World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

A review of the latest research medications and information on the inflammatory, molecular, pathological, and targeted aspects of breast cancer

Ankush Biswas [1], Arup Kumar Ghosh [2], Alamin Mondal [2], Arpan Das [2], Abid Ali SK [2] and Arin Bhattacharjee [3]

[1] *Department of Pharmacology, Global College of Pharmaceutical Technology, Nadia, India-741102.*
[2] *Global College of Pharmaceutical Technology, Nadia, India-741102.*
[3] *Department of Pharmaceutical Chemistry, Global College of Pharmaceutical Technology, Nadia, India-741102*

World Journal of Biology Pharmacy and Health Sciences, 2022, 12(02), 192–204

Publication history: Received on 17 October 2022; revised on 24 November 2022; accepted on 27 November 2022

Article DOI: https://doi.org/10.30574/wjbphs.2022.12.2.0210

Abstract

Cancer is a complex illness involving a wide variety of genes and proteins regulated by various epigenetic and hereditary transcriptional alterations. Several molecular alterations characterize breast cancer (BC), one of the most lethal forms of female malignancy. As western lifestyles become more common, cities expand, and people live longer, BC's prevalence and death rate continue to rise. Despite the availability of several cutting-edge methods for diagnosing and treating BC, it continues to be the leading cause of mortality among women. The clinical, pathological, and molecular aspects of BC are all highlighted in this overview. In addition, the involvement of risk factors, biomarkers, immunotherapy, and experimental medications through tumor targets and immune systems in the treatment of BC has been discussed. BC problems and future views also detail the many techniques for tumor targeting using nanocarriers, including clinical trials of these agents.

Keywords: Breast cancer; Risk factors; Molecular facets; Targeted therapy; Inflammatory breast cancer; Metastasis; Investigational drugs

1. Introduction

Many scientists have spent the better part of the past few decades trying to reduce cancer rates and fatalities throughout the world. These days, cancer is a leading cause of death in both emerging and developed nations including the United States (U.S.), Russia, Indonesia, Germany, Brazil, China, India, and many more. Despite advances in therapy and diagnostic methods, breast cancer (BC) remains the leading cause of cancer-related mortality among women (Bray et al., 2018; Godone et al., 2018; Lancaster et al., 2018). There will be an estimated 18.1 million new cases of cancer in 2018, according to data compiled by Globocan and the International Agency for Research on Cancer (IARC), with a projection of 29.5 million new cases in 2040. The specifics are shown in Fig. 1(A-C) (International Agency for Cancer Research (IACR) and World Health Organization (WHO), 2018): 2.08 million new cases of BC were recorded in 2018, and 3.05 million are projected for 2040 (Data source: Globocan 2018; http://gco.iarc.fr/). About 234,087 (11.2%) new instances of BC have been diagnosed in the United States, with 41,904 women succumbing to the disease. The numbers of cases found in China and India are around 367,900 (17.6%) and 162,468 (7.8%), respectively. According to the data, the death toll in China was around 97,972 (15.6%), while in India it was approximately 87,090 (13.9%). These numbers may be used as a proxy for future national economic performance developing the BC, and what the potential is for its future prevention and treatment (International Agency for Cancer Research; WHO; 2018).

The ducts, lobules, fatty tissues, connective tissues, lymph nodes, and blood arteries are all connected with breast cancer. Cells lining the ducts are a typical target for ductal carcinoma (DC), which is more prevalent in the BC subtype.

* Corresponding author: Ankush Biswas
Department of Pharmacology, Global College of Pharmaceutical Technology, Nadia, West Bengal, India-741102.

It may also develop in the cells of the lobules and other tissues. Differentiated ductal carcinoma is a kind of breast cancer that does not spread beyond the ducts in which it originates (Menta et al., 2018). However, invasive ductal carcinoma (IDC) spreads from the ductal or lobular tissue next to where it first began. Molecularly and clinically, BC is extremely transformative, resulting in morphological and histological change. The majority of breast cancers (70-80%) are found in the ductal and infiltrative carcinomas (DC and IDC), yet these cancers are not a single entity but rather exhibit heterogeneity in their morphology, molecular biology, and prognosis. DNA, mitochondria, lipids, and proteins may all change BC, linking the disease to mutations at the genetic level (Provenzano et al., 2018).

Surgery, chemotherapy, radiation treatment, and hormone replacement therapy are only a few of the major modalities used to treat breast cancer. Through their potential use in detection, diagnosis, and prognosis, biomarkers or molecular markers have emerged as essential tactics in the fight against BC. DNA sequences or codes are the results.

Figure 1 Worldwide rates of (A) the 10 most frequent malignancies, (B) breast cancer, and (C) breast cancer mortality among women of all ages. [Found at http:// gco.iarc.fr/] (Globocan, 2018)

Have value for BC administration or BC. Triple-negative breast cancer (TNBC) is a subtype of BC for which biomarkers are very useful (Chang et al., 2018).

The purpose of BC therapy is to alleviate symptoms and lengthen lives by boosting the response rate and advancing the disease. Remission rates are rising rapidly as a result of enhanced treatment effectiveness and patient compliance made possible by the availability of modern tools for detecting tumors and cancers at an earlier stage in conjunction with an upgraded drug therapy system. This is an area where the tailored method, a potent system for targeting tumors and

tissues with enhanced therapeutic effectiveness and bioavailability, might make its mark as a first mover (Miele et al., 2009; Chi et al., 2018).

Smart nanosystems based on nanotechnology have been among the first to identify cancer genetic markers, which might aid in the efficient targeting of BC. By interacting with inputs in one of two ways—by changing their properties or conformational structures—responsive materials allow smart nanosystems to display behaviors. Scientists have been inspired by the ability of biological systems to react to stimuli and process information to create integrated nano-says-terms with the potential to offer the same function and therapeutic response (Kwon et al., 2015). The clinical, pathological, and molecular features of BC were the primary focus of this study. It also focused on certain powerful experimental medications with diverse molecular targets against BC with their clinical updates. Potential obstacles and promising directions for the effective treatment of breast cancer have also been discussed.

When cancer cells in the epidermis obstruct the lymph vessels, the breast becomes red, puffy, and heated; this condition is known as inflammatory breast cancer (IBC). St. Charles L'Enfant, a physician in the 18th century, was the first to record medical evidence of IBC in a female patient, and he noted the presence of a symptom unique to the disease: a crimson, swelled breast (Menta et al., 2018). According to the tumor's metastatic stage, IBC is classed as a high-risk, advanced form of the disease known as T4d. Its dermal diffusion without the presence of the initial population has been shown in clinical trials (Uden et al., 2015). It is believed that IBC accounts for just 2-4% of all instances of BC in the United States. The mortality rate for people with BC is 7%, yet despite the rarity of IBC, this disease is responsible for 7% of all cancer deaths. From 1973 to 2002, there was an annual increase of 1.23 to 4.35 percent in IBC diagnoses, as reported by data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER). Although the yearly incidence of BC is growing by 0.42%, the diagnosis rate has risen much more quickly. However, the prevalence of new cases of IBC in Western Africa and Egypt is excessively high (10 %). It substantiates the worldwide effort to identify the distinctive biology and clinical features of IBC (Menta et al., 2018).

The incidence of IBC is rising, notably in Caucasian women at younger ages than noninvasive BC, according to a study of Caucasian and young African-American women. Hispanic women reported an average age of 50.5 years when they were diagnosed with IBC, whereas African-American women reported an average age of 55.2 years and Caucasian women reported an average age of 58.1 years. Redness, warmth, and a thicker breast of a larger size have all been linked to IBC patients.

2. Factors Increasing the Probability of Breast Cancer

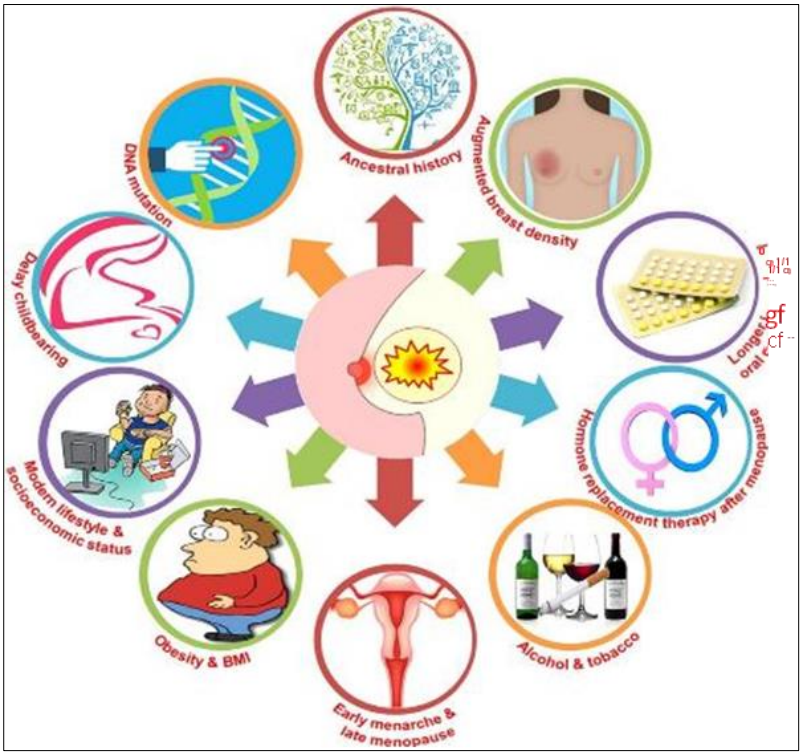

Figure 2 Risk factors of breast cancer

The BC is linked to a wide variety of potential dangers. Evidence suggests that the danger rises by a factor of two to three when ancestry goes back to BC. Cancer of the breast (BC) is caused by mutations in p53, BRCA1, and BRCA2. However, this has only been reported in a small number of BC patients. Some of the most important risk factors for breast cancer (BC) include a woman's reproductive system, including her genitalia, menstrual cycle, menopause, and childbearing. Hormones from the outside world may also play a role in causing BC. Patients who regularly take hormone treatment and birth control tablets (oral contraceptives, OC) are more likely to have adverse health effects than those who do not. Additionally, the contemporary way of life, obesity, cigarette smoking, and alcohol intake are all thought to be key risk factors in BC. The use of food and dietary supplements may contribute to the observed differences in the prevalence of BC between industrialized and developing countries. (Fig. 2) depicts many indicators associated with an increased risk of developing BC (International Agency for Research on Cancer (IARC), 2008; Lacey et al., 2009).

IBC is a female killer that has gained worldwide attention in recent years.

The rate at which BC is diagnosed is on the rise, not only in industrialized nations but also in the emerging nations of Asia.

In the U.S., for example,), most instances are detected at a late stage owing to a lack of knowledge and resources. There are several known risk factors for invasive breast cancer, including (a) a younger age at the first menstrual cycle and during the first birth stay compared with non-IBC, (b) pre-menopause being the primary cause in most IBC patients than the non- IBC, (c) civilization being an unbiased predictor of increased hazard for BC mortality, (d) socioeconomic reputation being an unbiased predictor of an advanced degree at diagnosis in breast cancer, and (e) obesity and (Liu et al., 2018; Danaei et al., 2005; Peto, 2001).

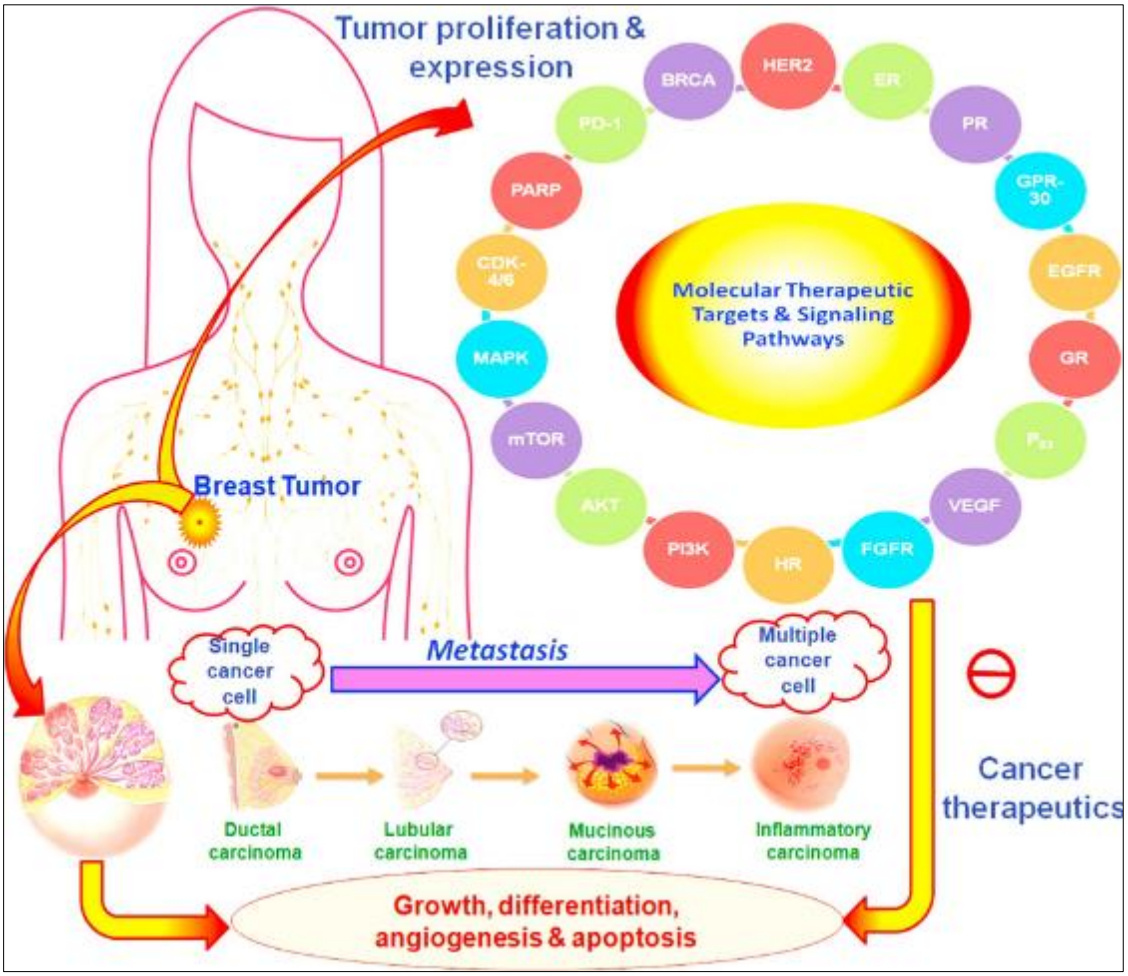

Figure 3 Molecular therapeutics targeting and signaling pathways in breast cancer

3. The invasion of breast cancer cells

The process of cell invasion is an innate route of the cellular system that involves the migration of cells inside tissues and the modification of cellular structures (extracellular matrix, ECM) to construct, renovate, and protect tissues through immunological development. In the event of a cancer cell, however, this pathway may become aberrantly controlled, leading to invasion of lymphatic vessels, tissues, blood, and so on. Metastasis refers to the spread of cancer beyond its original site as a result of the infiltration of malignant cells into surrounding normal tissues (see Fig. 3). Cancer and other fatal illnesses arise from this process of metastasis. This process is lethal, accounting for more than 90% of all deaths in humans; as such, it has been identified as a key area for therapeutic intervention. Drug targeting to specific cells or tissues remains difficult, even though several molecular targets of cancer cell invasion hav been identified via research (Veiseh et al., 2011).

Among the most prevalent malignancies, dependent BC is the most frequent and lethal. Several antiestrogenic molecules, which have been studied for their potential as a therapeutic to mimic the anti-mitogenic activity of estradiol (E2), have been shown to exert their effect by binding to the ER and ER: estrogen receptor estrogen tests have been inspired by the receptor (ER) to gain insight into the E2 and antiestrogenic mechanism of chemotherapeutic drugs. One of the most successful drugs against ER+ BC is tamoxifen (Novaldex®). The nature of the promoter determines whether 4-hydroxy-tamoxifen (4-HT) acts as an antagonist or agonist upon binding with ER (Maillard et al., 2005).

4. Molecular subtypes and risk factors for breast cancer

As a system of diseases with very variable clinical manifestations, BC is not a fixed entity. For the most part, 70–80% of cancers are classified as IDC; yet, rather than being a single entity, the observable variation within IDC, coupled with tumor form, molecular mechanism, and prediction, is crucial to comprehend. Molecular, histopathological, and clinical features all contribute to the complexity of BC. A common approach for classifying tumors has been to examine their morphology and histology. There are limits to these traditional procedures; newer, more sophisticated technologies, such as molecular techniques, are expected to enhance diagnostic and classification processes. Breast cancer (BC) is a complex illness that has been subdivided into intrinsic subtypes such as luminal breast cancer, basal-like TNBC, HER2+ breast cancer (HER2+BC), and invasive lobular breast cancer (ILBMC).

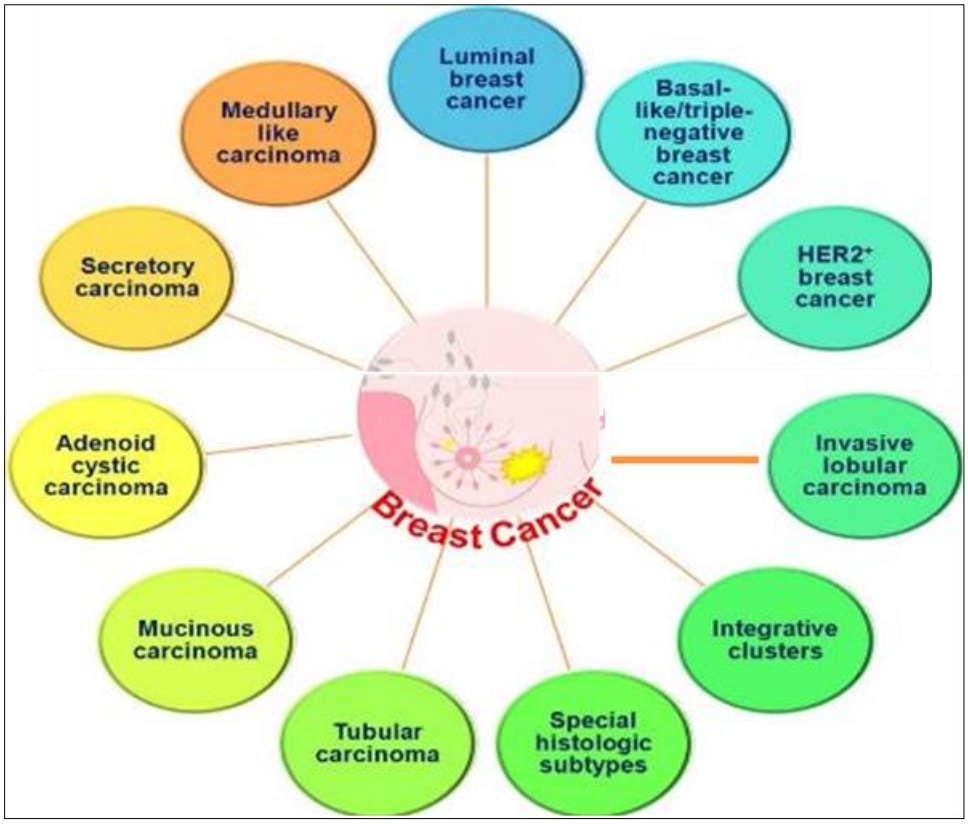

Figure 4 Molecular classification of breast cancer

Figure 4 shows several forms of cancer, including carcinoma, integrative clusters, and particular histological subtypes, as well as adenoid cystic carcinoma, tubular carcinoma, secretory carcinoma, mucinous carcinoma, and medullary like camedullary-likenzano et al., 2018).

Furthermore, 12-14% of BC cases are Claudin (ER-, claudin 3/4/7/low, vimentin+, E-cadherinlow, Zeb1+), 15-20% are basal-like (ER-, PR-, HER2-, K5/14+, EGFR+), 10-15% are HER2 enriched (HER2+, ER), normal breasts resemble (adipose tissue gene signature+), 40% are luminal A (ERHigh (ERLow, HER2Low, proliferationHigh). These molecular subtypes have distinct prognostic indices and may call for high-level clinical surveillance (Malhotra et al., 2010).

DNA alterations including gene rearrangement, mutation, and epigenetic modifications like promoter hyper-methylation cause oncogenes (growth-promoting genes) to be activated and tumor suppressor tumors (growth-inhibiting genes) to be silenced, ultimately leading to cancer. High throughput screening (HTS) tools, such as RT-PCR and the Elisa unit, have been developed to evaluate DNA copy number variations and gene expression profiles in a single test. The idea has been altered by HST, providing a new perspective on the presence of intra-tumoral variety and the chromosomal changes that underlie it (Provenzano et al., 2018; Ryu et al., 2018).

Germ-line and somatic mutations in genes, including those that trigger homology-directed repair (HDR), have been described in breast and ovarian cancer (BC). Accurate DNA repair, DNA-protein interactions, and overall cell health all depend on HDR.

Delayed replication divergences are further protected by double-strand changes, various lesions, and HDR elements. If either BRCA1 or BRCA2 is sabotaged, it greatly increases the risk of developing breast or ovarian cancer and also reduces the sensitivity of DNA-altering agents, which might impede therapy. Recent studies have given careful consideration to BRCA1 and BRCA2 and their genetic interactions with other repair mechanisms, their defense of stalled DNA replications, their effect on the response to aldehydes, and the linkages between their inactivity and the alteration of DNA signatures. The paradigm of PARP inhibitor (PARPi) in HDR-deficient cancers' response to treatment, and tumors are unable to access PARPi and other nutrients as a result of their processes, which are aided by the resistance they gain from the BRCA (Chen et al., 2018).

Molecular predictors of breast cancer recurrence after mastectomy have been revealed by Keen et al. Some post-mastectomy patients with breast cancer have participated in retrospective clinical studies. Patients' tumor samples have been shown to include potential prognostic indicators such as neurofibromatosis type 1 (NF1) and mitogen-activated protein kinase (MAPK). Inherent NF1 mutations and MAPK alterations are major contributors to BC relapse. They also noted that BC patients did not see any notable improvements.

Following having a mastectomy, the patient is undergoing adjuvant and radiation treatment. This molecular biomarker-driven approach to treating BC patients would be groundbreaking. A further benefit is that patients will need less radiation if they have this procedure (Keene et al., 2018).

5. Breast cancer's pathology and specificity

Numerous methods are used to discuss the extensive data on the clinical, pathological, and molecular features of IBC. The clinical features of IBC are used to distinguish it from other types of cancer. Inflammatory breast change (IBC) is characterized by I the transformation of a previously normal breast into a larger breast and (ii) the development of inflammatory skin changes in the breast tissue as a result of a history of cancer surgery on a breast that did not previously exhibit any signs of inflammation. Non-puerperal bacterial mastitis may be easily mistaken for IBC because of the wide variety of stimuli that both conditions respond to. It leads to delayed medical evaluation and treatment. IBC in lymph tissue from a tumor embolus leads to skin inflammation, but the inflammatory responses mediated by cells in the skin are at odds with one other (Menta et al., 2018).

5.1. Major advances in BC treatment have been made in a previous couple of decades.

Notable progress achieved throughout the globe. Several molecular signaling pathways and associated therapeutic targets in BC have been identified, which may be useful for the treatment of several malignancies, including IBC if the underlying pathology can be better understood. Ablative surgery, chemotherapy (neoadjuvant), radiation (locoregional), trastuzumab (adjuvant), and hormone therapy (adjuvant) are all ways to treat cancer (particularly non-metastatic IBC). Axillary lymph node dissection and neoadjuvant chemotherapy were used to control the spread of cancer to other lymph nodes in the body. Poor results from available therapies for IBC mean patients still only have a 30–40% chance of survival after 5 years, and their median survival time is just 2.5 years (Uden et al., 2015).

5.2. Targeted therapy is one kind of cancer treatment.

One of the most studied types of administration. Trastuzumab and tamoxifen are two examples of molecular targets and their antagonists; they block HER2+ and hormone receptor (HR) and G protein-coupled receptor 30 (GPR30) signaling, respectively. Epidermal growth factor receptor (EGFR), tumor protein 53 (P53), anaplastic lymphoma kinase, and vascular endothelial growth factor were the targets of lapatinib, INGN-201, crizotinib, and bevacizumab (VEGF). Locoregional radiation, adjuvant trastuzumab, and adjuvant hormone treatment were administered in that sequence unless the tumors were human epidermal growth factor receptor 2 (HER2) positive or estrogen receptor (ER) positive with progesterone receptor (PR) positive. This multi-pronged approach to therapy has dramatically increased patient survival rates (Uden et al., 2015).

In addition to EGFR and PD-1 (pro- grammed death-1), gram cell signaling and tumor targets include PI3K (phosphoinositide-3 kinase), CDK4/6 (cyclin-dependent kinase 4/6) (cyclin-dependent kinase 6), AKT (v-akt murine thymoma viral oncogene homolog), and mTOR (mechanistic target of rapamycin). Chemotherapeutic agents targeting these targets have been explored extensively for the treatment of IBC, and they can counteract cancer's harmful effects with minimal side effects. Targeted treatment has a major bearing on the efficient management of BC in the current era of medicine (Ju et al., 2018). Target molecules and associated signaling pathways are shown in detail in Fig. 3 and Table 1.

5.3. Molecular and biological indicators for breast cancer

Axillary lymph node metastases, tumor size, and tumor grade are all employed as prognostic indicators in the treatment of breast cancer patients. However, they have been linked to restrictions, such as repeatability and heterogeneity in tumor size and grading. As a result, its usefulness in BC management is limited by these constraints (Duffy et al., 2016, 2017). In this series, scientists are always looking for a new approach, and one promising avenue is molecular biomarkers. It can a biomarker that can be used for prognosis and prediction in BC treatment. These molecular markers include many of the features of modern diagnostic procedures, including the ability to screen for many genes at once, multiple analytes, and multiple parameters. MammaPrint, Oncotype DX, and uPA/PAI-1 are three of the most popular clinically authorized tests for predicting the outcome of a BC diagnosis (Paik et al., 2004).

The majority of its applications include the prediction of 21 RNA-level genes, while Oncotype DX is a multigene signature test based on RT-PCR. Predicting whether or not BC will return is its primary goal. Patients will be classified as high risk (RS > 30), intermediate risk (18-30), or low risk (RS 18) based on their risk recurrence score (RS). MammaPrint is a molecular biomarker test that uses microarray technology to predict a patient's risk of BC recurrence. Evaluation of the regulatory pathways of BC, in particular those involving the 70 genes tested here, is possible with this assay. Based on the likelihood of a recurrence of BC, patients are further divided into subgroups such as those at low and high risk. In light of this, the molecular biomarker test is often employed in the treatment of malignancies such as BC. The uPA/PAI-1 test is used to assess the protein level of a BC tissue sample, and it is supported by extensive scientific validation. These biomarkers, which are based on changes in protein levels, may be used to infer the progression of BC.

The molecular biomarkers Ki67 and IHC4 are widely employed since they have been shown to have a positive economic impact. IHC4 is a panel of biomarkers used for prognosis in cancer patients. These biomarkers include Ki67, HER2, PR, and ER. These molecular indicators are all examined by analyzing cancerous tissue. However, its widespread use is constrained by the scarcity of available cancer tissue samples. Therefore, tests based on biomarkers found in the blood or circulatory system (CA15-3, TPS, and CEA) that have been validated in clinical trials are used to diagnose and treat cancer (Barzaman et al., 2020; Oloomi et al., 2020).

ER is a biomarker with diagnostic and therapeutic applications for individuals with BC. The ER status of the cancer patient may be estimated with the use of this test. Evidence suggests that estrogens may stimulate tumor development by activating regulatory components (cyclin D and MYC). Because of the estrogen receptor, estrogen may exert its effect. Because of this, we may link its antiestrogenic effect to ER concentration. It has potential in endocrine treatment as well. With this in mind, PR may be utilized as an additional predictive biomarker alongside the ER. Through its interaction with the ER chromatin binding site, it has been shown that PR is a target of estrogen and is thus considered a biomarker for an active ER. That's why it's common to practice sending newly diagnosed BC patients for an ER-PR combo-biomarker test. In addition to the ER biomarker, the HER2 biomarker is also employed in the early diagnosis of breast cancer. Multiple signaling mechanisms, including cell membrane deformation, are involved in HER2 expression. Proliferative, invasive, and metastatic effects of MAPK and PI3K/AKT. Cellular metastasis in the context of malignant diseases. Novel molecular prognostic and predictive biomarkers for the therapy of BC in newly diagnosed patients have been sought recently. Micro- RNAs (mi- RNAs), circulating tumor cells (CTCs), and circulating tumor DNA are all biomarkers seen in breast cancer (BC) tissue and peripheral blood (ctDNA). These biomarkers are cutting-edge methods

for controlling BC. Carcinoembryonic antigen (CEA), Ki-67 antigen (Ki-67), mucin (MUC), mammaglobin (MAM), proto-on-cogene (c-Myc), and cytokeratin 19 are all biomarkers that may be detected in both tissue and blood (CK19). After confirming a diagnosis of BC using the RT-PCR method, treatment may be tailored to these biomarkers (Barzaman et al., 2020; Oloomi et al., 2020).

6. Immunotherapy for breast cancer, section

Immune cells, such as lymphocytes, have been shown to infiltrate BC, and this phenomenon has therapeutic implications for malignancies with poor prognoses or poor response to standard treatments, such as triple-negative and HER2-positive BC. Tumor-linked antigens, particularly neoantigens, an immunogenic mutation, pique the immune system's interest in many types of cancer. A mutated antigen with no synonymous base pairs. The finding motivates the researcher to develop cancer vaccinations. Developing a vaccine against BC and testing it in humans has been difficult despite several recent efforts, and there are currently no promising results available (Marmé, 2016). In addition, myeloid-derived suppressor cells and regulatory T-cells found in the bloodstream that are linked with BC tissues have been identified as possible biomarkers for predicting BC in patients. Several clinical studies focusing on immune responses, in addition to those using neoadjuvant and advanced therapies for BC, have been conducted (de la Cruz-Merino et al., 2017). Cytotoxic T-lymphocytes (CD3+, CD8+, CD103, CD49a, CD69) are at the forefront of cancer immunotherapy, especially in the context of recognizing and eliminating malignant neoplastic cells (Corgnac et al., 2018). Additionally, many distinct subsets of immune cells (CD11c+, CD68+ NK, and CD20+) BC tissues have cells that express both innate and adaptive immune responses (CD4+, CD8+). These immune cells were crucial to the development of BC, and understanding their significance will aid in its treatment and control (Goff and Danforth, 2020). The Food and Drug Administration (FDA) has only just authorized a proven and effective immunotherapy for the treatment of BC. In this treatment, patients with PD-L1+ TNBC get a combination of the anti-PD-L1 antibody atezolizumab and the chemotherapy drug nab-paclitaxel. Immune cell-based therapeutic studies targeting BC are underway, with a focus on cancer stem cell (CSC) antigens, PD-L1, PD-1, and CTLA4. To combat these immune cells and treat HER+ /TNBC, researchers are exploring the use of immune checkpoint inhibitors either alone or in combination with a humanized monoclonal antibody, trastuzumab, or chemotherapy (Quaglino et al., 2020).

6.1. Third, clinical updates on breast cancer investigational medications

Discovering the impact of investigational medications and their therapeutic strategies in BC is crucial, as is identifying novel molecular targets. The National Cancer Institute (NCI), a division of the NIH in the United States (https://www.cancer.gov/) (National Institutes of Health (NIH) and National Cancer Institute (NCI), 2018; Moo et al., 2018), lists most clinical trials of experimental medications being conducted in British Columbia. Table 1 summarises the results of clinical studies aimed at preventing and treating BC. More emphasis needs to be put on the direction of adherence to medication treatment re- commendations on the community level via carrying out and interacting with network oncologists, physicians, and scientists (Barnard and Klimberg, 2017). (Barnard and Klimberg, 2017).

6.2. Concerns, and a Look Ahead, in Breast Cancer Treatment

For many countries, BC is the leading killer of women. Approximately 250,000 new instances of invasive BC are diagnosed annually in the United States. Only individuals with BC who are diagnosed at an early stage have a chance of outliving those who are diagnosed later. Thus, the use of chemotherapeutic drugs results in a lower death rate among those with BC who get an early diagnosis. The cancer-fighting chemo drugs come with their own set of problems, unfortunately. Patients with BC have a favorable subordination of the effectiveness of traditional anticancer medicines. Most conventional anticancer medicines, for instance, lack the tumor cell selectivity necessary to provide therapeutic impact. Furthermore, several cancer therapies are found to be distinctively toxic, which limits their future usage in BC treatment. Not only that, but low solubility reduces absorption and bioavailability, which in turn reduces therapeutic effectiveness. As a result, anticancer medications are used often, despite continuing adverse effects.

Poor adherence to treatment is correlated with a worse therapeutic outcome in those with BC. As of late, nanocarrier delivery systems have been developed to address these concerns. The mediated delivery method that may be useful in the treatment of BC has been the subject of much preclinical and clinical research (Tagami and Ozeki, 2017; Harwansh et al., 2019).

The future view of experimental pharmaceuticals is shifting paradigm via nanocarrier-based drug delivery technologies. The results of their clinical trials might be used as a starting point for new treatments that satisfy a need not met by currently available medications. Compared to conventional medication delivery methods, nanocarriers provide several benefits. These have the potential to shield bioactive moieties from the damaging effects of a physiological pH environment and enzyme degradation (Puri et al., 2009; Li et al., 2017; Gokce et al., 2010). For instance, bioactive

compounds like medicines, proteins, and nucleotides may be readily destroyed with the assistance of gastrointestinal enzymes, protease, and nuclease respectively. It is possible to shield bioactive compounds from enzymes by encasing them in a nanocarrier's payload. Also, nanocarriers may hide medications' undesirable qualities while keeping them active for longer. In addition, these nanocarriers may deliver drugs or bioactive chemicals directly to the location of a tumor. In this context, nanoparticles have been re-well-recognized for biological applications when near DNA or RNA and chemotherapeutic agent transport. However, the biggest problem is that they aren't biocompatible and may disrupt immune cells. More research is needed to determine whether or not nanocarriers can be used as nanomedicines in the treatment of BC (Yingchoncharoen et al., 2016; Feynman, 1959; Freitas, 1999; Gourley, 2005; Emerich and Thanos, 2007). 2007; Galindo-Rodriguez et al., 2005; Moghimi and Szebeni, 2003; Labhasetwar, 2005).

They have mastered the principles of cellular biology thanks to years of dedicated study into cancer nanotechnology. The foundation of cutting-edge research all across the globe is the elucidation of cellular processes and morphologies. Furthermore, its mile hopeful that the information obtained from a few years of scientific inquiry, especially clinical trials in anticancer-based nanoparticles might be promising in the treatment of BC patients (Singh et al., 2017; Harwansh et al., 2020). (Singh et al., 2017; Harwansh et al., 2020).

Several examples of nano-formulations that have been studied at different stages of preclinical and clinical development as potential cancer treatments are included below. Lee and colleagues have developed a method to efficiently transport paclitaxel within MCF-7 breast cancer cells using solid lipid nanoparticles. In contrast to cremophor EL-based paclitaxel formulations now available on the market, they found that this new formulation was very cytotoxic to BC cell lines (Lee et al., 2007).

According to research published in 2010, polymer-lipid hybrid nanoparticles were used to consciously create a synergy between the anticancer drugs doxorubicin and mitomycin-C. It was tested in MDA435/LCC6 human BC cells, which are resistant to many drugs. They said that, compared to when they were using the medications for free, 20-30 times fewer dosages were necessary. DNA double-strand breaks and apoptosis were used to demonstrate the mechanism of action (Shuhendler et al., 2010). Meanwhile, curcumin-loaded nanoparticles (nano-CUR6) and their pure curcumin were tested against metastatic breast cancer cell lines (MDA-MB-231). Comparative cell proliferation and clonogenic experiments have shown that nano-CUR6 has more potent anticancer effects than curcumin (Yallapu et al., 2010; Muqbil et al., 2011).

Furthermore, genistein was shown to block ATPase action. enzymes, protein kinases that target tyrosines in particular, and topoisomerase II all play roles in the recycling of phosphatidylinositol. Breast cancer prevention studies have shown that genistein may work through an estrogen receptor-mediated mechanism (Gadgeel et al., 2009; Szkudelska et al., 2011; Yamasaki et al., 2010; Ullah et al., 2011). Moreover, epigallocatechin gallate (EGCG) encapsulated nanoparticles have preserved their pharmacological activity. In the BC cell lines, MBA-MD-231, it blocked intracellular signaling mediated by hepatocyte growth factors (Barras et al., 2009; Shutava et al., 2009; Zu et al., 2009; Granja et al., 2017).

In addition, new developments in drug use have New approaches to treating cancer using data from computational biology, proteomics, and genomes being examined for patients with breast cancer. Because of this, the process is known as "repurposing" drugs. This fresh strategy has the potential to provide several promising leads in the fight against BC since it is safer, cheaper, more effective, and has fewer side effects. BC therapy options have included a wide variety of anticancer therapeutic approaches, including mitotic inhibitors, an aromatase inhibitor, a CDK4/6 inhibitor, alkylating drugs, an mTOR inhibitor, antimetabolites, and anthracyclins. It has been reported that a few leads, including abemaciclib, palbociclib, and ribociclib, can inhibit CDK4, CDK6, and aromatase. Fulvestrant is known to have CDK4 and CDK6 inhibiting activity. Tamoxifen and exemestane are reported for aromatase inhibitory activity. Histone deacetylase inhibitors like vorinostat and anti- not have been proposed. An mTOR, or mechanistic target of rapamycin, signaling pathway inhibitor, everolimus, has been described.

With some emerging novel therapeutic techniques for the treatment of breast cancer patients, prospects should be considered. For BC patients, several ground-breaking innovative techniques exist in this arena, including immunotherapy, antibody-drug conjugates, monoclonal antibodies, molecularly targeted therapy, signaling pathways, and cell cycle. Extensive research is required in this area to produce better clinical outcomes that could benefit BC patients by extending their survival and life expectancy (Nagarajan and McArdle, 2018).

7. Conclusion

Worldwide, breast cancer is recognized as a fatal condition for women. To diagnose and treat patients, a variety of techniques have been used, including biomarker-based prognostic and predictive diagnostic tests, chemotherapy, radiation, immunotherapy, and surgical methods. Traditional approaches like hormone treatment had lower

therapeutic effectiveness. Because chemotherapy has a greater ability to kill immune cells and activate an immunological response, it is still the first line of treatment in BC. However, they have several negative effects, which restrict their potential usefulness. Additionally, targeted therapy, which involves focusing on several cell signaling pathways, is thought to be an effective strategy for treating BC patients. Additionally, adjuvant chemotherapy treatment performed better than chemotherapy alone. Additionally, nanotechnology-based drug delivery systems, such as nanoparticles, are thought to be a successful method for delivering anticancer drugs to tumors since they are more effective than conventional methods.

Another strategy is biomarker/molecular markers, which are regarded as the best method for detecting and treating various malignancies, including BC. These markers, which are based on various clinically proven tests including MammaPrint, Oncotype DX, and uPA/PAI-1, may offer a useful approach to improve clinical outcomes and breast cancer patient survival rates. Additionally, the crucial function that immunotherapy plays in BC should always be given top emphasis. In-depth research with significant clinical outcomes is needed in this area.

Compliance with ethical standards

Acknowledgments

We would like to thank the different authors whose findings enabled us to write the paper

Disclosure of conflict of interest

There are no conflicts of interest listed by the authors.

Contribution statement for authors using Credit

Conceptualization, methodology, first draught writing, and investigation were all done by Ranjit K. Harwansh. Resources, Data curation, Visualization, Writing - review & editing, Rohitas Deshmukh

References

[1] Aggarwal, S., Verma, S.S., Aggarwal, S., Gupta, S.C., 2019. Drug repurposing for breast cancer therapy: old weapon for new battle. Semin. Cancer Biol. https://doi.org/10. 1016/j.semcancer.2019.09.012.

[2] Barzaman, K., Karami, J., Zarei, Z., Hosseinzadeh, A., Kazemi, M.H., Moradi-Kalbolandi, S., et al., 2020. Breast cancer: biology, biomarkers, and treatments. Int. Immunopharmacol. 84, 106535.

[3] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 68 394-4.

[4] Provenzano, E., Ulaner, G.A., Chin, S.F., 2018. 2018. Molecular classification of breast cancer. PET Clin 13, 325–328.

[5] Chang, L., Weiner, L.S., Hartman, S.J., Horvath, S., Kado, D.M., 2018. Breast cancer treatment and its effects on aging. J. Geriatr. Oncol S1879-4068:30117-6.

[6] Chen, C.C., Feng, W., Lim, P.X., Kass, E.M., Jasin, M., 2018. Homology-directed repair and the role of BRCA1, BRCA2, and related proteins in genome integrity and cancer. Annu Rev Cancer Biol 2, 313–316.

[7] Chi, Y., Xu, H., Wang, F., Chen, X., Fan, Q., 2018. ZKSCAN3 promotes breast cancer cell proliferation, migration, and invasion. Biochem. Biophys. Res. Commun. 503, 2583–2589.

[8] Corgnac, S., Boutet, M., Kfoury, M., Naltet, C., Mami-Chouaib, F., 2018. The emerging role of CD8+ tissue-resident memory T (TRM) Cells in antitumor immunity: a unique functional contribution of the CD103 integrin. Front. Immunol. 9, 1904.

[9] Cristofanilli, M., Turner, N.C., Bondarenko, I., Ro, J., Im, S.A., Masuda, N., et al., 2016. 2016. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomized controlled trial. Lancet Oncol. 17, 425–439.

[10] Danaei, G., Hoorn, S.V., Lopez, A.D., Murray, C.J., Ezzati, M., 2005. Comparative risk assessment collaborating group (cancers), Causes of cancer in the world: comparative risk assessment of nine behavioral and environmental risk factors. Lancet 366 1784-3.

[11] de la Cruz-Merino, L., Chiesa, M., Caballero, R., Rojo, F., Palazón, N., Carrasco, F.H., et al., 2017. Breast Cancer immunology and immunotherapy: current status and future perspectives. Int. Rev. Cell Mol. Biol. 331, 1–53.

[12] Duffy, M.J., O'Donovan, N., McDermott, E., Crown, J., 2016. Validated biomarkers: the key to precision treatment in patients with breast cancer. Breast 29, 192–201.

[13] Duffy, M.J., McDermott, E.W., Crown, J., 2017. Use of multiparameter tests for identifying women with early breast cancer who do not need adjuvant chemotherapy. Clin. Chem. 63 (4), 804–806.

[14] Emerich, D.F., Thanos, C.G., 2007. Targeted nanoparticle-based drug delivery and diagnosis. J. Drug Target. 15 163-3.

[15] Feynman, R., 1959. Engineering and science. California Institute of Technology. Freitas, R.A., 1999. Nanomedicine, Basic Capabilities. I Vol. Texas: Landes BioScience.

[16] Gadgeel, S.M., Ali, S., Philip, P.A., Wozniak, A., Sarkar, F.H., 2009. Genistein enhances the effect of epidermal growth factor receptor tyrosine kinase inhibitors and inhibits nuclear factor kappa B in nonsmall cell lung cancer cell lines. Cancer 115, 2165–2166.

[17] Galindo-Rodriguez, S.A., Allemann, E., Fessi, H., Doelker, E., 2005. Polymeric nano- particles for oral delivery of drugs and vaccines: a critical evaluation of in vivo stu- dies. Crit. Rev. Ther. Drug Carrier Syst. 22 419-4.

[18] Goff, S.L., Danforth, D.N., 2020. The role of immune cells in breast tissue and immunotherapy for the treatment of breast cancer. Clin. Breast Cancer. https://doi.org/ 10.1016/j.clbc.2020.06.011. In Press, Journal Pre-proof.

[19] Gokce, E.H., Ozyazici, M., Souto, E.B., 2010. Nanoparticulate strategies for effective de-livery of poorly soluble therapeutics. Ther. Deliv. 1 149-7.

[20] Gourley, P.L., 2005. A brief overview of biomicronano technologies. Biotechnol. Prog. 21, 2–10.

[21] Granja, A., Frias, I., Neves, A.R., Pinheiro, M., Reis, S., 2017. Therapeutic potential of epigallocatechin gallate nano delivery systems. Biomed Res. Int. 2017, 5813793.

[22] Harwansh, R.K., Deshmukh, R., Barkat, M.A., Rahman, M.A., 2019. Bioinspired poly- meric-based core-shell smart nano-systems. Pharm. Nanotechnol. 7 (3), 181–205.

[23] Harwansh, R.K., Bahadur, S., Deshmukh, R., Rahman, M.A., 2020. The exciting potential of nanoparticles lipidic system for effective treatment of breast cancer and clinical updates: a Translational Prospective. Curr. Pharm. Des. 26 (11), 1191–1205.

[24] International Agency for Cancer Research (IACR), World Health Organization (WHO), 2018. Globocon. Updated October 2018: http://gco.iarc.fr./today/data/factsheets/cancers/20-Breast-fact-sheet.pdf 2018; Accessed date: 10 October 2018.

[25] International Agency for Research on Cancer (IARC), 2008. World Cancer Report. Lyon; 2008.

[26] Ju, J., Zhu, A.J., Yuan, P., 2018. Progress in targeted therapy for breast cancer. Chronic Dis. Transl. Med. 4, 164–165.

[27] Keene, K.S., King, T., Hwang, E.S., Peng, B., McGuire, K.P., Tapia, C., et al., 2018.

[28] Molecular determinants of post-mastectomy breast cancer recurrence. NPJ Breast Cancer 4, 34.

[29] Kwon, E.J., Lo, J.H., Bhatia, S.N., 2015. Smart nanosystems: bio-inspired technologies that interact with the host environment. Proc. Natl. Acad. Sci. U.S.A. 112, 14460–14466.

[30] Labhasetwar, V., 2005. Nanotechnology for drug and gene therapy: the importance of understanding molecular mechanisms of delivery. Curr. Opin. Biotechnol. 16 674-0.

[31] Lacey, J.V., Kreimer, A.R., Buys, S.S., Marcus, P.M., Chang, S.C., Leitzmann, M.F., et al., 2009. Prostate, lung, colorectal and ovarian (PLCO) cancer screening trial project team, Breast cancer epidemiology according to recognized breast cancer risk factors in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial cohort. BMC Cancer 9, 84.

[32] Lancaster, R., Gulla, S., Santos, J.D.L., Umphrey, H., 2018. Breast cancer screening and optimizing recommendations. Semin. Roentgenol. 53, 280–283.

[33] Lee, M.K., Lim, S.J., Kim, C.K., 2007. Preparation, characterization and in vitro cytotoxicity of paclitaxel-loaded sterically stabilized solid lipid nanoparticles. Biomaterials 28 2137-6.

[34] Li, Z., Tan, S., Li, S., Shen, Q., Wang, K., 2017. Cancer drug delivery in the nano era: an overview and perspectives. Oncol. Rep. 38, 611–614.

[35] Liu, K., Zhang, W., Dai, Z., Wang, M., Tian, T., Liu, X., et al., 2018. Association between body mass index and breast cancer risk: evidence based on a dose-response meta-analysis. Cancer Manag. Res. 18 143-1.

[36] Maillard, S., Ameller, T., Gauduchon, J., Gougelet, A., Gouilleux, F., Legrand, P., et al., 2005. Innovative drug delivery nanosystems improve the anti-tumor activity in vitro and in vivo of anti-estrogens in human breast cancer and multiple myeloma. J. Steroid Biochem. Mol. Biol. 94 111-1.

[37] Malhotra, G.K., Zhao, X., Band, H., Band, V., 2010. Histological, molecular, and functional subtypes of breast cancers. Cancer Biol. Ther. 10 955-0.

[38] Marmé, F., 2016. Immunotherapy in breast cancer. Oncol. Res. Treat. 39 (6), 335–345.

[39] Menta, A., Fouad, T.M., Lucci, A., Le-Petross, H., Lim, B., 2018. Inflammatory breast cancer: what to know about this unique, aggressive breast cancer. Surg. Clin. North Am. 98 787-00.

[40] Miele, E., Spinelli, G.P., Miele, E., Tomao, F., Tomao, S., 2009. Albumin-bound formulation of paclitaxel (Abraxane® ABI-007) in the treatment of breast cancer. Int. J. Nanomed. Nanosurg. 4 99-5.

[41] Moghimi, S.M., Szebeni, J., 2003. Stealth liposomes and long circulating nanoparticles: critical issues in pharmacokinetics, opsonization, and protein-binding properties. Prog. Lipid Res. 42, 463–468.

[42] Moo, T.A., Sanford, R., Dang, C., Morrow, M., 2018. Overview of breast cancer therapy. PET Clin. 13 339-4.

[43] Muqbil, I., Masood, A., Sarkar, F.H., Mohammad, R.M., Azmi, A.S., 2011. Progress in nanotechnology-based approaches to enhance the potential of chemopreventive agents. Cancers (Basel) 3 428-5.

[44] National Institutes of Health (NIH), National Cancer Institute (NCI), U.S., 2018 https:// www.cancer.gov/ 2018; Accessed date: 01 August 2018.

[45] Oloomi, M., Moazzezy, N., Bouzari, S., 2020. Comparing blood versus tissue-based bio-markers expression in breast cancer patients. Heliyon 6 (4), e03728.

[46] Paik, S., Shak, S., Tang, G., Kim, C., Baker, J., Cronin, M., et al., 2004. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N. Engl. J. Med. 351 (27), 2817–2826.

[47] Peto, J., 2001. Cancer epidemiology in the last century and the next decade. Nature 411, 390–395.

[48] Puri, A., Loomis, K., Smith, B., Lee, J.H., Yavlovich, A., Heldman, E., et al., 2009. Lipid-based nanoparticles as pharmaceutical drug carriers: from concepts to clinic. Crit. Rev. Ther. Drug Carrier Syst. 26 523-0.

[49] Quaglino, E., Conti, L., Cavallo, F., 2020. Breast cancer stem cell antigens as targets for immunotherapy. Semin. Immunol. 47, 101386.

[50] Ryu, J.M., Choi, H.J., Kim, I., Nam, S.J., Kim, S.W., Yu, J., et al., 2018. Korean Hereditary Breast Cancer Study Group, Prevalence and oncologic outcomes of BRCA 1/2 mutations in unselected triple-negative breast cancer patients in Korea. Breast Cancer Res. Treat. https://doi.org/10.1007/s10549-018-5015-4.

[51] Shah, A.N., Cristofanilli, M., 2017. The growing role of CDK4/6 inhibitors in treating hormone receptor-positive advanced breast Cancer. Curr. Treat. Options Oncol. 18 (1), 6.

[52] Shim, J.S., Liu, J.O., 2014. Recent advances in drug repositioning for the discovery of new anticancer drugs. Int. J. Biol. Sci. 10 (7), 654–663.

[53] Szkudelska, K., Nogowski, L., Szkudelski, T., 2011. 2011. Resveratrol and genistein as adenosine triphosphate-depleting agents in fat cells. Metabolism 60, 720–729.

[54] Shuhendler, A.J., Cheung, R.Y., Manias, J., Connor, A., Rauth, A.M., Wu, X.Y., 2010. A novel doxorubicin-mitomycin C co-encapsulated nanoparticle formulation exhibits anti-cancer synergy in multidrug-resistant human breast cancer cells. Breast Cancer Res. Treat. 119, 255–259.

[55] Yamasaki, M., Mukai, A., Ohba, M., Mine, Y., Sakakibara, Y., Suiko, M., et al., 2010. 2010. Genistein induced apoptotic cell death in adult T-cell leukemia cells through estrogen receptors, Biosci Biotechnol. Biochem. 74, 2113–2115.

[56] Shutava, T.G., Balkundi, S.S., Lvov, Y.M., 2009. (-)-Epigallocatechin gallate/gelatin layer-by-layer assembled films and microcapsules. J. Colloid Interface Sci. 330 276-3.

[57] Tagami, T., Ozeki, T., 2017. Recent trends in clinical trials related to carrier-based drugs. J. Pharm. Sci. 106 2219-6.

[58] Uden, D.J.P.V., Laarhoven, H.W.M.V., Westenberg, A.H., de Wilt, J.H., Blanken-Peeters, C.F., 2015. Inflammatory breast cancer: an overview. Crit. Rev. Oncol. Hematol. 93 116-6.

[59] Ullah, M.F., Ahmad, A., Zubair, H., Khan, H.Y., Wang, Z., Sarkar, F.H., et al., 2011. Soy isoflavone genistein induces cell death in breast cancer cells through the mobilization of endogenous copper ions and the generation of reactive oxygen species. Mol. Nutr. Food Res. 55, 553–559.

[60] Veiseh, O., Kievit, F.M., Ellenbogen, R.G., Zhang, M., 2011. Cancer cell invasion: treatment and monitoring opportunities in nanomedicine. Adv. Drug Deliv. Rev. 63, 582–586.

[61] Yallapu, M.M., Gupta, B.K., Jaggi, M., Chauhan, S.C., 2010. Fabrication of curcumin-encapsulated PLGA nanoparticles for improved therapeutic effects in metastatic cancer cells. J. Colloid Interface Sci. 1 19-9.

[62] Yardley, D.A., Ismail-Khan, R.R., Melichar, B., Lichinitser, M., Munster, P.N., Klein, P.M., et al., 2013. Randomized phase II, double-blind, placebo-controlled study of ex- emestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. J. Clin. Oncol. 31 (17), 2128–2135.

[63] Yingchoncharoen, P., Kalinowski, D.S., Richardson, D.R., 2016. Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come. Pharmacol. Rev. 68, 701–707.

[64] Nagarajan, D., McArdle, S.E.B., 2018. 2018. The immune landscape of breast cancers. Biomedicines 6, 20.

[65] Zu, Y.G., Yuan, S., Zhao, X.H., Zhang, Y., Zhang, X.N., Jiang, R., 2009. Preparation, activity, and targeting ability evaluation in vitro on folate-mediated epigallocatechin-3- gallate albumin nanoparticles. Yao Xue Xue Bao 44 525-1.