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Current Pharmaceutical Design, 2021, *27*, 1-22

REVIEW ARTICLE

Recent Advances in Diagnostic and Therapeutic Approaches for Breast Cancer: A Comprehensive Review

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ARTICLE HISTORY

Received: September 11, 2020
Accepted: January 22, 2021

DOI:
10.2174/1381612827666210303141416

Abstract: A silent monster, breast cancer, is a challenging medical task for researchers. Breast cancer is a leading cause of death in women with respect to other cancers. A case of breast cancer is diagnosed among women every 19 seconds, and every 74 seconds, a woman dies of breast cancer somewhere in the world. Several risk factors, such as genetic and environmental factors, favor breast cancer development. This review tends to provide deep insights regarding the genetics of breast cancer along with multiple diagnostic and therapeutic approaches as problem-solving negotiators to prevent the progression of breast cancer. This assembled data mainly aims to discuss omics-based approaches to provide enthralling diagnostic biomarkers and emerging novel therapies to combat breast cancer. This review article intends to pave a new path for the discovery of effective treatment options.

Keywords: Breast cancer, omics, genes, diagnosis, biomarkers, therapy.

1. INTRODUCTION

Breast cancer has been described as the most prevalent life-threatening cancer in women. Worldwide, breast cancer causes more than 50,000 deaths annually, accounting for 18% of all women deaths [1-4]. A recent publication has estimated that approximately 80% of women diagnosed with breast cancer each year are aged > 45. In the USA, the health burden of breast cancer is increasing at a drastic rate, with 232,240 newly diagnosed patients and 39,620 deaths per year [5, 6].

Male breast cancer is a rare disease accounting for only 0.5-1% worldwide. The main reason for the low mortality rate in males is a low concentration of breast tissue and the difference in the milk endocrine environment. The milk glands comprise multiple components like milk storage gland, milk duct, adipose tissue, and stromal tissues [7]. The high mortality rate in the females is due to the compact and dense quantity of epithelial and stromal tissues that have less fatty tissue [8]. All stages of breast cancer are displayed in Fig. (**1**).

Breast cancer is a heterogeneous disease and consists of various subtypes linked with multiple clinical outcomes. The aggressive nature of breast cancer, high metastatic rate, multifactorial occurrence, and poor diagnostic and prognostic options have limited the development of promising therapies. Breast cancer may therefore be considered as a complex and multifactorial disease that is attributed to both sporadic and familial factors. In terms of family history, only up to 20% of patients may transfer breast cancer, although its tendency depends on genes [9].

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Somatic and germline mutations lead to instability in chromosomes, abnormality in cell cycle regulation, and inappropriate DNA repairing [10]. Thus, all these DNA disintegrations, unfortunately, lead to breast cancer [11, 12]. It is diagnosed that BRCA1, BRCA2, TP53, SKT11, PTEN, CDH1, MSH12, chek2, palb2, and ATM are major germ lines that become altered in breast cancer inheritance. BRCA1 and BRCA2 germ lines are more predisposed due to their high penetrance. Almost 40% of inherited breast cancer occurs by alteration in BRCA1 and BRCA2 germ lines. Breast cancer risk due to BRCA1, BRCA2, BRCA1/2 genes is 36- 90%, but at the age of 80-years, this risk accounts for 72% and 69%, respectively [13].

HER2-positive breast cancer patients have extra copies of genes in their cells that encode a protein known as Human epidermal growth factors receptor 2 (HER2-Positive). This protein increases by two-fold the rate of division of cells in cancer cells and enhances metastatic nature. Thus, HER2-positive breast cancer is a second lethal cause of death after lung cancer [14] and is commonly found in females [15].

Etiological studies prove that the pathogenicity of breast cancer varies from its types to subtypes [5]. BRCA1 [16] and BRCA2 are the most disposed genes involved in breast cancer [16], but there are several genes according to their penetrance, including Tp53, ATM, PTEN, LKB 1, HRAS1, NAT1, NAT2, GSTM1, GSTP1, GSTT1, CYP1A1, CYP1B1, CYP2D6, CYP17, CYP19, ER, AR, AR, COMT, UGT1A1, TNF α, HSP70, HFE, TFR, VDR, APC, APOE, CYP2E1, EDH17B2, HER2, and TβR-I (Table **1**).

This is a review of the current literature/landmark trials in the diagnosis and treatment of breast cancer. We have attempted to cover this vast topic in this review and hope that it will serve as a reference for clinicians who treat patients with breast cancer.

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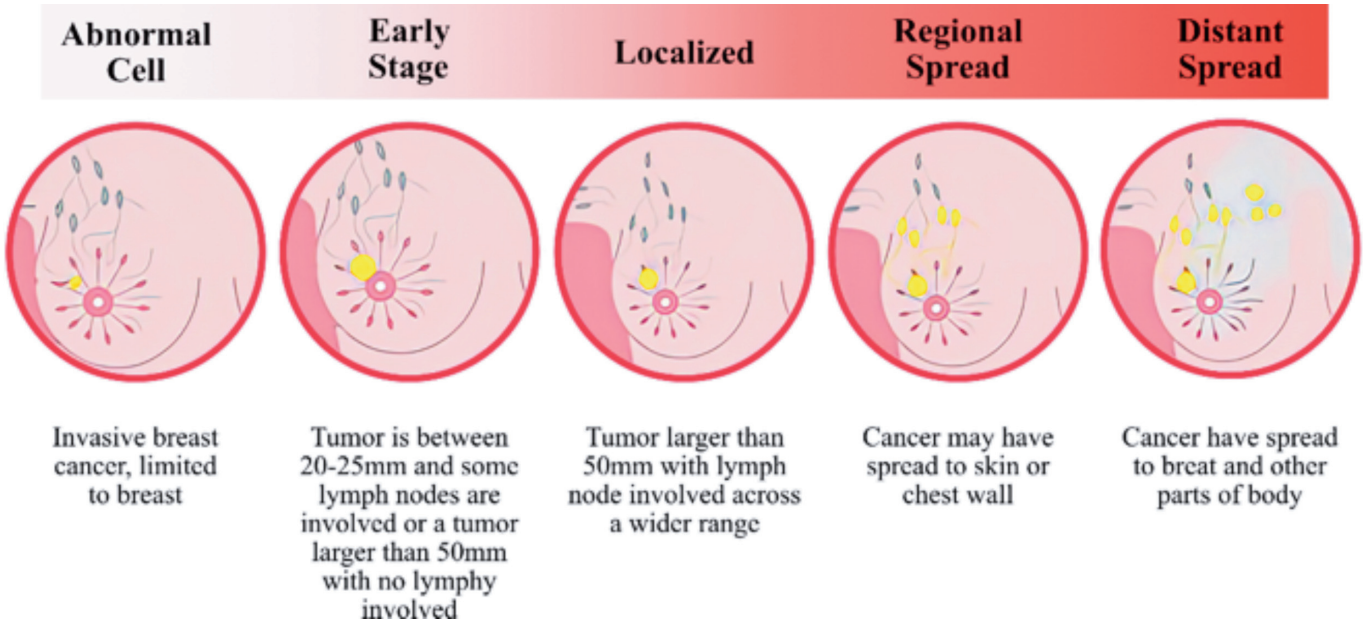

Fig. (1). Schematic representation of stages in breast cancer. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Table 1. Genetics of breast cancer.

Gene Name		Cytogenetic Location	Function	Refs.
BRAC1	Breast cancer type 1 susceptibility gene	17q21.31	Cell-cycle control, DNA repair, and chromosomal stability	[17, 18]
BRCA2	Breast cancer type 2 susceptibility gene	13q13.1	Cell-cycle control, DNA repair, and chromosomal stability	[19]
Tp53	Transformation-related protein 53	17p13.1	Regulate DNA repair and cell division	[20-23]
ATM	Ataxia telangiectasia mutated	11q22.3	Coordinates DNA repair and maintains the stability of the cell's genetic information	[24, 25]
PTEN	Protein-tyrosine phosphatase PTEN	10q23.31	Tumor suppressor, regulation of cell cycle, modified fats and protein, the formation of new blood vessels and maintenance of the stability of cell	[26, 27]
LKB1	Serine/threonine kinase 11	19p13.3	Regulates cell growth, controls cell division, as a tumor suppressor, helping in the orientation of cell, provides energy to cell, and promotes apoptosis	[28-30]
HRAS1	Harvey rat sarcoma viral oncogene homolog	11p15.5	Regulates cell division	[30, 31]
NAT1 and NAT2	N-acetyltransferases1 and N-acetyltransferases2	8p22	Activation of aryl-amine, hydrazine and carcinogens	[32, 33]
GSTM1	Glutathione S-transferase mu	1p13.3	Detoxifies the electrophilic compounds	[34]
GSTP1	Glutathione S-transferase pi 1	11q13	Regulation of metabolic pathway MP, detoxification of numerous chemicals	[35]
GSTT1	Glutathione S-transferase Theta1 gene	11q	Regulation of metabolic pathway MP, detoxification of numerous chemicals	[36, 37]
CYP1A1	Cytochrome P450 family 1 subfamily A member 1	15q24.1	Regulates the estrogen pathway, metabolism of estrogens and PAHs. But in breast cancer, its functions are still unknown	[38]
CYP1B1	Cytochrome P450 family 1 subfamily B member 1	2p22.2	Helps in the breakdown of drug and fats and the level of this enzyme exceeds in breast tissue	[36]
CYP2D6	Cytochrome P450 family 2 subfamily D member 6	22q13.2	Involved in MP, metabolism of many commonly prescribed drugs	[36]
CYP17	cytochrome P450 family 17	10q24.3	Regulates estrogen pathway	[39]
CYP19	cytochrome P450 family 17	11q21.1	Catalyzing the conversion of androgens into estrogen	[23]
ER-gene	Estrogen receptor	6q25	Regulates estrogen pathway, binding and transfer of estrogens to the nuclei; ER modulates transcription of several growth factors	[40, 41]

Gene Name		Cytogenetic Location	Function	Refs.
PR-gene	Progesterone receptor	11q22-23	Regulate estrogen pathway	[42]
COMT-gene	Catechol-O-methyl transferase	22q11.2	Regulates estrogen pathway, conjugation and inactivation of catechol estrogen	[43]
UGT1A1-gene	Uridinediphosphateglucuronosyltransferase 1A1	2q37	Helps in the progression of metabolic pathways (MP), regulation of EP, phase II drug metabolism, and maintains intracellular steady-state levels of estrogen.	[36]
TNFα	Tumor necrosis factor α	6p21	Controls immunological pathway (IP), a central mediator in the inflammatory response and immunological activities of tumor cells.	[41]
HSP70-gene	Heat shock protein 70	6p21	Acts as a molecular chaperone, is involved in regulation of structure, subcellular localization, and turnover of cell proteins	[44]
TFR and HFE	Transferrin receptor (TFR) and haemo- chromatosis (HFE)	6p21 and 3q	Take part in iron metabolism	[44]
VDR	Vitamin D receptor	12q	Regulates the process of cell differentiation.	[45]
APC	Aberrant methylation of the adenomatous polyposis coli	5q22	Inhibits the progression of cells from G1 to S phase, apoptosis and cell--cell interactions	[46]
APOE	Apolipoprotein E	19q13.2	Involved in lipid metabolism	[47]
CYP2E1	Cytochrome P450 2E1	10q24.3-ter	Involved in a metabolic pathway, metabolism of acetone, ethyl glycol and ethanol	[45]
EDH17B2	17 beta-hydroxysteroid dehydrogenase 2	17q12-21	Helps in the regulation of EP, catalyzes the reaction between estrogen and estradiol.	[45]
HER2	Human epidermal growth factor receptor 2	17q21	Involved in proto-oncogene, control of cell growth and proliferation	[45]
TβR-I	Transforming growth factor-β receptor-1	9q33-34	Controls cell growth	[45]

2. ADVANCEMENTS IN TECHNOLOGIES TO COMBAT BREAST CANCER

The heterogeneous nature of breast cancer draws the attention of researchers to find more enthralling and promising diagnostic and treatment options. This study intends to emphasize recent approaches in breast cancer diagnosis and treatment to untangle the intricate molecular mechanisms underlying and to uncover molecular candidates with effective diagnostic and prognostic value.

2.1. Omics-based Biomarkers for Breast Cancer Diagnosis

Omics is characterized by high throughput interfaces that accelerate the investigation of genomics, proteomics, transcriptomics, and metabolomics in an equitable manner. Omics-based approaches are considered as the weapon of choice to bisect the complex biological systems at different dimensions in the field of oncology [48, 49]. This powerful vision of omics has contributed largely to unfold candidate biomarkers for cancer diagnosis and prognosis [49]. Within the field of omics, RNA-based transcriptome analyses are an indispensable approach for interrogation of RNA metabolism, biogenesis, and transcriptome analysis [50, 51]. The ncRNAs are of two types with respect to the difference in length: one type is small ncRNAs (smaller than 200 bp) including microRNA, tRNA, rRNA, *etc*. [52], and the second type is long non-coding RNAs (greater than 200 bp) [53]. Only 2% of the genome is encoded into proteins and 75% of genome is transcribed into non-coding RNAs. Our study sought to highlight role of miRNAs, cirRNAs, and LncRNAs as a biomarker for the diagnosis of breast cancer.

2.1.1. miRNAs

One of the important master gene regulators, MicroRNAs (miRNAs) are small, non-coding, multifunctional, conserved, and single-stranded RNA molecules ranging in length from 19-25 nucleotides [54]. miRNAs have emerged as leading players in the carcinogenic process due to post-translational regulatory activity in gene expression of many biological functions (Fig. **2**) [55]. miRNAs perform diverse regulatory roles in the numerous aspects of cell development, differentiation, apoptosis, and cell proliferation [56].

Breast cancer is a growing public health threat and challenge that imposes serious economic burdens all over the world. In breast cancer, the tumor develops in the ductal and glandular regions of the breast [57]. Altered miRNAs in breast cancer have reshaped our understanding of the regulatory role of miRNAs in a breast cancer cell [57-59]. miRNAs are emerging as a game-changer in the regulation of initiation, progression, and metastasis of breast cancer. More than half of miRNAs encoding genes are present in cancer-linked regions [60]. miRNAs associated with breast cancer are divided into oncogenic RNAs (oncomiRNAs) and tumor suppressor RNAs (ts miRNAs). Both miRNAs target multiple aspects of tumor development through the complex regulatory mechanism. These mechanisms include tumor growth, proliferatory signals, metastasis, invasion, apoptosis pathways, angiogenesis, and cell energy [61, 62].

In recent years, the precise role of miRNAs in exploring cancer malignancy has shed light on the potential use of miRNAs as a biomarker for cancer diagnosis (Fig. **3**) [63]. Identification of miRNAs, their targets, and the function they perform has revealed their true potential as a novel compound in cancer diagnosis and management [64]. A different level of expression of miRNAs marks the difference between healthy and disease clinical trials, which is of great consideration for diagnosis of disease for which no diagnostic marker exists [65].

2.1.1.1. miRNAs in Tumor Initiation

Cancer stem cells which are termed tumor-initiating cells contribute to cancer progression. These breast cancer-initiating cells are self-renewal due to Bmi-1 (Hedgehog pathway). Different miRNAs (miR-200c, Let-7, miR-30) perform regulation of Bmi-1 for BT-IC self-renewal. Let-7 directly targets Ras, miR-30 targets

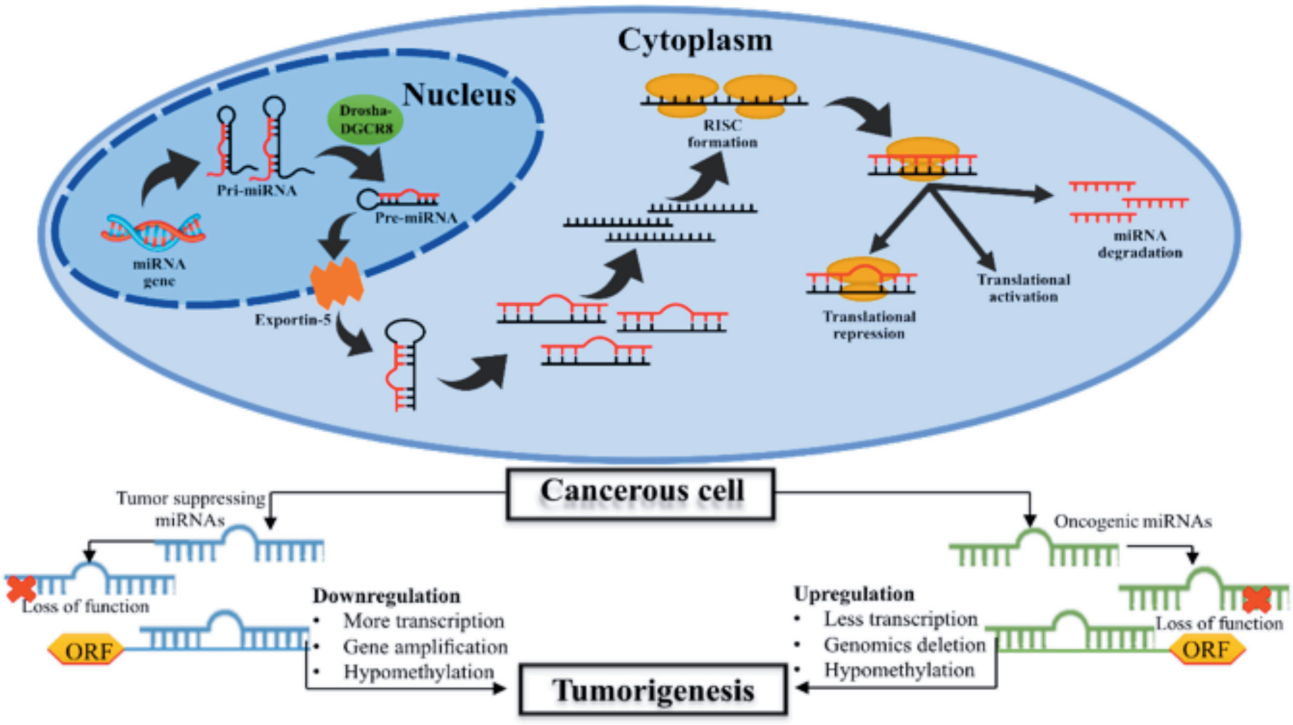

Fig. (2). miRNAs biogenesis and its role as a biomarker in breast cancer. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

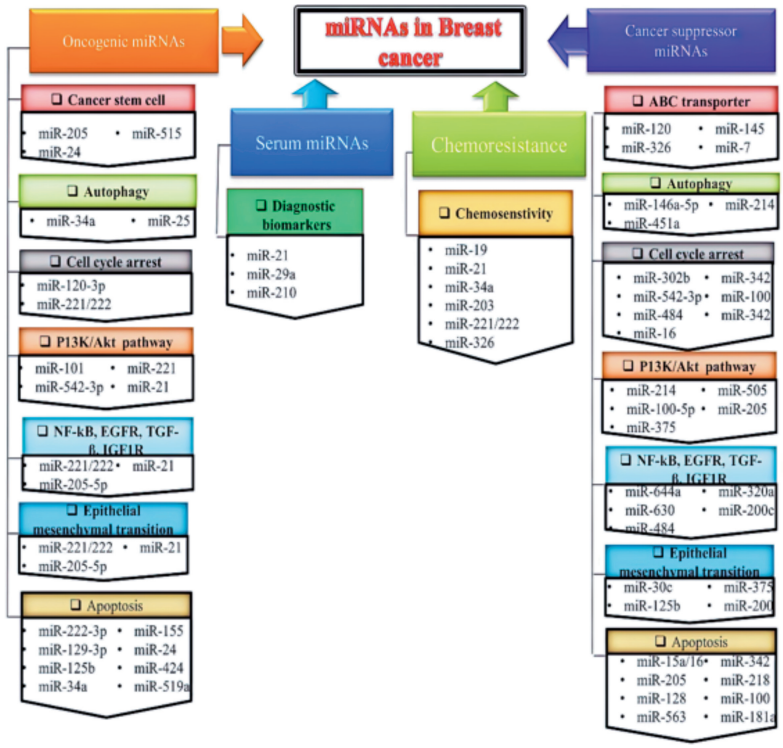

Fig. (3). Schematic representation of the role of miRNA biomarker in breast cancer. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

ubiquitin-conjugating enzyme 9 (Ubc9) and Integrin β3 (ITGB3) and regulates the self-renewal ability of breast cancer-initiating cells in the early process of breast tumorigenesis [66, 67].

2.1.1.2. miRNAs in Cell Proliferation and Cell Cycle

One of the major hallmarks of breast cancer is cell proliferation. By targeting multiple factors such as cyclin and kinase, growth promoters, interruptions in the cell cycle, and cell proliferation, miRNAs perform multiple regulatory functions. One of the targets of miRNAs is the cyclin E1 gene which is an important regulator of the cell cycle [68]. miR-483-3p directly targeted cyclin E1 and decreased cyclin E1 prevent cancer cells from proceeding into the S phase for DNA synthesis. Up-regulation of miR-143 decreases breast cancer cell viability. Studies have shown that miR-455 overexpression and downregulation of miR-424 impose a negative impact on cell proliferation. Other studies also support the role of miR-543 in inhibiting cell proliferation and cell cycle and promoting apoptosis of cells. Overexpression of miR-1207-5p, miR-135b, and miR-492 and suppressed expression of miR-15a/16 promote cell proliferation and cell cycle progression. miR-26a, miR-30b, miR-365, miR-22, and miR-708 are also involved in the regulation of cell proliferation and cell cycle [58, 66].

2.1.1.3. miRNAs in Metastasis and Cell Invasion

Metastasis accounts for major deaths in breast cancer. In metastasis, the tumor invades the neighbor's tissues from the primary site. For metastasis cancer, cells have migratory, stem-like capabilities and invasive abilities. Epithelial-mesenchymal transition (EMT) is one of the important factors of metastasis [69]. Families of miRNAs that contribute to metastasis and increased invasion are miR-373/520, miR-155, miR-29a, miR-10b, miR-21, and miR-9 [57].

Elevated miR-200c and miR-141 both promote metastasis in breast cancer. miR-124a and miR-26b promote anti metastasis and anti-invasive activities in breast cancer cells. miR-200 family, miR-200b and miR-200b also induce metastasis by increasing migratory abilities of cancer cells. Up regulation of miR-122 and miR-374a expression increases migration and cancer cell invasion. In contrast, miR-148a, miR-340, miR-340, miR-33b miR-497, miR-211-5p, miR-211-5p, miR-494, miR-335, miR-133a, and miR-124 and miR-240-5p, miR-7, miR-17/20, miR-30, miR-22, miR-22, miR-126, miR-145, miR-146, miR-193b, miR-205, miR-206, miR-335, miR-448, miR-661 and let-7 inhibit metastasis and invasion activity of cancer cells [57, 58].

2.1.1.4. Role of miRNAs in Hypoxia and Angiogenesis

One of the major regulators of angiogenesis is hypoxia which promotes cell proliferation and metastasis [70]. The regulatory role of miRNAs in hypoxia and angiogenesis provides new insight into the mechanism of regulation of miRNAs in breast cancer [71]. Recent researches have elucidated the up-regulation of miR-210 and overexpression of miR-191 in breast cancer in hypoxic conditions. miR-29b functions as an anti-angiogenesis and anti-tumorigenesis agent. miR-497 targets VEGF and HIF-1α and has an anti-angiogenesis and anti-tumorigenesis effect. miR-24 is also hypoxia-inducible miRNA. Downregulation of miR-140-5p in cancer tissues promotes anti-angiogenesis and anti- tumorigenesis effect. Many studies have investigated the role of miR-100 as an angiogenesis and tumorigenesis suppressor [58].

2.1.2. Circular RNAs

Circular RNAs, circular, endogenous, and regulatory RNA molecules, that were once considered extras, are in the spotlight as a key player in the regulation of multiple diseases like diabetes and cancer. The role of cirRNAs in recent years has directed towards determining cancer prognosis, drug resistance and treatment efficacy [72]. There is a huge body of literature that supports the vital role of cirRNAs in multiple cancer pathways, such as they act as sponges for miRNAs which has made them a hotspot for cancer research (Fig. **4**) [73, 74].

Aberrant expression of cirRNAs at different stages of cancer cell proliferation, metastasis, invasion, and apoptosis suggests their potential role as a diagnostic and prognostic biomarker for breast cancer [75]. The association of cirRNAs with breast cancer makes them ideal candidate biomarkers for cancer diagnosis. Studies show that hsa_circ_100219, hsa_circ_406697, and hsa_circ_006054 are down-regulated and hsa_circ_104689, hsa_circ_103110, and hsa_circ_104821 are up-regulated in breast cancer [76]. Studies have shown a very low amount of circRNA-000911 in breast cancer cell lines. Downregulation of circTADA2A-E6 inhibits metastasis and progression in breast cancer cells [77].

hsa_circ_005239 is one of the cirRNAs which are overexpressed in breast cancer and promote proliferation and colony-forming ability of breast cancer cells; these cirRNAs act as a sponge to miR-34a [78]. Elevated expression of hsa_circRNA_0005505 promotes metastasis and invasion of cancer cells by acting as a sponge to miR-3607 for its action [79]. The upregulation of hsa_circRNA_0000479 and hsa_circ_008717 in breast cancer cells regulates cell proliferation and apoptosis. The upregulation of CircDENND4C promotes the proliferation of breast cancer cells in the hypoxic environment. The upregulation of Hsa_circ_0001982 in breast cancer cells regulates cell invasion and apoptosis by targeting miR-143. Upregulation of Hsa_circ_0008039 in breast cancer cells acting as a sponge to miR-432-5p regulates cell migration and cell cycle. hsa_circ_0011946 serves as a sponge of miR-26a/b by targeting replication factor C subunit 3 (RFC3) and promotes migration and invasion in breast cancer cells [72].

2.1.3. LncRNAs

LncRNAs are an emerging theme in the area of noncoding RNAs. Recent studies have demonstrated a broad spectrum of lncRNAs that are involved in tumor progression, apoptosis, cell growth, and regulation of breast cancer-driving pathways [80]. Recent systematic genomic studies have revealed over 8000 lncRNAs in the human genome, which perform multiple biological functions [81]. Several recent studies have shown that lncRNAs are important regulators of breast cancer pathways at epigenetic, transcriptional, and post-transcriptional levels [82]. LncRNAs function in gene regulation through a number of mechanisms (Fig. **5**) which involve chromatin alteration, epigenetic regulation, and marking X-chromosome inactivation. LncRNAs can fix complementary RNA and disturb RNA processing and localization [83]. The dealing of lncRNAs with proteins can disturb protein function and localization along with facilitating the establishment of riboprotein complexes [84].

2.1.3.1. Oncogenic lncRNAs in Breast Cancer

There have been extensive oncological studies on the role of lncRNAs in breast cancer progression and metastasis. Oncogenic lncRNAs are well known for their anti-apoptosis, metastasis, and angiogenesis activity. H19 is well characterized oncogenic RNA in breast epithelium cells which have been reported to be overexpressed in cancerous cells. H19 acts as a precursor of miR675 and suppresses pRB expression [85, 86]. Steroid receptor RNA activator (SRA) is the first lncRNA that does not perform any catalytic and epigenetic function. The up-regulation activity of SRA in

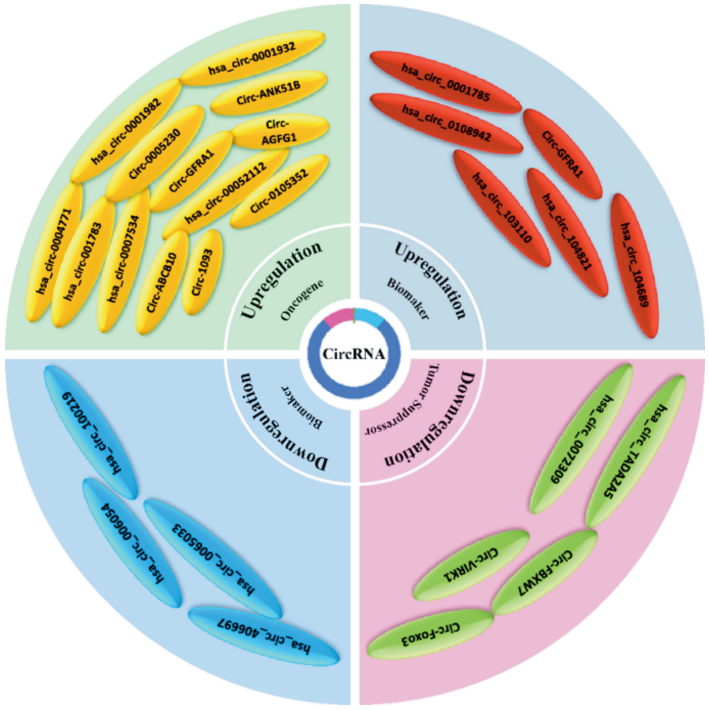

Fig. (4). Overview of circular RNAs in breast cancer diagnosis. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

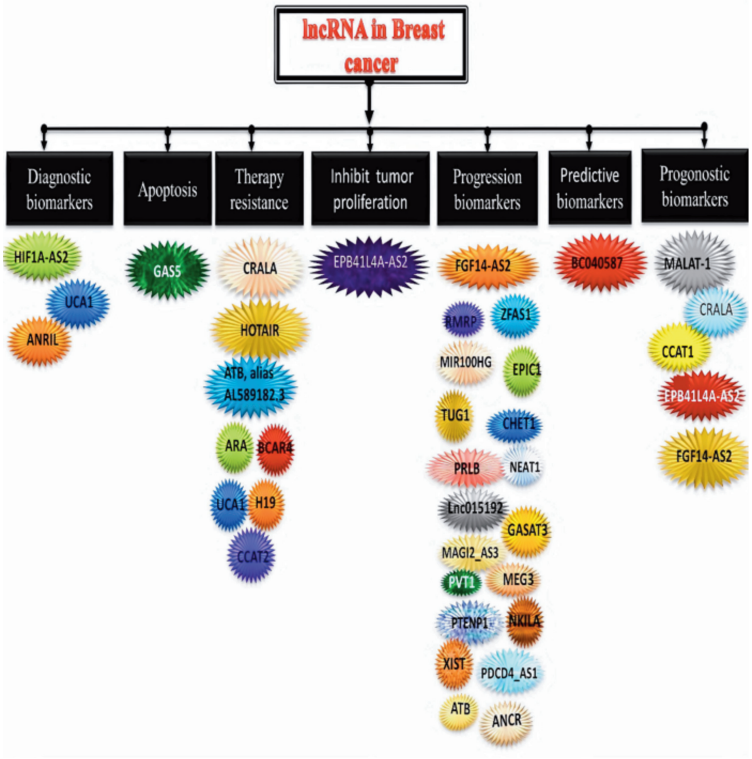

Fig. (5). Concise overview of LncRNA in breast cancer. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

breast cancer cells promotes cell proliferation and differentiation, suggesting it as an oncogenic RNA [87, 88]. LINC00324 (00324 non-long intergenic coding) is downstream of the CTC1 gene which is involved in DNA replication. Its overexpression is associated with patient survival [89]. ARA(Adriamycin resistance-associated) is an intronic lncRNA that modulates multiple cancer concerning pathways like metabolic pathways, cell cycle pathways, cell adhesion-related pathways, and MAPK signaling pathway [90]. AN-RASSF1 is an antisense RNA transcribed from tumor suppressor gene RASSF1, which promotes cell proliferation and acts as oncogenic lncRNA [91]. Urothelial carcinoma-associated 1 (UCA1) is a lncRNA that promotes breast cancer cell proliferation by suppressing p27 [92]. PTPRG-AS1 (tyrosine phosphatase protein, receptor type, G, antisense) is an antisense oncogenic lncRNA. Its lower expression is associated with longer life expectancy [93].

HOX transcript antisense RNA (HOTAIR) is a well-known lncRNA that acts as an epigenetic regulator. Up-regulated expression of HOTAIR in breast cancer tissue suggests it as a potential biomarker [94, 95]. HOTAIRM1 is overexpressed in the basal-like BC subgroup and has recently been revealed as an lncRNA, which has been exposed to relate with polycomb repressive complexes 1 (PRC1) and 2 (PRC2) [96]. SOX2OT elevates the expression of SOX2, which indicates its potential oncogenic role [97]. LSINCT5 is stress-induced antisense lncRNA transcribed by RNA polymerase III. Overexpression of LSINCT5 promotes breast cancer cell proliferation [98, 99]. CYTOR is an intergenic lncRNA that is involved in multiple cancer concerning pathways and functions as a tumor marker and oncogenic lncRNA [100]. ANRIL is an antisense non--coding lncRNA that promotes cell proliferation by modulating multiple cancer concerning pathways and acts as an oncogenic lncRNA [101]. MALAT1 (Metastasis Associated Lung Adenocarcinoma Transcript 1) is an intergenic lncRNA that is highly expressed in breast cancer cells and is associated with metastasis [93].

2.1.3.2. Tumor Suppressive lncRNAs in Breast Cancer

Some lncRNAs are cataloged as tumor suppressor lncRNAs because of their tumor repressor activity. The growth arrest-specific 5(GAS5) is best studied overlapping coding RNA, which controls cell proliferation and apoptosis and acts as a potential tumor suppressor. It is reported that the expression of GAS5 is downregulated in breast cancer cells as compared to normal cells. GAS5 is regulated by miR21, an oncogenic micro RNA that regulates multiple genes involved in cell growth and apoptosis [102, 103]. Maternal expression 3 (MEG3) is a well-characterized lncRNA. A low expression of this lncRNA is involved in breast cancer cells, and it plays an important role as a tumor suppressor. It acts as a sponge for multiple miRNAs as miR-21, miR-29, miR-9, and miR- 494. Its supportive role is due to the fact that it increases the level of nuclear factor expression κB (NF-κB) and expression of p53 and represses the pathways that lead to oncogenic behavior [104-106]. LINC01355 is a long intergenic non-coding RNA that represses cell proliferation, the reason for which they are called suppressor lncRNAs [107]. NBAT1 Neuroblastoma associated transcript 1 is a long intergenic non-coding RNA that interacts with PRC2 member (complex repressive polyombomb 2) EZH2 (zeste 2 enhancer) to suppress breast cancer cell migration and invasion [108]. Zfas1 is an overlapping antisense novel RNA present in mammary glands, which is expressed differently during pregnancy and lactation. Expression of this lncRNA is low in breast cancer cells and it acts as a tumor suppressor [109].

2.2. Recent Advancement in the Treatment of Breast Cancer

The increasing prevalence of breast cancer in the world is a major concern for women morbidity and it has gained a great deal of attention from researchers. Different conventional treatment methods such as surgery, radiotherapy, chemotherapy, and drugs have made a notable impact on the lives of patients, but not all are safer [110-112]. Despite the remarkable progress in recent years, all conventional methods of treatment have low specificity, cellular uptake, and toxicity [113]. These therapies have a short and acute toxic effect on normal patient cells. Even drug-based chemotherapy anthracyclines and taxanes have limited use in treatment [114-116]. The dramatic shift from the use of conventional treatment for breast cancer management to photodynamic therapy, immunotherapy, gene therapy, nanotechnology, and computational drug designing has led to improved therapeutic options for breast cancer management (Fig. **6**) [117].

2.2.1. Hyperthermia or Thermotherapy

Hyperthermia is a temperature-based oncological intervention of the 20th century for cancer management. In hyperthermia, the artificial elevation of temperature of cancer tissue causes necrosis of cancer cells. Hyperthermia may reduce tumor growth and may make the tumor more prone to radiation and anticancer drugs [118, 119]. Heat reduces the survival rate of cancer cells and inhibits repairing DNA damage [120]. Different ablations are used for breast cancer management as radiofrequency ablation, ethanol ablation, cryoablation, laser ablation, and more recent microwave ablation. The role of computation modeling in breast cancer hyperthermia treatment is the current advancement [121].

Combinations of hyperthermia with radiotherapy and chemotherapy have proven to be beneficial to improve local control of breast cancer [122]. After radiotherapy and chemotherapy, thermotherapy inhibits the growth of damaged breast cancer cells [120]. Although hyperthermia has the potential for cancer management, it still works best in combination with other therapies, not yet standalone therapy. Hyperthermia may lead to pain, swelling, burns, blood clots, infections, and skin infection [123].

2.2.2. Photodynamic Therapy

Photodynamic therapy is an elegant light-based therapy that uses nontoxic photosensitizer and laser light for cancer cell death. The antitumor activity of PDT makes use of three mechanisms, (1) direct cytotoxic effect on cancer cells, (2) indirect effect of PDT on tumor vasculature, and (3) activation of systemic immunity [124, 125]. When the light of appropriate wavelength and energy interacts with the drug, it results in the production of molecular oxygen, which causes necrosis in targeted cancerous cells [126].

The efficient selectivity of photosensitizer and less systemic toxicity make them a good tool for targeting tumor cells. Photofrin, Metvix, Levulan, Foscan, Visudyne, and Laserphyrin are some officially approved clinical trials for breast cancer management [127]. Photosensitizer targets receptors like Estradiol, Human epidermal growth factor receptor, and gonadotropin-releasing hormone receptor in breast cancer [128].

However, PDT allows heterogeneous distribution of photosensitizer in tumor cells (Fig. **7**) than intravenous application, and skin sensitization must be considered before the application of photodynamic therapy in breast cancer management [129, 130].

2.2.3. Immunotherapy

Immunotherapy has been proven to be beneficial against cancer by boosting the immune system to make it a more powerful fighter against cancer. The relationship between the immune system (three phases; elimination, equilibrium, escape) and tumor development is supported by an increasing body of literature. Immunotherapy works by targeting multiple regulatory checkpoints in

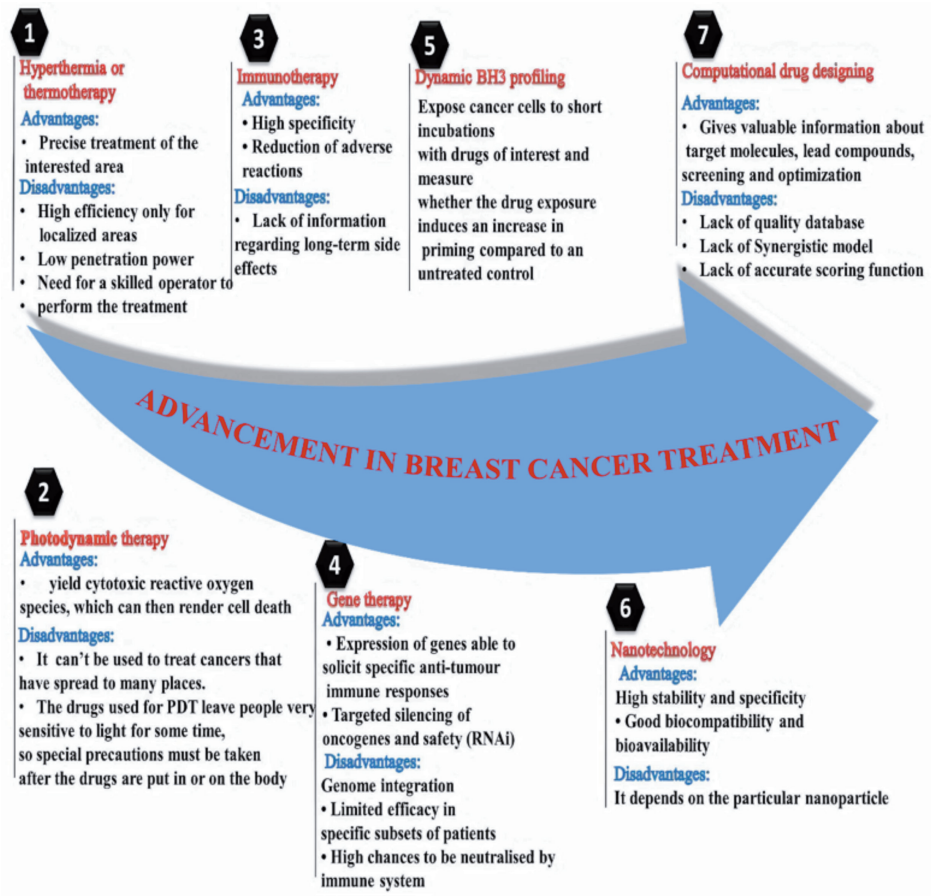

Fig. (6). Advancement in Breast cancer treatments. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

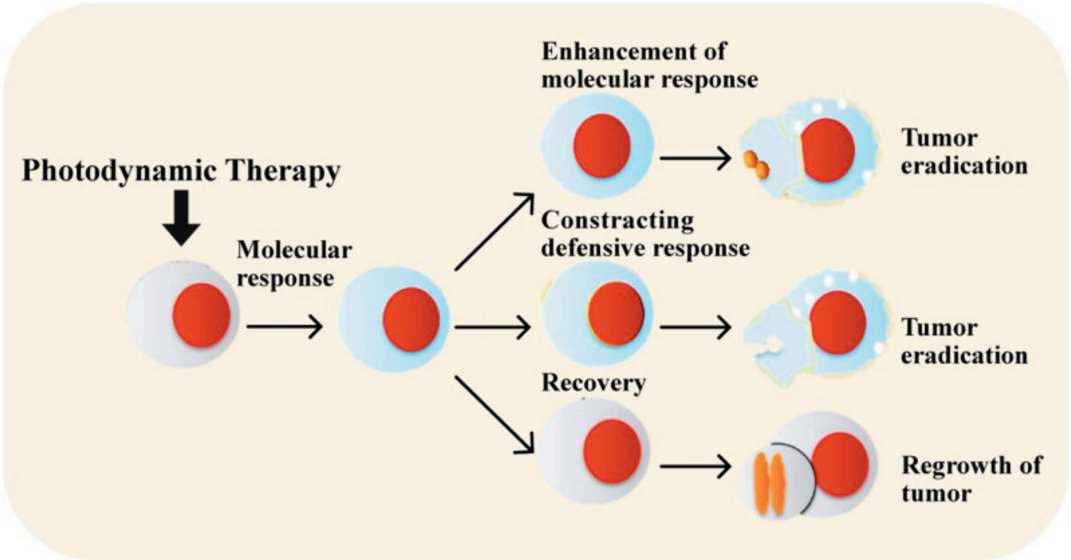

Fig. (7). Overview of photodynamic therapy in breast cancer. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

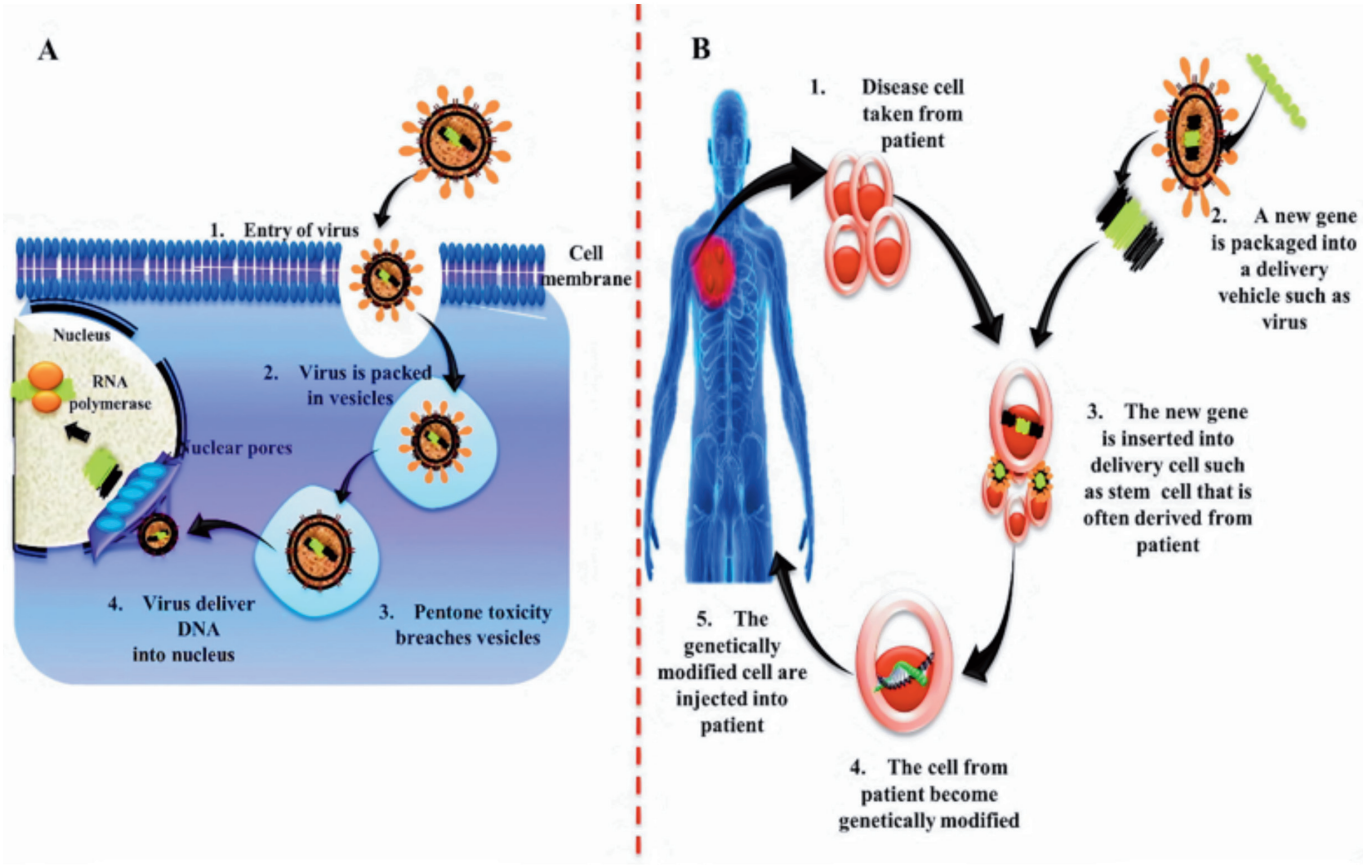

Fig. (8). A: How gene therapy works, B: Overview of gene therapy. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

the immune system to treat breast cancer [131]. FDA-approved immune therapies are cellular immunotherapy, molecular immunotherapy, and vaccination therapy [132]. Three classes of immunotherapies are adoptive T cells transfer, bivalent antibodies, and checkpoint inhibitors [133]. As compared to radiation therapy and chemotherapy, immunotherapy is more targeted. Despite the targeted role of immunotherapy in breast cancer,still there are some questions regarding toxicity, efficacy, and targeting, which need further consideration [134].

2.2.4. Gene Therapy

Gene therapy has put forward numerous innovative platforms to target multiple genes in breast cancer. A genetically unstable environment of tumor cells sparks the use of gene therapy to deal with breast cancer. In gene therapy, manipulated genetic material is delivered to cells that affect cancer cells in multiple ways, reducing the growth of cells and thereby destroying cancer cells (Fig. **8**) [135].

Delivery of genes and their controlled expression in cancer cells is a formidable task in the management of cancer [136]. Gene therapy works with protocol; (1) oncogenes suppression, (2) increased immunological responses, (3) introduction of suicide genes, and (4) use of drug resistance genes for bone marrow protection [137]. The expression of therapeutic genes needs to be strictly controlled for the regulation of the desired gene product [136]. Indeed mounting studies on gene therapy highlight the potentiality of gene therapy, vectors of toxicity, immunity, and multiple technical issues that still pose limitations for effective treatment of breast cancer [138]. Improved vector delivery options could provide a new paradigm for the most promising treatment options [139].

2.2.5. Dynamic BH3 Profiling

The prediction of clinical response of specific drug dynamic BH3 profiling is an innovative approach that measures death signals caused by a specific drug. Through interrogation of the BCL-2 family, DBP predicts chemotherapy sensitivity [140]. Cytotoxicity prediction capacity of BH3 profiling is confirmed in five breast cancer cell lines treated with different agents [141]. Through the comparison of different death signals induced by chemotherapeutics agents, DBP will lead to the exploitation of effective drugs for precision medicine [142].

2.2.6. Nanotechnology

The use of nanotechnology opens up exciting new possibilities in the diagnosis and treatment of leading diseases like cancer. Nanotechnology intends to reduce the toxic effect of conventional methods, which is the major barrier in the treatment of breast cancer. In the last 10 decades, a variety of nanoparticles have been developed to target metastatic breast cells and these have also proved to be very fruitful in targeted drug delivery. The main physiological reason behind these NPs is to operate molecules at nanoscale for developing smart active fabricate multifunctional devices (SAFMD) which can cross the biological barrier, arrive to the target cell, and deliver the drug [113]. In drug-based chemotherapy (DBC), the

Table 2. The role of nanotechnology in breast cancer.

Sr. No.	Nanoparticles	Therapeutic Properties	Cell Lines	Refs.
1	Liposomes	Effective in drug-like oligonucleotides, peptides, and siRNA-based genes therapy. LNPs knockdown microRNA to reduce breast cancer growth.	MCF-7, MDA MB, T-47D, MCF-10	[162-164]
2	Polymer-Based Nanoparticles (Polyhydroxy Alkonates, Cyclodextrins, PLGA)	PNPs Tamoxifen drug carrier and drug accumulator, having less toxicity band, high loading capacity, and inhibition of Pro-inflammatory cytokinins, are used to target MRP1.	MDA-MB-231	[165-168]
3	Gold Nanoparticles	Disulfate and thiolate coating Au, serve as a biomarker. Thesefunction as Radiosensitizer and photothermal agent, stay in blood vessel gap for phagositization, despite the presence of blood-brain barrier. AuNPs cause apoptosis to generate radicles. It reduces the expression of MMP, VEGFR, PIKT13, and AKT.	MCF-7, MDA-MB-231	[169-172]
4	Iron Oxide Magnetic Nanoparticles	Eradicate tumor cell by Hyperthermia method. Used for packaging of anti-cancer drugs to reduce toxicity. They function in cell death and cell cycle arrest.	MCF-7, MDA-MB-231, MB-474, T -47D	[173-175]
5	Silver Nanoparticles	These cause programmed cell death by Phosphoribosyl Transferase by increasing permeability of the mitochondrial membrane and cytochrome C release. AgNPs also activate ER receptors and regulate protein.	MCF-7	[176-178]
6	Quantum dots	Conjugation of QD with antibodies is used to target cancer cells for drug delivery and passive targeting by retention effect.	MCF-7, BT-474, MAD-M-B-231	[179-181]
7	Mesoporous Silica Nanoparticles	These prevent pre-activation of the drug, especially protein/gene, and lead to better drug delivery without penetrating tumor cells. They are beneficial than antibodies due to having specificity for a tumor cell.	NDA-MB-231	[182]
8	Carbon Nanotubes and Carbon dots	SWNT detect breast cancer cell by Raman signal and NIP absorbance of the tumor. CNTs with oxygen accelerate PTX inhibitory role in BC cell proliferation by downregulation of HCF-Iα cells and carbon nanotubes, reducing macrophages and blood vessels at the tumor site. Nano dots inhibit cancer cells by lowering their viability.	MCF-7, MDA-MB-231 and HeLa	[183-185]
9	Dendrimers and micelles	These surface bind with the transmembrane receptor Neuropilin-1 leading to increased targeting.	MCF-7, MDA-MB-231	[186, 187]
10	Viral Nanoparticles	Induce proliferation and cell death. Viral particles reduce cell division.	HER2+, MDA-MB-231	[188-190]

long-term use of monoclonal antibody trastuzumab leads to an adverse cardiac abnormal function. These cardiac complications, including other physiological irregularities, demand the discovery of novel drug delivery systems (nanoparticles) by oncologists [117, 143-145]. Consequently, to overcome all these problems, a new method is acknowledged as nanotechnology for breast cancer (Fig. **9**). Most exposable organs in the human body are the liver, brain, lungs, and bone which have cancer stem cells (CSC) or tumor imitating cells (TICs) [146, 147]. Notch, hedgehog, and Wnt are stem cells signaling pathways that play a critical role in the progression of tumorigenesis like leukemia and breast cancer [148, 149]. Thus, Notch target therapy has yielded a good result in breast cancer [150]. Despite performing multiple outstanding roles in diagnosis and treatment, there are some limitations of notch-target therapy that must be clarified to overcome this medical challenge (Table **2**).

Nanotechnology is the technique of characterization of nanoparticles by improving their shapes and sizes up to the nano range (1-100nm) [151]. FDA-approved nano platform and PEGylated liposomal doxorubicin are elegant milestones in the "era of nanomedicine" [152-154]. Nanoparticles with small surface area and large surface area/volume ratio possess unique biological activity for targeting mutant cells [155-157]. Metallic nanoparticles like silver, gold, uranium, titanium, and Zinc are more successful because they have a greater surface area, and significant antifungal, antimicrobial, anti-diabetic and anticancer activities [158, 159]. Silver nanoparticles are the most commonly used metallic nanoparticles [160, 161] due to their strong polarity with the membrane and less toxicity.

Inorganic (Silica, iron oxide) and organic (polymeric, liposomes, micelles) nanoparticles possess competitive features in the era of drug therapy [191, 192]. The advanced breast cancer nanotechnology-based method of nanomedicine has been studied which has increased the demand for target-based drug discovery and delivery. To avoid complications in targeting cells, different nanoparticles (NPs) are applied for encapsulation, binding (electrostatic, covalent), or absorption of cancerous cells [193]. Reported data reveal that several drugs are available which possess efficient solubility and bioavailability and these have shown maximum catalytic activity on the MCF-7 cell line.

The non-toxicity of nanoparticles on different breast cell lines such as MDA-MB-231, SkBr-3, and MCF-7 has been investigated through a number of studies [33-36]. Doxorubicin (DOX) as a chemotherapeutic mediator is used with nanoparticles for drug delivery. "Active targeting" is the most prominent representative to treat the tumorigenesis in a well-fashioned manner. In this method, several ligands are used to ligate with NPS/drugs, which bind with the specific localized receptor on tumor cells. In the world of nanotechnology, peptide ligands are mostly used to enhance biological activity, such as beta-alanine, gamma-aminobutyric acid, and glycine. Active targeting takes place in the microenvironment (matrix, blood vessel) and is more advantageous than passive targeting in terms of toxicity, cellular uptake, and specificity [195].

2.2.6.1. Liposomes

Liposomal nanoparticles (LNPs) are spherical vesicles of a phospholipid bilayer that target specific tissues and act as potential drug carriers [189]. Liposomes are encapsulated in phospholipid bilayer for better delivery and to reduce the toxic effect of non-target cells [196]. Amphiphilic LNPs, like DOX, have an aqueous inner core with lower cytotoxicity due to strong endosomal escape capacity [197]. Liposomes have a high tendency of incorporation by using a membrane layer, which improves their efficiency for treating cytosolic carcinogens [162]. Multidrug Resistance is eliminated by using DOX with siRNA, which promotes apoptosis in MCF-7/Adr cancer cells by combining chemotherapy and RNA interference (RNAi) therapy. Thus, VEGF, siHF1-A, and siVEGF stimulate cancerous angiogenesis, which in turn increases the supply of nutrients

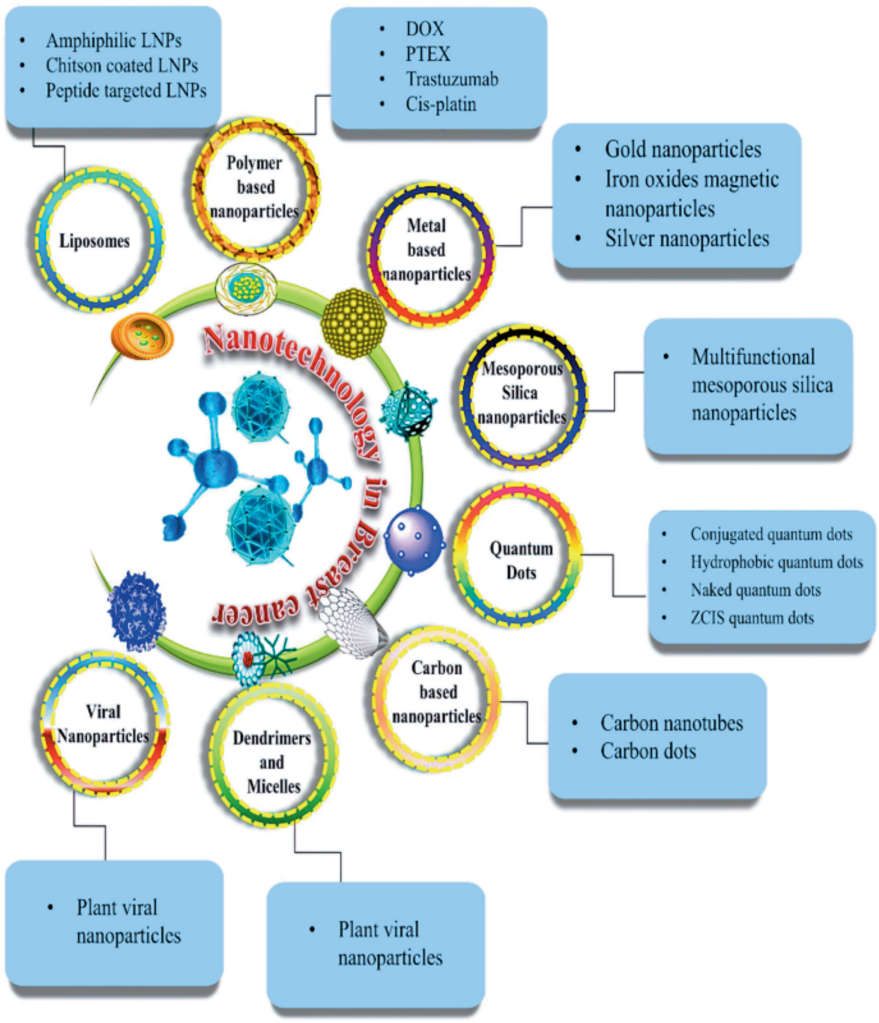

Fig. (9). Role of nanotechnology in breast cancer. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

and oxygen for their rapid proliferation [198]. siRNA-technology is the most promising cancer therapeutic option for silencing the specific target gene expression, which indirectly provides a better medium for the inhibitor to stop the translation process [163].

The use of nanoparticles for siRNA delivery for silencing VEGF expression seems to be a promising strategy to repress breast cancer growth [198]. For the efficient treatment of $HER2^{+}$ breast cancer, anti-HER2 monoclonal antibodies and conjugated nanoparticles are studied [199, 200]. Recent studies have investigated the use of nanoparticles to deliver therapeutic miRNAs in cancer cells [164]. Chitosan covered with supplementary liposomal nanoparticles has upgraded siRNAs stability by protecting them from serum deprivation [201]. Ligand-targeted liposomes are gaining recent research interest due to their improved cellular uptake and seem to have immense therapeutic potential for breast cancer treatment [202]. Overall, liposomes are the best nanocarrier as these are biodegradable and encapsulate therapeutic agents. The ligation of Polyethylene glycol (PEGylation) with the receptor of targeted cell provides safe transmission of drug into cytosolic environment. Thus, ligated PEGylation enhances the formation of liposomes, enzymes, carbohydrates, antibody nucleotides, organic molecules, and nanoparticles in microenvironment. Monomethoxy PEGylation has a CH3O (CH2-CH2O) n-CH2-CH2-OH structure that is valuable for lipid molecular modification. Non-PEGylated LNPs in combination with DOX and Cyclophosphamide are used for metastatic breast cancer treatment [203]. Doxil and Caelyx are the chief PEGylated liposomal nanoparticles against T-47 D, MCF-10, and MCF-7 BC cells which possess anti-cancer activity [201]. Co-delivery of liposomes displays supreme anti-proliferation, anticancer, tumor cell apoptosis, and cytotoxicity [204]. In liposomes, cationic lipids cause toxicity, and nanocarrier is degraded at a higher level by the Mononuclear Phagocyte System (MPS) [219].

2.2.6.2. Polymer-based Nanoparticles (PNPs)

PNPs are colloidal particles formed by copolymer and polymer matrix. Natural polymers are most widely used and are eco-friendly such as cellulose, chitosan, collagen, chitin, and sericin in nanotechnology. Nano precipitation, emulsification, and salting-out are common methods for chemical polymer-based nanoparticle formation. The drugs are loaded on the surface of PNPs by conjugation, adsorption, and encapsulation which amplify the permeability

and solubility inducing the slow release of drugs to target cells. Polymer-based nanoparticles such as *polyhydroxyalkanoates, cyclodextrins, PLGA* are used as nanocarriers. In breast cancer, PNPs are used for tamoxifen drug carriers to treat estrogen receptor-positive breast cancers as well as to prevent the incidence of breast cancer in high-risk populations. N (2 hydroxypropyls) meth-acrylamide with tyrosine inhibitors are used for HER2 drug delivery. Photodynamic therapy (PDT) [165, 166] is experiencing a great demand in recent years for TNBC treatment by light radiation, which promotes apoptosis of cancer cells.

PLGA tamoxifen has nucleus fragmentation and less toxicity as compared to pure tamoxifen. Layer by layer DOX and siRNA co-delivery are used to target multidrug resistance protein 1 (MRP1). Anticancer activity of Methotrexate (MTX) in the presence of cytosolic enzyme and hydrofolate reductase inhibits the pro-inflammatory cytokinin [167, 168]. Co-encapsulation of MTX-ACL into single lipid bilayer nanoparticles is best for breast cancer treatment, which proves the efficiency of PNPs instead of LNPs due to easy inoculation into the living system [205].

2.2.6.3. Metal-based Nanoparticles

Metal-based nanoparticles have been extensively investigated due to their unique physicochemical properties in medical sciences. The mostly used metal nanoparticles for breast cancer treatment are gold, supra-magnetic iron oxide, silver, and quantum dots.

Gold nanoparticles have been found to be efficient for imaging, treatment, and diagnosis which derive from chloroauric acid in aqueous media as a small solid round shape particle with few nm to more than 100 nm in size [206-208]. Surface coated thiolate or disulfides can bind gold to increase the catalytic activity of the biomarker and drug delivery agent. Gold nanoparticles are used as distinction agents of photothermal agents, drug carriers, and radiosensitizers [169]. The retention effect and permeability of AuNPs on the tumor surface are due to the selective accumulation of macromolecular drugs in tumor tissues. The tumor vasculature is a foremost constituent of the microenvironment that can impact tumor behavior and treatment response and can be considered over anti-angiogenic drugs.

Gold nanoparticles are activated with a ligand or functional molecule that enhances their efficacy. Nanoparticles eradicate cancer by inducing apoptosis with the help of generated radicles. Paclitaxel is ligated with gold nanoparticles which can be useful as a theranostic agent for cancer therapy without having any cytotoxic effect on normal cells. In Breast cancer, large neutral amino acid transporter (LAT1) is used with AuNPs, which increases their accumulation in tumor cells without any change in normal mammary ducts [172]. Quercetin loaded gold nanoparticles down-regulate the epithelial mesenchyme transition in malignancy role I MCF 7 and MDA-MB -231 cells. AuNPs reduces the expression level of several proteins such as MMP, VEGFR, PIKT 13, and AkT [171]. Gold nanoparticles are an efficient drug delivery vehicle to target multiple cancer concerning pathways [170]. Oligonucleotide conjugated with AuNPs acts as a gene regulatory agent to activate lymphocyte pathways in the human body [209]. AuNPs show a hyper-thermic effect emitting heat as a result of any light on the tumor cell in the form of visible wavelength [210].

Superparamagnetic nanoparticles comprise of magnetic nanoparticles, which help to overcome the cytotoxic effect of therapies and anti-cancerous drugs [211]. *Iron oxide nanoparticle* has an inner core with magnetite Fe_3O_4 or maghemite Fe_2O_3 [173]. Direct iron oxide nanoparticles do not spread because they accumulate in blood plasma, so hydrophilic coating magnetic core is used for target delivery specifically. Thus, mostly used stabilizer polymers are dextrans, PVA, magnetic nanoparticles for external magnetic field elevation. PEG chain on the surface of magnetic nanoparticles prevents it from steric hindrance. PEG and folic acid attachment to MPNs improve delivery and cellular uptake in breast cancer. Magnetic nanoparticle eradicates tumor cells by the Hyperthermia method. Iron oxide loaded particles with baicalein cause cell death and cell cycle arrest in triple breast cancer therapy [174]. Iron oxide nanoparticles (IONPs) are used in drug delivery systems such as Doxorubicin, TMX, quercetin, *etc*., by conjugating different reagents like antigens-receptors and ligand-antibodies. IONPs with siRNA also suppress various cellular growth pathways in breast cancer. IONPS have cyclooxygenase 2 (COX-2) siRNA that release COX-2 protein, which down-regulates breast cancer pathways and metastasis. IONPS also attach with multivalent Nucant such as DOX, N6L that have greater cytotoxic effects [212]. SPIONs are coated with lauric acid; human serum albumin has been examined in breast cancer treatment against T-47D, BT-474, MCF-7, and MDA-MB-231 cell lines [175].

Silver nanoparticles cause programmed cell death by phosphoribosyltransferase (UPRT) expressing cells and by non-UPRT expressing cells [85]. Bax-Silver NPs increase the permeability of the mitochondrial membrane to release cytochrome C which activates apoptosis pathways against MCF-7 cells [82]. Ag-NPs also disrupt endoplasmic reticulum receptors like Orphan 7-transmembrane G-protein-coupled receptors which activate some regulatory G-protein, causing apoptosis of breast cancer cells [178].

2.2.6.4. Quantum Dots

Quantum dots (QDs) are non-crystal semiconductors being 2-10nm in size which have a metal inner core with a narrow spectrum. Conjugated QDs with ligand or antibodies spread on the target cancer cells. These conjugated QDs have optical characteristics, large surface area, but the major drawback is their insolubility in water [180]. It is reported that exposure of QDs to MCF-7 and BT-474 cell lines produces five biomarkers ER, PR, EGFR, MTOR, and HER2 [179]. ZCIS-QDs nanoparticles have been investigated as elegant nanoprobes to target HER2+ cancer cells [181]. QDs provide new directions for emerging nanoplatforms for clinical applications [213].

2.2.6.5. Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) are *inorganic nanomaterial* with high surface area, high loading capacity, porous and modifiable surface. Due to its porous surface, it is a virtuous carrier for the drug delivery system and averts pre-maturation of medicine, specifically degradable reagents including protein or gene. Multifunctional MSNs are prepared by conjugation of poly-ethylenimine poly-lysine copolymer through disulfide bond with folate-linked polyethylene glycol (PEG). The multifunctional MSNs also encapsulate DOX into mesoporous channels carrying siRNA [182]. Aptamer conjugated MSNs form a disulfide bond through gel retardation to deliver epirubicin to breast cancer cells [214].

2.2.6.6. Carbon-based Nanoparticles

Carbon-based nanoparticles are graphene carbon nanotube and fullerene dots which replace QDs with other metal-based nanoparticles with the best mechanical, optical, and biological properties [214-216]. *Carbon nanotubes* are allotropes, benzene rings, having inner graphene sheets and cylindrical long hollow structures. There are two major types of nanotubes, single-walled (SWNPs) and multiwalled (MWNTs), for drug delivery systems [183]. By conjugation with HRR2 and Ig_Y, carbon nanotubes perform both detection and destruction in the cancer cell. Annexin V protein binds with

phospholipid and endothelial tumor-derived cell lines [217].

CNTs with oxygen perform PTX inhibitory role in BC cell proliferation by the downregulation of HCF-1α under hypoxia conditions. MWCNTs have better drug loading and target drug delivery in breast cancer treatment in terms of reduction of macrophages as well as blood vessel density [218]. MWNTS bind with glucosamine and accelerate membrane permeability with the eradication of tumor cells. The inhibition of tumor formation is directly proportional to MWNTS bonding.

In 2010, new *Carbon dots*(CDs) reported from green tea showed inhibition of cancer cells in MCF-7, MDA-MB-231, and HeLa cells of humans. Dox-CDs reduced tumor cells by lowering viability and accelerating treatment effect by accumulation to enhance the anti-tumor efficiency [184, 185].

2.2.6.7. Dendrimers and Micelles

Dendrimers are small artificial molecules like liposomes with a hydrophobic core and hydrophilic periphery. They are formed by the convergent or divergent synthesis of monomers. Micelles have a colloidal shape (5-100 nm) with a hydrophobic core and hydrophilic shell. These can allocate both water-soluble and hydrophobic drugs in therapy [186]. Micelles involve surface modification, such as surface binding for active targeting of transmembrane receptors Neuropilin -1(Np-1) in breast cancer [187]. Efficacy of Dendrimers and Micelles has been reported against MCF-7 and MDA-MB-231 cell lines.

2.2.6.8. Viral Nanoparticles

VNPs are best for uptake, penetration, and targeting as compared to liposomes. Plant-based nanoparticles possess strong beneficial activity against HER2+ cell lines [189]. Viral protein nanoparticles exhibit potential efficiency in breast cancer treatment due to their biological properties. Virus from potato accelerates the eradication of cancer and reduces the mitotic phase of BC cells with upregulation of the apoptotic factors. To overcome multiple resistance in therapies, a nano bomb-like targeting system has been recently investigated, in which antitumor drug DOX is loaded in ammunition (MTN) part that controls the unnecessary release of drug for targeted drug delivery [190].

In breast cancer treatment, nanoparticles (synthetic and viral) have offered drug delivery options to pave a new path for targeted therapeutic options. Mostly used Chemotherapeutics in breast cancer treatment that are allocated to nanoparticles are Doxorubicin (DOX), Paclitaxel (PTX), and Docetaxel (DTX) [188]. Drawbacks of nanomaterials like cellular uptake, long-term toxic effect, and excretion mechanism are needed to be investigated for future use [143]. To outweigh the benefits of nanotechnology, these challenges must be overcome [177].

2.2.7. Computational Drug Designing

The discovery of drugs without computational aid is problematic [220]. Conventional drug designing is a very lengthy and time--consuming process as it still requires a long time to introduce a new drug. Extreme side effects and toxicity of conventional drug designing can be avoided by using *in silico* approaches to introduce novel targets for drug designing [221]. Any gene that is essential to support cellular growth can perhaps be a drug target [222]. Significant advances in Bioinformatics and computational biology have contributed considerable progress in the area of drug designing. This is an era of big data with scientists using different sequence technologies for identifying new drug targets using computational approaches [223-225].

Bioinformatics enables researchers to determine the structure of a protein involved in a particular disease. In structural bioinformatics, different structural modeling and molecular docking approaches are used to determine the structure of the protein (Fig. **10**) and thus provide a framework to the medicinal chemist to design potential drugs [226-229]. Computational drug designing is a new paradigm for the treatment of breast cancer. Structural bioinformatics is very helpful to discover computationally derived inhibitors against breast cancer [230, 231] and many other diseases like neurodegenerative disorders [232, 233].

Almost 90 genes have been reported that are involved in breast cancer, but much less computational work has been done on them yet. However, there are some computationally derived inhibitors available for some gene variants of breast cancer.

BRAC1 (Breast cancer type 1 susceptibility gene) is a tumor suppressor gene that comprises 22 exons that form 200kDa protein with 1863 amino acids. The BRAC1 gene is located on q-arm of chromosome 17 at position 21.31 [234] from base pairs 43,044,295 to 43,125,364 [17]. BRCA1 protein may play a critical role in cell division, DNA repairing, and in regulating the functional ability of other genes, which help in the embryonic development of the fetus [18]. Nearly 1600 mutations have been discovered in the BRCA1 gene, and many of these mutations result in the non-functional protein. In the case of females, BRAC1 gene mutation leads to breast cancer, while in males, it results in prostate cancer [16].

BRCA2 (Breast Cancer Type 2 susceptibility gene) is another tumor suppressor gene. BRCA2 gene is located on the long q-arm of chromosome 13 at position 13.1, from base pairs 32,315,508 to 32,400,268. BRCA2 gene controls the proper cell division by monitoring different checkpoints that are involved in the cell cycle. This gene is also responsible for repairing damaged DNA that occurs as a result of various factors such as exposure to radiation, carcinogens, mutagens, environmental factors, and recombination of genetic material. The repairing of damaged DNA is accomplished by the formation of BRCA 2 proteins that interact with other proteins inside the nucleus and maintain the genetic identity of the cell. BRCA 2 gene is quite bigger than BRCA1. Recent studies have shown that 1800 mutations account for the BRCA2 gene that disrupts the functions of the protein. Olaparib (active poly (ADP-ribose polymerase (PARP)) inhibitor has been found to be effective against BRCA1/2-Malformed Protein [19]. On the computational level, more efforts are being made to target BRC1/2 interacting proteins for the development of computationally derived inhibitors.

Tp53 gene (transformation-related protein 53) is present at the short (p) arm of chromosome 17 at position 13.1 from base pairs 7,668,402 to 7,687,550 [22]. The function of this gene is to make tumor suppressor protein p53 which helps in the regulation of cell cycle and DNA repair in the nucleus [23]. It also helps to prevent the proliferation of tumors by inducing cell apoptotic process [20, 21]. Due to the uniqueness in terms of the functionality of p53, it is also known as Guardian of Genome [235]. SP600125 inhibits the progression of cancerous cells by targeting the mitotic checkpoint 1 at the BC-cell line [236].

ATM gene (ataxia telangiectasia mutated) is located on 11q22.3 chromosome from base pairs 108,222,484 to 108,369,102 [25]. This gene encodes ATM-Protein, which controls the rate of cell growth and cell division in the nucleus. ATM-Protein regulates cellular development by repairing the damaged DNA and activating the repairing enzyme factory (REF). Germline and somatic mutations in ATM genes, unfortunately, lead to breast cancer [24]. However, the exact role of this gene is unknown yet. KU59403 is a potential ATM inhibitor with potency, selectivity, and solubility for breast cancer [237].

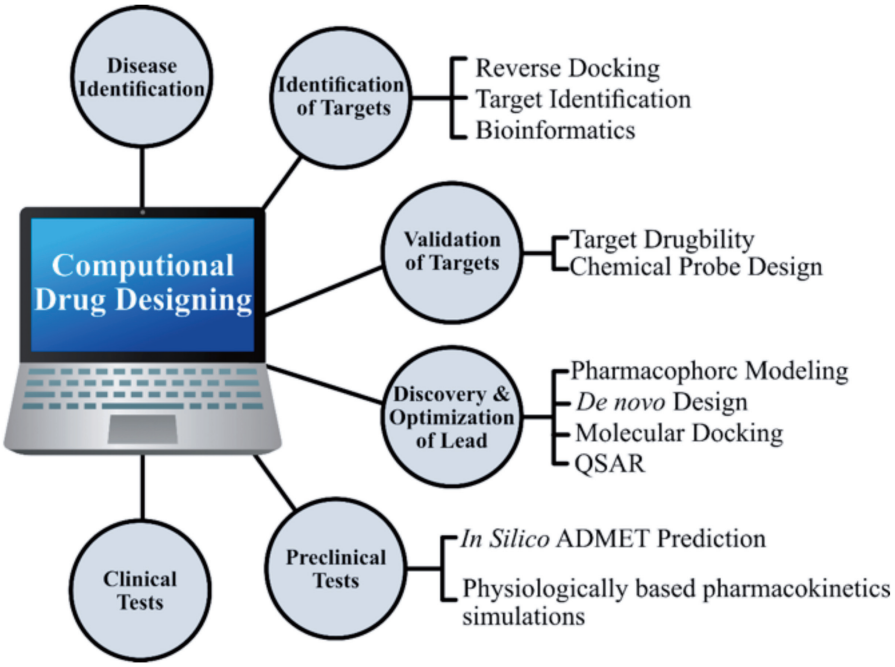

Fig. (10). Overview of computational drug designing. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

PTEN gene (protein-tyrosine phosphatase PTEN) is present on 10q23.31, from base pairs 87,863,625 to 87,971,930 on chromosome 10 [27]. PTEN gene provides instruction for making PTEN-Enzymes that perform multiple functions; for *e.g*., they act as a tumor suppressor, control the migration of cells, activate the other metabolic pathways for the regulation of cell cycle, modified fats, and protein by removing phosphate [26], and maintain the stability of cell [238]. Germline mutations in the PTEN gene lead to breast cancer which also reduces the sensitivity of genes for drugs, specifically cancer-treating drugs (Herceptin). NAUK1 is a potential inhibitor that targets the PTEN synthetic-sick or synthetic-lethal (PTEN-SSL) gene for treating PTEN deficient breast cancer [239].

LKB1/STK11 gene (serine/threonine kinase 11 (Peutz-Jeghers syndrome) is present on 19p13.3, from base pairs 1,205,778 to 1,228,431 on chromosome 19. STK11 gene encodes the instructions for the formation of an enzyme called serine/threonine kinase 11 [240]. SKT11 enzymes perform various important functions inside the cells, including regulation of cell growth, control of cell division, acting as a tumor suppressor, helping in the orientation of cell, providing energy to the cell, promoting apoptosis and the development of the fetus [28, 29]. Germline mutations in SKT11 genes activate the breast cancer process and transfer it from one generation to another. Honokiol (HNK) is a bioactive inhibitor in breast cancer that enhances the expression of the LKB1 gene to reduce the symptoms of the disease [241].

NAT1 and NAT2 are located on 8p22 loci on the short (p) arm of chromosome 8 at position 22 from base pairs 18,386,585 to 18,401,219 [33]. NAT1 and NAT2 encode an enzyme that helps in the activation of aryl-amine, hydrazine, and carcinogens. Polymorphism in NAT1 and NAT2 leads to the deposition of the drug, which converts the normal cell into a cancerous cell, specifically in breast cancer. Naphthoquinone acts as as an inhibitor to control the accumulation of the drug and also degrade the stored drug in breast tissues [32].

GSTM1 gene is found on 1p13.3 (short (p) arm of chromosome 1 at position 13.3) from base pairs 109,687,817 to 109,693,745. GSTM1 gene has two supergene families with eight classes as follows: alpha, kappa, mu, omega, pi, sigma, theta, and zeta. GSTM1 translates an enzyme glutathione S-transferase which belongs to the mu class. These enzymes are concerned with the detoxification of electrophilic compounds such as carcinogens, therapeutic drugs, and environmental toxins with the help of glutathione. This mu class gene performs crucial functions; any change in its function may lead to cancer due to malformed toxins, drugs and carcinogens. To overcome this condition, ethacrynic acid is effectively used as an anticancer inhibitor in breast cancer [34].

Much less work has been done on the above-mentioned genes. Researchers are trying to figure out pathways and possible inhibition involved in their mutated expression. Further progress like the Quantitative structure-activity relationship (QSAR) and availability of computational tools has enabled researchers to discover ligands and novel inhibitors [242-245]. Shortly, it is hoped that conventional drug designing would be replaced by computational drug designing as it has emerged as an advanced and powerful approach.

CONCLUSION

Breast cancer constitutes an alarming burden worldwide that may arise due to an increase in growth and aging of the population. This review aimed to summarize novel updates of the 20th century regarding breast cancer diagnosis and treatment. Major novel concepts discussed in the review article are computationally derived inhibitors, biomarkers, nanotechnology, and recent therapies for breast cancer diagnosis and treatment. Although chemotherapy, gene therapy and immunotherapy are possible treatment options for breast cancer treatment, at the moment, computationally derived inhibitors and nanoparticles are new strategies for prognosis and breast cancer management. Although many studies have validated these emerging technologies, still there is a need for further re-

search to figure out their efficacy and precision. Side effects of therapies must be considered before clinical application for achieving fascinating results in the future.

AUTHORS' CONTRIBUTIONS

All authors drafted the manuscript and approved the final version.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This research was funded by the Deanship of Scientific Research at Princess Nourahbint Abdulrahman University through the Fast-track Research Funding Program.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors highly acknowledge the Government College University, Faisalabad, Pakistan, for its support.

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