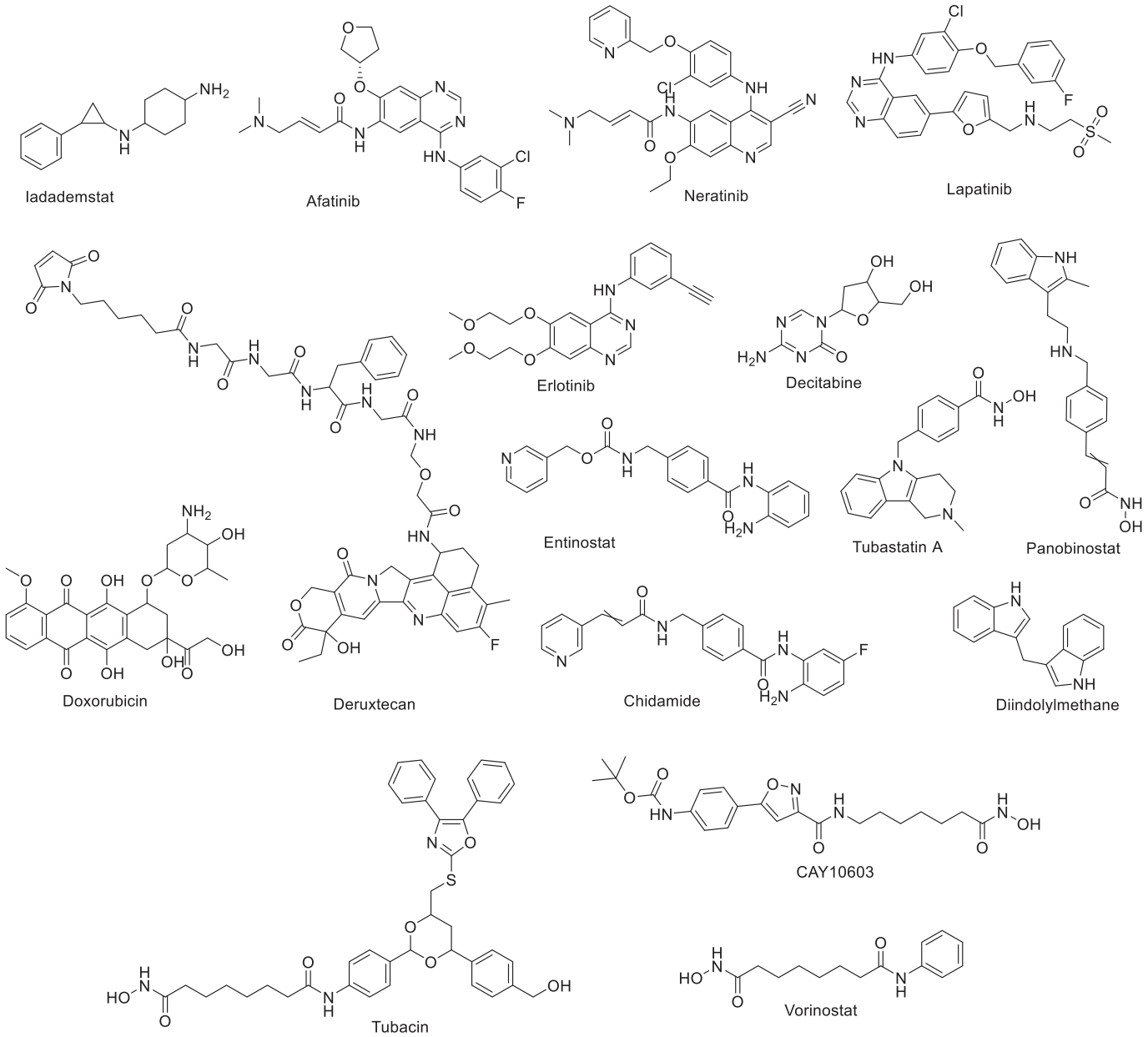



**Fig. 6.** Chemical structures of some current epigenetic medications for breast cancer.

**Table 2**
Epigenetic chemotherapeutics currently in clinical trials for breast cancer.

| Epigenetic drug | Other interventions | Status | Phase | Trial No |
|---|---|---|---|---|
| Azacytidine (CC-486) | Nab-paclitaxel | Completed, has results | 1, 2 | NCT00748553 |
| | Entinostat, laboratory biomarker analysis, pharmacological study | Active not recruiting, has results | 2 | NCT01349959 |
| | Biomarker analysis, immunohistochemistry staining and 2 more | Withdrawn | NA | NCT01292083 |
| | Fulvestrant | Terminated, has results | 2 | NCT02374099 |
| | Durvalumab | Completed | 2 | NCT02811497 |
| Decitabine | LBH589, tamoxifen | Terminated, has results | 1, 2 | NCT01194908 |
| | Paclitaxel | Unknown | 1 | NCT03282825 |
| | Carboplatin | Terminated | 2 | NCT03295552 |
| | Doxorubicin, cyclophosphamide, paclitaxel and 3 more | Recruiting | 2 | NCT02957968 |
| Entinostat | Capecitabine | Recruiting | 1 | NCT03473639 |
| | Exemestane, placebo | Active, not recruiting | 3 | NCT03538171 |
| | | Completed, has results | 2 | NCT00676663 |
| | Exemestane, goserelin acetate, placebo | Active, not recruiting, has results | 3 | NCT02115282 |
| | Exemestane, placebo | Unknown | 2 | NCT03291886 |
| | Fulvestrant, placebo | Withdrawn | 2 | NCT02115594 |
| | Lapatinib ditosylate, trastuzumab, laboratory biomarker analysis | Completed | 1 | NCT01434303 |
| | Anastrozole, therapeutic conventional surgery, diagnostic laboratory biomarker analysis | Terminated | 2 | NCT01234532 |
| | Nivolumab, ipilimumab and 2 more | Active, not recruiting | 1 | NCT02453620 |
| | Atezolizumab, bevacizumab and 5 more | Recruiting | 1, 2 | NCT03280563 |
| Romidepsin | Cisplatin, nivolumab | Active, not recruiting | 1, 2 | NCT02393794 |
| | Abraxane | Terminated, has results | 1, 2 | NCT01938833 |
| | Laboratory biomarker analysis | Completed | 2 | NCT00098397 |
| Valproic acid | VPA-FEC100 | Terminated, has results | 2 | NCT01010854 |
| | Hydralazine, core-needle biopsy | Terminated | 2 | NCT00395655 |
| | Bevacizumab, cetuximab, laboratory biomarker analysis and 3 more | Active, not recruiting | 1 | NCT01552434 |
| Vorinostat (MK0683) | Olaparib | Recruiting | 1 | NCT03742245 |
| | Paclitaxel, trastuzumab and 3 more | Completed, has results | 1, 2 | NCT00574587 |
| | Alone | Completed | 1 | NCT00719875 |
| | Laboratory biomarker analysis | Terminated, has results | 2 | NCT00132002 |
| | Conventional surgery | Completed, has results | 2 | NCT00262834 |
| | Therapeutic conventional surgery, laboratory biomarker analysis | Withdrawn | NA | NCT01695057 |
| | Genetic protein expression analysis, immunochemistry staining and 3 more | Completed | 1 | NCT00788112 |
| | Suberoylanilide hydroxamic acid (SAHA) | Terminated | 2 | NCT00126451 |
| | Tamoxifen | Completed, has results | 2 | NCT00365599 |
| | | Terminated, has results | 2 | NCT01194427 |
| | Tamoxifen, pembrolizumab | Terminated, has results | 2 | NCT02395627 |
| | | Recruiting | 2 | NCT04190056 |
| | Carboplatin, Nab-paclitaxel, placebo | Active, not recruiting, has results | 2 | NCT00616967 |
| | Ixabepilone, laboratory biomarker analysis, pharmacological study | Completed | 1 | NCT01084057 |
| | Lapatinib | Terminated, has results | 1, 2 | NCT01118975 |
| | Paclitaxel, bevacizumab | Completed, has results | 1, 2 | NCT00368875 |
| | Anastrozole, letrozole and 5 more | Completed, has results | NA | NCT01720602 |
| | Laboratory biomarker analysis and Biopsy procedure | Completed, has results | NA | NCT01153672 |
| | Trastuzumab | Completed, has results | 1, 2 | NCT00258349 |
| Belinostat | Ribociclib | Recruiting | 1 | NCT04315233 |
| | Carfilzomib, copanlisib HCl and 12 more | Recruiting | 1 | NCT03432741 |
| Panobinostat (LBH589) | Alone | Completed, has results | 2 | NCT00777049 |
| | | Terminated, has results | 2 | NCT00777335 |
| | | Withdrawn | 1 | NCT00993642 |
| | Trastuzumab | Terminated, has results | 1, 2 | NCT00567879 |
| | Letrozole, RNA analysis and 5 more | Completed, has results | 1, 2 | NCT01105312 |
| | Trastuzumab, paclitaxel | Completed | 1 | NCT00788931 |
| | Capecitabine, lapatinib | Completed, has results | 1 | NCT00632489 |
| BR(E)2ASTOME | Next Generation Sequencing and Network Analysis | Not yet recruiting | 2 | NCT04996836 |
| Everolimus (RAD001) | Exemestane | Completed, has results | 4 | NCT01743560 |
| Hydralazine | Alone | Withdrawn | 1, 2 | NCT00575978 |
| Neoadjuvant tamoxifen + goserelin | Neoadjuvant letrozole, endocrine therapy + palbociclib and 13 more | Active, not recruiting | 2 | NCT02624973 |
| Cycloxan-containing chemotherapy | Acupuncture | Completed | NA | NCT02457039 |
| ISB 1302 (CD3 Bispecific Ab) | D1, D8, D15, D22 and 5 more | Terminated | 1, 2 | NCT03983395 |
| Abraxane | Nab-paclitaxel, phenelzine sulfate | Completed | 1 | NCT03505528 |
| ZEN003694 | Talazoparib | Active, not recruiting | 2 | NCT03901469 |
| 5-Fluoro-2′-deoxycytidine (FyCyd) | Tertahydrouridine (THU) | Completed, has results | 2 | NCT00978250 |

Table adopted from [115] and updated at (https://clinicaltrials.gov/).

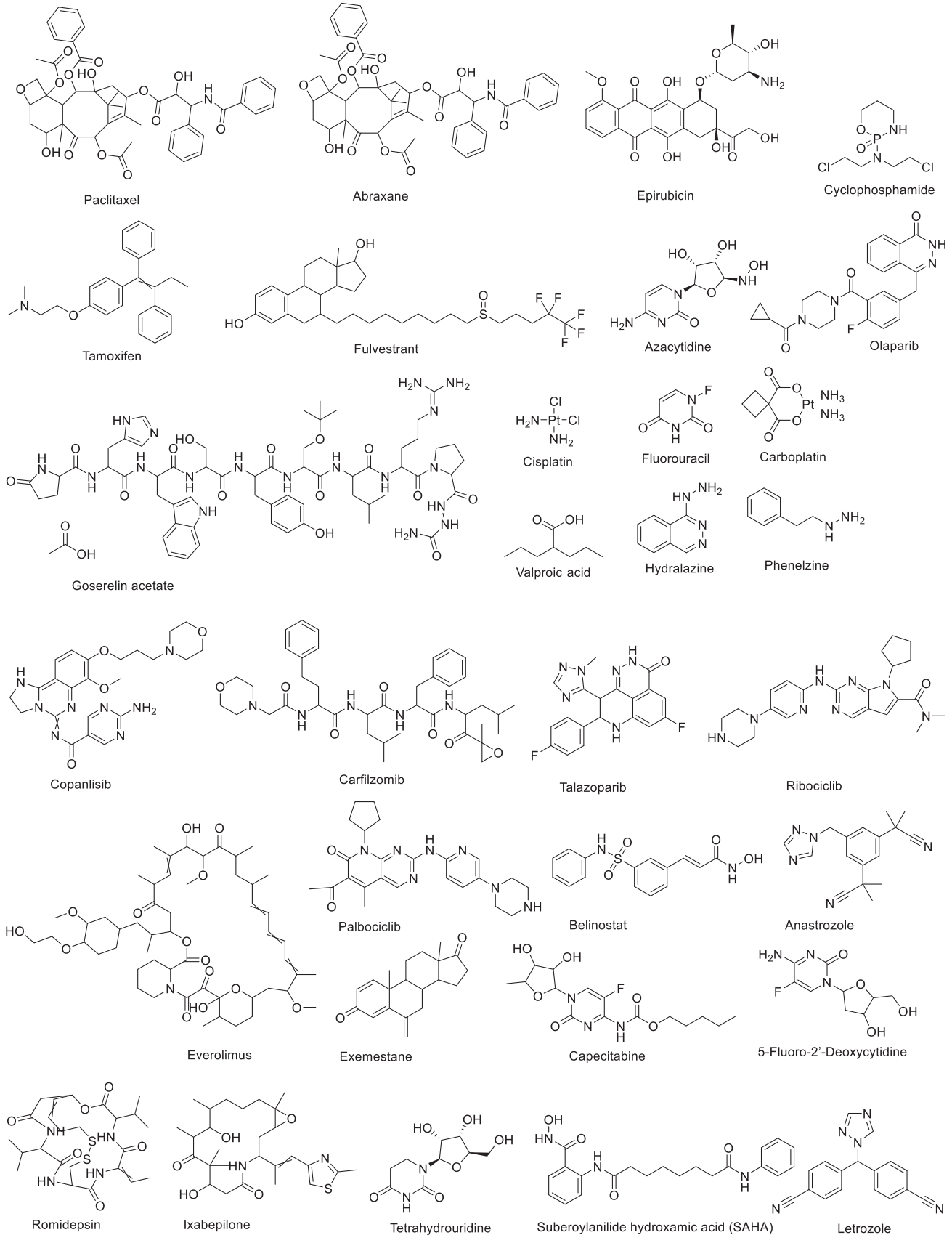



**Fig. 7.** Chemical structures of some epigenetic drugs currently in clinical trials for breast cancer.

**Table 3**
Summary of repurposable epigenetic inhibitors/modulator of breast cancer and their mechanisms of action.

| BC Subtype | Repurposing drug | Epitarget | Epigenetic mechanism | Reference |
|---|---|---|---|---|
| TNBC | Liraglutide<br>Liraglutide-paclitaxel/ methotrexate | DNMT, CDH, ESR | Inhibition of DNMT activity, cell migration and viability.<br>Upregulation of CDH, ESR and ADAM 33 | [17] |
| Unspecified BC | Valproic acid | HDAC | Alteration of metabolic pathways<br>Activation of cell growth- and cell proliferation-inhibiting metabolites<br>Elevation of ROS level<br>Induction of ferroptosis by L-cysteine deregulation<br>Promotion of cell death | [89] |
| TNBC | Decitabine | DNMT | Induction of epigenetic modulation on glycosylation of glycoproteins<br>Enhancement of apoptotic and senescence markers, chemosensitivity, EMT and migration | [68] |
| TNBC | Tocilizumab, cisplatin | IL-6, STAT3, NF-κB | Suppression of IL-6/ STAT3 signalling<br>Suppression of the IL-6/STAT3/NF-κB inflammatory loop<br>Inhibition of BC epigenetic tumourigenesis<br>Enhancement of cisplatin cytotoxicity | [16] |
| MDR BC | Chidamide, doxorubicin | HDAC | Induction of P53-mediated cell cycle arrest<br>Synergistic apoptotic effects<br>Upregulation of Bax, Bcl-2 and caspase cascade | [90] |
| TNBC | Belinostat | HDAC, CXCL1 | Inhibition of HDAC<br>Induction of apoptosis by enhancing the expression of CXCL1 | [83] |
| Unspecified BC | Metformin | Bax, Bcl-2, cyclin B1, P21, lncRNA | Dose-dependent induction of cell cycle arrest and apoptosis<br>Inhibition of cell proliferation<br>Upregulation of acH3K9 and downregulation of acH3K18<br>Enhancement of lncRNA and MALAT1 expressions<br>Suppression of expressions for cyclin B1 and *c-Myc* phosphorylation | [100] |
| TNBC | Tubacin + erastin | HDAC, voltage-dependent ion channel | Enhancement of synthetic cytotoxicity of cysteine depletion in non-mesenchymal tumour cells<br>Induction of apoptotic gene expressions, ATF3, CHOP and HOMX1 expressions<br>Enhancement of cell death *via* PKCγ signalling | [82] |

deaths globally, prominently affecting females, yet with limited effective therapeutic options. Most of the current medications are beleaguered by various factors including low efficacy, incessant resistance, loss of durability, immune evasion, frequent recurrence of the disease, complex disease aetiology and high metastasis characteristics of BC. The global menace requires multimodal approaches to understanding its prognosis and identifying effective therapeutic channels. In this review, epigenetics studies revealing several pathways to BC oncogenesis *via* the inducement of changes in genetic factors without affecting the genomic sequences have been overviewed. Similarly, the counter-epigenetic mechanisms to reverse such changes were surveyed as emerging effective therapeutic strategies for combating BC. Through the analysis, BC subtypes were identified basically as *in situ*, invasive and non-invasive. The further classification shows the luminal A and B, HER2+ and the basal-like family to which the renowned highly resistant TNBC belongs. Notably, the epigenetic oncogenesis reportedly occurs through the DNMT-mediated hypermethylation of DNA, histone modification, lack of expression for ERα, HER2/ERBB and PR (especially in the case of TNBC), overexpression of transcription factors including YB-1 protein, ID4 and CDK9-cyclin T1 complex. Others oncogenic pathways include the epigenetic suppression of the TSGs such as BRCA1/2, PCDHB15, ST5, LSD1 and LIFR. The upregulation of HDAC 2 and some tumour promoter factors such as BRD4, Pellino protein, SOX2, OCT4, NANOG, CDH10, SphK2, HIF-1α, MiD49 and MiD51, and hypoxia-mediated accumulation of G9a were also strongly implicated as tumourigenesis and metastatic pathways to BC. Scientifically, the regulatory reversal of the mechanisms constitutes effective epigenetic channels for mitigating BC initiation, progression and metastasis.

Progressively, some of the currently prescribed epigenetic medications with mechanisms of action through the targets have been highlighted. A series of chemotherapeutic agents have also been evaluated at various experimental stages. Dozens are currently in clinical trials while others are still at preclinical levels as summarized in the tables. The agents demonstrated mechanisms of reversing oncogenic epigenetic pathways, implicating several relevant targets. Interestingly, some of them exhibit network anticancer pharmacology, amenable to overcoming drug resistance and challenges of complex aetiology associated with BC. Moreover, some of them are FDA-approved drugs (especially those in clinical trials) with established pharmacokinetics and pharmacodynamics profiles. This would aid cost-effectiveness and time-saving in further translational studies to transform them into clinically applicable medications. Others include natural products, synthetic compounds, metal complexes and nanoparticles for easier accessibility and derivatization. Additionally, some of the agents such as antibodies, miRNAs and peptides are biological, and as such, would enhance biocompatibility and suitability for immune-related diseases such as BC.

However, despite the interesting activities, most of the studies were

**Table 4**
Summary of some natural product epigenetic inhibitors/modulators of breast cancer and their mechanisms of action.

| BC subtype | Natural product | Epitarget | Epigenetic mechanism | Reference |
|---|---|---|---|---|
| Unspecified BC | Brazilin | DNMT | Inhibition of DNMT expression<br>Activation of p38 MAPK<br>Amplification of p53 | [91] |
| TNBC | Genistein | DNMT | Induction of cell cycle arrest at G2/M phase in MDA-MD-231<br>Activation of Ras/MAPK/activator protein-1 | [95] |
| TNBC and unspecified BC | Epigallocatechin-3-gallate | DNMT, HDAC, HER2 | Inhibition of DNMT and HDAC<br>Downregulation of TSGs<br>Suppression of SCUBE2 methylation | [97,98] |
| TNBC | Quercetin and silibinin | Mitochondrial DNA | Regulation of apoptotic signalling pathway<br>Modulation of expressions for Bcl2 and p53 genes, and SOD activity | [28] |
| ER(−) BC | Combined broccoli sprouts and green tea polyphenols | DNMT, mitochondrial DNA | Promotion of DNA methylation<br>Upregulation of *Pdx1* and *Tmem 132d* genes<br>Regulation of cell division | [2] |
| Unspecified BC | Apigenin | Mitochondrial DNA | Induction of ROS and G2/M phase cell cycle arrest on BC cells<br>Regulation of p53 and caspase cascade signalling<br>Induction of apoptosis on MCF-7 cells | [112] |

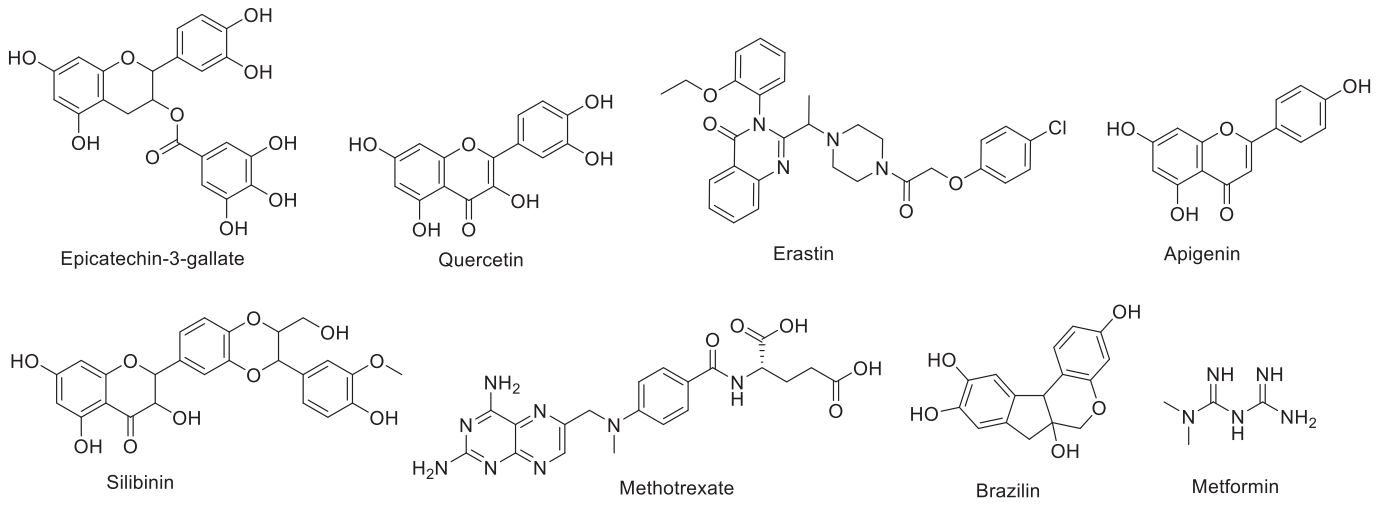



**Fig. 8.** Chemical structures of some active repurposable and natural products for epigenetic chemotherapy.

carried out through *in vitro* models where physiological aftereffects could hardly be succinctly observed. As such, more rigorous assessment through *in vivo* animal models is required especially for the candidates in preclinical trials to further observe their safety profiles. Importantly, the complexity associated with the epigenetic oncogenic pathways could hypothetically translate to the counter therapeutic pathways. As such, adequate scientific efforts are required to discriminatively specify and tailor the targeted chemotherapeutic effects towards suppressing the oncogenic mechanisms without activating the oncogenic promoters. Some metal-based agents such as metal complexes and nanoparticles are usually prone to systemic and environmental toxicity due to the associated effects of metal accumulations and diverse off-target effects, especially on normal cells. These are some of the key limitations of various metal-based drugs including FDA-approved ones. Advantages of nanotechnology could be employed by designing such promising candidates into nano-based agents for acute delivery to targets at effective doses. Such agents could also be synthetically modified using more biocompatible metal substitutes while conserving the efficacy.

Finally, the review represents a model for a wider understanding of epigenetic oncogenic pathways to BC development and profer channels for reversing the changes using epigenetic therapeutic mechanisms. It advances the science of therapeutic designs for ameliorating the global burden of BC for further translational studies.

## CRediT authorship contribution statement

**Yusuf Ayipo**: Conceptualization, Data curation, Writing-Original draft preparation; **Wahab Osunniran**: Data curation, Visualisation; **Akeem Jimoh**: Writing-Original draft preparation, Data curation, Visualisation; **Abdulfatai Ajiboye**: Data curation, Visualisation; **Mohd Nizam Mordi**: Supervision, Writing-Reviewing and editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

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

## Acknowledgement

This work was financially supported by the Fundamental Research Grant Scheme, Ministry of Higher Education, Malaysia, HICoE (grant no. 203.CDADAH.6711955). YOA is grateful to the Tertiary Education Fund

Nigeria for PhD scholarship and Universiti Sains Malaysia for Graduate Assistant Scheme (grant no. 308.AIPS.415401).

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