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Drug Repurposing and Molecular Insights in the Fight Against Breast Cancer

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Breast Cancer (BC) is a complex disease with high incidence in developed countries. According to the World Health Organization (WHO), it is accounted for 11.7% of all new cancer cases worldwide in 2020, with an estimated 2.3 million new diagnosis every year. A 2.5% annual reduction in the disease mortality could prevent 2.5 million deaths worldwide between 2020 and 2040. In the current work systematic review was conducted for drugs under clinical trials or approved for treatment of BC. It was observed that many drugs were repurposed for BC treatment over the course of time even though they were originally developed for some other disease. This is called as Drug Repurposing. It is an approach that has gained significant attention in recent years as a promising alternative to traditional drug discovery, which is often costly, time-consuming, and has a high failure rate. Thirteen drugs were observed to be repurposed for BC treatment and we dig deep into their molecular background and reasons for their efficacies in BC treatment. Molecular targets of these drugs in the human system were predicted and protein interaction networks were analysed to work out the genes responsible for their repurposed events. Few genes seen in the disease progression, were BRCA1, BRCA2, PALB-2, ATM, TP53, PTEN, and HER2/neu participate in various biological pathways, such as the PI3K/Akt/mTOR and ER pathways, and biological processes such as the tumor microenvironment, epithelial-mesenchymal transition, and DNA damage response pathways. Mutations or alterations in these genes or pathways can lead to the development and progression, and understanding their roles that can help in the development of new diagnostic and therapeutic strategies. This study offers an in-silico perspective and a powerful tool to find potentially effective drugs by analysing the molecular mechanisms and signalling pathways involved in the disease progression.

Keywords: Breast Cancer; Drug Repurposing; Drug Discovery; Precision Medicine; Therapeutic Potential.

Breast Cancer (BC) stands as a prominent malignancy originating from breast lobules or the glandular milk duct epithelial cells, and it's a leading cause of global mortality [1,2]. The disease presents a significant unmet medical need and poses a substantial global health challenge. While its higher incidence in underdeveloped regions contributes to the extensive global burden, implementing effective prevention and treatment strategies can significantly improve outcomes and

survival rates for those affected. Interestingly, the prevalence of BC is noticeably higher in regions boasting elevated levels of human development [2].

Reflecting its impact, the World Health Organization (WHO) noted that breast cancer accounted for 11.7% of all new cancer cases globally in 2020, with approximately 2.3 million new diagnoses. A mere 2.5% annual reduction in breast cancer mortality could potentially prevent 2.5 million deaths worldwide between 2020 and 2040. In the United States, it remains the most diagnosed cancer among women, with an estimated 284,200 new cases of invasive cancer and 49,290 non-invasive cases projected for diagnosis in 2021. In India, there's been a recent upsurge in its incidence, with approximately 160,000 new cases diagnosed in 2020. The age-standardized rate of the disease in India is around 25 per 100,000 women, somewhat lower than the global average. However, the disease tends to affect women at a younger age in India compared to Western countries. Generally, the risk of breast cancer escalates with age, with most cases diagnosed in women over 50. A fraction, roughly 5-10% of cases, is presumed to be hereditary, attributed to genetic mutations passed down in families. In 2020, the disease accounted for approximately 2,261,419 new diagnoses and 684,996 deaths [2,3]. Routine mammogram screening is advised for women at an average risk, typically starting around age 40 or 50, based on country-specific guidelines.

Although BC often presents a poor overall survival rate, early diagnosis and proper therapy during the primary stage offer promising prospects for recovery [4]. Risk factors for disease progression typically fall into two categories: causal and non-causal. Non-causal factors include age, obesity, alcohol consumption, unhealthy diet, hormonal imbalances, irregular periods, and specific genetic or epigenetic factors, whereas causal factors are thought to stem from the presence of mutant genes [5]. Recent years have witnessed the emergence of computational analysis as a potent tool in drug repurposing research. By parsing extensive data, including genomic and proteomic information, computational analysis can unearth new drug targets and potential candidates for a myriad of diseases, including BC. This approach shows promise in saving substantial time and resources by identifying viable drug candidates that can be further evaluated in preclinical and clinical trials. The review aims to delve into drug repurposing and its potential benefits, highlighting reduced costs and shorter development timelines. It also navigates the challenges associated with conventional drug development methods and how system biology approaches can expedite the process. The study will encompass diverse approaches employed in drug repurposing, spanning from network pharmacology to systems biology modeling.

Background

Breast cancer (BC) is a complex disease that originates in the cells forming the milk-producing parts of the breast. Initially, cancer cells confine themselves within the duct or lobule without causing noticeable symptoms or spreading easily. However, with time, these cells might proliferate and intrude into nearby breast tissue, lymph nodes, or other parts of the body. It stands as the most prevalent type of cancer globally, representing the leading cause of cancer-related fatalities among women. While it can occur at any age post-puberty, the likelihood increases with age. A multitude of factors contribute to the risk of developing BC, encompassing being overweight, excessive alcohol consumption, a family history of BC, radiation exposure, certain reproductive patterns, smoking, and the use of hormone therapy post-menopause. Additionally, specific gene mutations might predispose some individuals to a higher likelihood of BC. Typically, the appearance of a painless lump or thickening in the breast serves as an initial indicator, accompanied by other signs like alterations in breast size, shape, or appearance, skin changes like dimpling or redness, abnormal nipple discharge, and more. Seeking medical attention upon noticing these changes is crucial, often requiring tests like breast imaging and tissue biopsy to determine the nature of the lump.

The repositioning of drugs, or drug repurposing, is a dynamic approach recognized for its efficiency and safety in drug research. Notably, the US NCCN reports that over half of disease-specific medications are used for purposes diverging from their original intended uses. Entities like the NCATS, part of the NIH, have invested substantial funds—$575 million—to drive efforts in exploring novel applications for existing drugs. Drug repurposing, defined by Ashburn and Thor (2004) as finding new uses outside the original

medical indication for existing drugs, represents a significantly faster, cost-effective, and safer strategy compared to developing entirely new medications [6]. Past successes in this domain, such as Aspirin transitioning from an anti-inflammatory drug in 1897 to an anti-clotting agent in 1956, and Zidovudine transforming from an anti-cancer drug in 1964 to an anti-HIV medication in 1987, underscore the potential within drug repositioning. A plethora of resources, from the Drug Repositioning Portal to scientific publications, serve as invaluable sources for information on repositioned drugs. Nevertheless, rigorous searches and thorough evaluation of data remain crucial to affirm a drug's potential for a new application suggested by a particular article. For instance, although Ceftriaxone was initially considered a potential treatment for Amyotrophic Lateral Sclerosis, subsequent studies didn't validate its efficacy. Hence, comprehensive analysis of information available through official platforms like the US FDA website and clinical trials database is imperative to appraise the outcomes from drug repositioning initiatives.

Current therapies in breast cancer treatment

According to research, cancer cure chances are greater when the disease is detected and treated early, and the adverse effects of various treatment options are understood. The death rate has undoubtedly dropped because of the numerous therapeutic approaches that have been created and refined with the passage of time and technology, and these treatments have made it easier for most cancer patients to recover [7]. Conventional treatments, however, have several limitations, and the fundamental problem with these strategies is that they are general [7]. Breast cancer treatment encompasses a range of drugs, each designed to target the disease through distinct mechanisms. Chemotherapy, a cornerstone in cancer treatment, employs various classes of drugs. Alkylating agents like Cyclophosphamide and Thiotepa damage DNA, impeding cell growth and gene expression. However, their dual response poses complexities—Cyclophosphamide, acting as an immunomodulator at lower doses and an alkylating agent at higher doses, necessitates careful dosage considerations. Anthracyclines, such as Doxorubicin and Epirubicin, intercalate with DNA, inhibiting its production, but their potential side effects require careful administration within chemotherapy regimens. Antimetabolites like 5-Fluorouracil and Methotrexate disrupt cell growth by mimicking biological molecules, hindering DNA and RNA synthesis, but their usage demands cautious management due to adverse reactions. Mitotic inhibitors, including Docetaxel and Vinblastine, halt cell division, playing vital roles in breast cancer treatment protocols.

Targeted therapies have revolutionized breast cancer treatment, providing more precise and potentially less invasive options. Palbociclib, a CDK4/6 inhibitor, impedes cells from transitioning from G1 to the S phase, significantly affecting the progression of hormone-sensitive breast cancers. Hormone therapies, designed for estrogen and progesterone receptor-positive breast cancers, include Selective Estrogen Receptor Modulators (SERMs) like Tamoxifen, Toremifene, and Raloxifene, as well as Aromatase Inhibitors such as Anastrozole, Exemestane, and Letrozole. These drugs work by either blocking the effects of estrogen or reducing its production in postmenopausal women, thereby impeding the growth of hormone-sensitive cancer cells. Selective Estrogen Receptor Degraders (SERDs) like Fulvestrant target and destroy estrogen receptors without inducing estrogen-like effects, showing promise in certain types of breast cancer. Luteinizing Hormone-Releasing Hormone (LHRH) analogs like Goserelin, initially designed for other conditions, have been repurposed for hormone-sensitive breast cancer treatment.

Another significant targeted therapy includes the mTOR Kinase Inhibitor, Everolimus, which obstructs the PI3K/AKT/mTOR pathway, crucial for cancer cell growth and survival. Its approval in advanced breast cancer cases, particularly when unresponsive to other therapies, reflects its importance in advanced disease management.

These drugs operate in diverse ways, aiming to halt cancer progression, but they also present a spectrum of potential side effects, efficacy variations among individuals, and the development of resistance over time. Treatment decisions are tailored to the patient's cancer type, stage, and health profile, striving to balance therapeutic benefits with possible adverse effects. Individualized treatment plans and ongoing research in drug development

continue to shape the landscape of breast cancer management, emphasizing the need for precision medicine and evolving treatment strategies to navigate the complexities inherent in these diverse drug treatments.

Current pharmacological options (repurposed drugs) for the treatment of Breast Cancer

The clinically authorized medications that were first prescribed for conditions other than breast cancer are covered in the section that follows. However, these medications are currently being investigated for treatment.

Alkylating Agents

These are agents that harm DNA by alkylating the guanine base, which prevents them from attaching to the complementary strand. As a result, Malignant cell development as well as gene expression is inhibited. The cell cycle is affected by the alkylating chemicals at every stage.

A well-known immuno-modulator, cyclophosphamide, inhibits regulatory T-cells and boosts T - cell with effector functions in the stroma of the carcinoma. It has a dual response, meaning that with low dosages it has an immunosuppressive effect while in higher doses, it functions as an alkylating agent wherein it destroys lymphoid and tumor cells [8,9]. BC patients often get 600 mg/m2 of cyclophosphamide intravenously (IV), along with other anti-cancer medications (Docetaxel, Paclitaxel, Doxorubicin). Healthy patients are recommended to have either 4 cycles of Cyclophosphamide and Adriamycin or 6 cycles of Cyclophosphamide, Methotrexate, and 5-fluorouracil [10,11].

Thiotepa, an N, N', N-triethylene-phosphoramide derivative, was discovered in 1953 as an inflammatory therapy for transplantation in hemophilia [12]. The medication was then recommended for solid tumors in 1959 as well as for BC in 1963 (0.3 to 0.4 mg/kg IV, repeated every 1-4 weeks) [13,14]. Patients with metastatic BC as well as those who had had a relapse after adjuvant therapy responded well to the drug combination of thiotepa, vinblastine, and Adriamycin (VATH) [15].

Anthracyclines

Anthracyclines are antibiotics that intercalate between the neighbouring DNA base pairs to create a ternary complex with DNA Topoisomerase II. In highly replicative cancer cells, the ternary complex inhibits the resealing activity of the enzyme, which prevents DNA and RNA production. Doxorubicin, daunorubicin, epirubicin, and idarubicin are a few examples of common anthracyclines. Doxorubicin was authorized for medicinal use in 1974. Additionally, it took around two decades of research for approving anthracyclines in treating cancer. After that, chemotherapy regimens that included doxorubicin (a type of anthracycline) were commonly used with different doses and schedules. Doxorubicin was given by IV injection (usual dose: 60–75 mg/m2 every 21 days) along with other drugs such as cyclophosphamide, Taxotere, and 5-fluorouracil [16]. Myocet is a type of doxorubicin that is wrapped in tiny fat bubbles without PEG, a coating that helps the drug stay longer in the body. It is used with another drug called cyclophosphamide to treat BC that has spread to other parts of the body. Myocet is only approved in Europe and Canada. Doxil is another type of doxorubicin that has PEG on its fat bubbles. It is different from Myocet [17].

Antimetabolites

Antimetabolites are drugs that interfere with the metabolism of cancer cells by mimicking important biological molecules. One of these drugs is 5-Flourouracil (5-FU), which is like uracil, a building block of DNA and RNA. 5-FU blocks an enzyme called thymidylate synthetase, which normally converts uracil to thymidine, another building block of DNA. 5-FU also gets incorporated into RNA instead of uracil, which disrupts both DNA and RNA synthesis in the cell. This affects the growth of fast-dividing cells, such as cancer cells. 5-FU was first used as a treatment for keratoacanthomas (KAs), which are skin tumors that usually heal on their own, by Klein and his team in 1962 [18]. Later, 5-FU was used to treat several cancers, including BC [19]. Every 28-day cycle, the standard medication dosage for 5-FU is 500 mg/m2 or 600 mg/m2 IV (six cycles in total). For the treatment of BC, Lokich et al. (1985) first described the administration of 5-FU together with methotrexate (M) [20]. Since then, a variety of regimens of combination treatment have been used to treat metastatic BC that include 5-FU (F) together with other medications such as doxorubicin (A), cisplatin (C), cyclophosphamide (CX), and epirubicin (E) (ECF, CMF, CAF) [21]. Other mixtures, such as 5-FU and paclitaxel in 1998 [22] together with doxorubicin and high dosage

5-FU/paclitaxel [23] were discovered to be effective in treating BC.

By attaching to the dihydrofolate reductase (DHFR) enzyme, the folate/folic acid antagonist methotrexate prevents the creation of the DNA and RNA molecules themselves. The enzyme DHFR transforms folic acid into dihydrofolate, it is then converted to tetrahydrofolate (THDF) by the enzyme thymidine synthetase. Purine and pyrimidine production is reduced in cells because of methotrexate binding to DHFR, which prevents the cell cycle from progressing through the S-phase. Methotrexate was developed in the 1940s as a substitute for folic acid, a nutrient that was lacking in the diet and leading to more cases of acute lymphoblastic leukemia (ALL), a type of blood cancer [24,25]. Jane C. Wright discovered methotrexate's ability to treat BC in 1951 [26]. Methotrexate was used as a sole cytotoxic agent for advanced therapy in the 1960s and 1970s [27]. Gianni and Bonadonna group, however, presented the first therapy with 12 cycles of CMF combination in 400 mastectomy patients with advanced cancer and positive lymph nodes in 1976, and they reported just 5.3% treatment failure with tolerable toxicity [28,29]. In actuality, the CMF program was the first-ever treatment plan for BC. Furthermore, it was discovered that CMF was still efficacious after six cycles. Methotrexate's immunosuppressive properties have been investigated for potential therapeutic use in autoimmune illnesses including rheumatoid arthritis [30]. Cyclophosphamide (600 mg/m2), methotrexate (40 mg/m2), and fluorouracil (600 mg/m2) are typically given at 6- to 8-cycle intervals during the CMF regimen.

Another pyrimidine antimetabolite is capecitabine, a prodrug for 5-FU. Capecitabine must go through three sequential enzyme reaction cascades in the gut, liver, and tumor cells to be converted to 5-FU. The enzyme that catalyzes the final conversion step is significantly expressed in cancerous cells in contrast to normal cells. As a result, the tumor-specific conversion of capecitabine to 5-FU prevents systemic exposure to 5-FU. [31]. Additionally, capecitabine is more effective than 5-FU and is safer and simpler to give. In 1998, capecitabine was initially employed to treat colon cancer [32]. Capecitabine (1250 mg/m2 orally twice daily for 14 days, followed by a 7-day break in a 21-day cycle for 8 cycles) is frequently prescribed to treat aggressive or metastatic breast tumors that are resistant to docetaxel or paclitaxel. [33]. It may be used alone or in combination with cabazitaxel [34], vinorelbine [35], or ixabepilone [36].

Gemcitabine is a chemotherapeutic agent that is tri-phosphorylated (dFdCTP) within the cell through a series of enzyme-catalyzed reactions. This dFdCTP incorporates into newly produced DNA under the guise of being an analog of cytidine, causing an irreversible mistake that prevents DNA replication and results in cell death [37,38]. Treat enteroviruses like Coxsackievirus B3 (CVB3), Larry Hertel's team at Eli Lilly and Company began producing gemcitabine in 1980. MERS-CoV, CVB3, EV71, human rhinoviruses (HRVs), HIV, hepatitis C virus (HCV), poliovirus, and influenza virus were also treated with the medicine [39,40]. After then, it underwent pre-clinical testing for its anti-tumor property. 1995 saw the FDA's approval of the medication for pancreatic cancer [41] and in 1998 for non-small lung cancer [42]. Finally, in 2004 paclitaxel and gemcitabine, a combination therapy for metastatic BC, received approval [43,44]. Some drugs are given together to treat cancer that has spread to other parts of the body when the usual drugs that contain anthracycline do not work. One of these combinations is gemcitabine and paclitaxel, which are given by IV injection on certain days of a 21-day cycle. Gemcitabine is given for 30 minutes on Days 1 and 8, and paclitaxel is given for 3 hours on Day 1 before gemcitabine. This combination is used as the first choice of treatment for this type of cancer. Other combinations that use gemcitabine with different drugs, such as vinorelbine (GemVin), cisplatin (GemCis), or capecitabine (GemCap), have also shown better results and longer survival for patients who have already received other treatments [45].

CDK4/6 Inhibitor

A CDK4/6 inhibitor called Palbociclib prevents cells from moving from the G1 to the S phase. Along with hormone therapy, Palbociclib (125 mg, 28-day cycle with aromatase inhibitor) is used as a targeted treatment for advanced and metastatic ER+/HER2 BC. Recently, either letrozole, an aromatase inhibitor, or Palbociclib was used in the open-label PALOMA clinical trials (PALOMA-1 or PALOMA-2 Trials) [46,47] or hormone treatments with fulvestrant (PALOMA-3 trails) [48]. According to phase III clinical studies

for PALOMA-3, individuals with metastatic BC are now living longer overall. Inhibiting CDK4/6 activity postpones the development of hormone treatment resistance and dramatically increases patients' progression-free survival (PFS) [49,50].

Hormone Therapy or Endocrine Therapy

Endocrine treatment is often administered for 5 to 10 years. In patients with estrogen and progesterone BC, this treatment either directly targets the synthesis of hormones (estrogen and/or progesterone) or adversely affects the functional consequences.

SERMs are drugs that block the effects of estrogen by attaching to hormone receptors in a different way. Some of these drugs have been repositioned as BC treatments, such as tamoxifen (1977), toremifene (1997), and raloxifene (2007). The oldest SERM, tamoxifen, has been used to treat early-stage BC in both pre-and post-menopausal women for more than 30 years. Only postmenopausal women with advanced BC should use tamoxifen; toremifene and raloxifene are safe, similarly effective substitutes [51,52]. Multiple Results the Raloxifene Evaluation (MORE) clinical study, which was created to treat postmenopausal women's osteoporosis, also had the other goal of assessing how well it reduced the disease risk. Raloxifene Use for the Heart (RUTH), Tamoxifen with Raloxifene Study, and Evista Continuing Outcomes (CORE) clinical studies were developed because of MORE (STAR) [53].

Only postmenopausal women get aromatase inhibitor hormone treatment to treat early-stage or late-stage ER+ BC [54]. It works by inhibiting the aromatase enzyme, which stays active in the adipose tissue of post-menopausal women or females without functioning ovaries. Thus, in post-menopausal women with BC, the aromatase inhibitor lowers the amount of oestrogen that would otherwise support the cancer cells' development. The early uses of the aromatase inhibitors (anastrozole, exemestane, and letrozole) were to stimulate the ovaries and induce ovulation in females who were infertile or had polycystic ovarian syndrome. Aromatase inhibitors were developed as an alternative to tamoxifen in postmenopausal individuals and can be used as neoadjuvant or adjuvant treatment, either alone or in combination [55].

SERDs are drugs that stop and destroy estrogen receptors without having any estrogen-like effects. Fulvestrant is an example of a SERD that has been repositioned as a BC treatment [56]. Fulvestrant is a drug that blocks and destroys estrogen receptors, which are involved in some types of BC. It was first used in 2002 as a "SERD hormone therapy" for women who had stopped having periods and had HR+ HER2 BC that had spread to other parts of the body and did not respond to regular hormone therapy [57]. It is used in conjunction with anti-PI3K/AKT/mTOR pathway medications including pictilisib (FERGI) and buparlisib, as well as CDK4/6 inhibitors like Palbociclib (PALOMA-3) and ribociclib (MONALEESA-3) (BELLE-2 and BELLE-3) [58].

The signaling system that promotes the manufacture of oestrogen in the ovaries is interfered with by luteinizing hormone-releasing hormone (LHRH) analogs, resulting in temporary menopause. Goserelin was first used to treat prostate cancer and for assisted reproduction in 1987. In 1989, goserelin was then authorized for the treatment of hormone-sensitive BC in pre-menopausal women. It can be used separately or with other hormone therapy [59]. A Phase II clinical trial is now being conducted on goserelin as an adjunct to the typical neoadjuvant treatment for patients with triple negative breast cancer. By 2023, the goserelin phase II study is expected to be finished [60].

mTOR Kinase Inhibitor

Everolimus is a drug that blocks a pathway called PI3K/AKT/mTOR that helps cancer cells grow and survive. It was first used for other types of cancer, such as pancreatic cancer in 2011, kidney cancer in 2009, and to prevent the rejection of kidney transplants in 2010. In 2012, the US FDA approved everolimus for HR+, HER2+ BC that had spread to other parts of the body and did not respond to letrozole or anastrozole, which are drugs that lower estrogen levels. This approval was based on a phase III clinical trial called "BOLERO-2" that showed that everolimus combined with exemestane, another drug that blocks estrogen, improved the outcomes of these patients.

Mitotic Inhibitor

Mitotic inhibitors are drugs that stop cell division or mitosis by affecting the microtubules that help the chromosomes move. This makes the cell cycle pause in the G2/M phase or prevents

the formation of the spindle that separates the chromosomes. Some examples of mitotic inhibitors are docetaxel, paclitaxel, and vinblastine. Docetaxel and paclitaxel make the cell cycle stop in the G2/M phase, while vinblastine stops the spindle from developing.

Docetaxel and paclitaxel are drugs that stop cell division in BC cells that are in early, advanced, or metastatic stages in women who have or have not stopped having periods. They are used as extra treatments before or after surgery, either alone or with other drugs that kill cancer cells. Paclitaxel was first found in a type of tree called pacific yew in 1971. It was used to treat a condition where the arteries become narrow again after surgery. Docetaxel and paclitaxel were first used for ovarian and prostate cancer, respectively, in 1992. After that, they were repositioned as additional drugs for BC treatment regimens. Paclitaxel was given by IV injection for 3 hours every 3 weeks for 4 times with a regimen that contained doxorubicin, another drug that stops cell division. Docetaxel was given by IV injection for 1 hour after doxorubicin and cyclophosphamide, another drug that kills cancer cells, every 3 weeks for 6 cycles [61–63]. Taxanes are drugs that are often used to treat BC that has spread to other parts of the body. Doctors around the world use different combinations of drugs that include taxanes as a normal way to treat BC [64].

A naturally occurring Vinca alkaloid called vinblastine is present in Vinca rosea, the white-flowered periwinkle. In 1958, Robert Noble and Charles T. Beer made this discovery. Vinblastine's discovery serves as a stunning illustration of serendipity in medication development. The team instead looked to assess the extract's anti-diabetic effects in rats and discovered Pseudomonas-mediated septicemia that was followed by a sharp drop in WBC and granulocytopenia. In rats treated with Vinca rosea extract, further research in this approach revealed peripheral granulocytopenia and leukopenia. Finally, they showed vinca rosea extract and vinblastine had carcinostatic action in rats with transplantable mammary adenocarcinoma and sarcoma [65,66]. In 1965, vinblastine received approval to treat lymphoma. Additionally, since the 1980s, chemotherapy for advanced and metastatic BC has included the use of vinblastine (2-4 mg/mm2 IV once weekly or every other week), mitomycin, and MVP (mitomycin C, vinblastine, and cisplatin) [67,68].

Furthermore, the study explored the biological basis behind the successful use of repurposed drugs in BC treatment. The methodology used for this is summarized below:

Methodology

Literature review

A thorough search of relevant literature on breast cancer treatment using computational analysis was conducted following PRISMA 2020 guidelines. It was achieved by searching various a list of potential repurposed drugs for breast cancer treatment based on previous studies and clinical trials were compiled. Then conducted a comprehensive literature search of the molecular targets, mechanisms of action, and clinical outcomes of these drugs in breast cancer. The various databases, including PubMed, Scopus, and Web of Science, to gather relevant literature published between 2000 and 2022. We included studies that reported the use of these drugs in breast cancer treatment and their potential anticancer properties.

Prediction of protein receptors for drugs and construction of a protein-protein interaction (PPI) networks

A bioinformatics software called as Swiss Target Prediction was used to predict the probable receptors for drugs. This information was later used to construct a PPI network of molecular targets of identified drugs for finding key nodes and interactions amongst them. Publicly available databases, such as STRING was used to construct PPI network which was further analyzed using Cytoscape.

RESULT AND DISCUSSION

The PRISMA 2020 guidelines were used to guide the systematic review process. The diagram (Fig. 2) represents a standardized approach to documenting the identification, screening, eligibility, and inclusion/exclusion of studies. A comprehensive search was conducted using various electronic databases and other sources, resulting in a total of 392 articles found. After removing duplicates, 392 articles remained for screening. The first screening process included reviewing titles and abstracts to assess for relevance, resulting in

133 articles that were eligible for full-text review. The full-text review further assessed for eligibility based on predefined inclusion and exclusion criteria, resulting in 97 articles that were included in the systematic review. A detailed description of the search strategy and inclusion/exclusion criteria can be found in the methods section.

Exploring the Efficacy and Mechanisms of Existing Drugs for Breast Cancer Treatment

BC is a type of cancer that affects the breast cells and is the main cause of death for women around the world. In the US, about half of the women who got BC did not have any known risk factors for it, except for being female and older than 40 years. The risk factors are things that can increase the chance of getting BC, such as age, weight, alcohol use, past radiation exposure, family history, reproductive history (when the first period and the first pregnancy happened), smoking, and hormone therapy after menopause. However, even if these risk factors are changed, the risk of getting BC can only be reduced by up to 30%. Some women also have inherited gene mutations that make them more likely to get BC. These are genes that have a big effect on BC risk, such as BRCA1, BRCA2, PALB-2, and others like ATM, TP53, and PTEN. Women have a higher risk than men (who get BC in about 0.5-1% of cases) [69]**.** Women who have changes in some important genes that increase their BC risk may choose to have both breasts removed to lower their risk, but this is not a choice for all women. The number of deaths and the chance of living for 5 years after diagnosis have improved lately, but this is only true for tumors that have not spread. BC that has spread to other parts of the body will affect 2.3 million women around the world in 2020 and cause 685 000 deaths. It will still be a serious health problem [70]**.** The number of deaths from BC is increasing steadily, so there is a need for a drug that can make people live longer. Most BC cases are ER+ BC, which means that the cancer cells grow when they are exposed to estrogen, a hormone. About 65% of them are also PR-positive, which means that they grow when they are exposed to progesterone, another hormone. There is another type of BC called triple-negative, which does not have receptors for estrogen or progesterone, and does not express HER2, a protein that helps cancer cells grow [71]. Various therapies have been created during the past 20 years, including chemotherapy, radiation, hormone therapy, and immunotherapy [72]. But because of the illness's development, recurrence, and treatment resistance, therapeutic failures were expected [73]. The creation of an innovative treatment strategy is necessary. Drug repurposing may therefore be a useful method for developing future therapies. Several drugs have been repurposed for the breast cancer showed in Table 1 below:

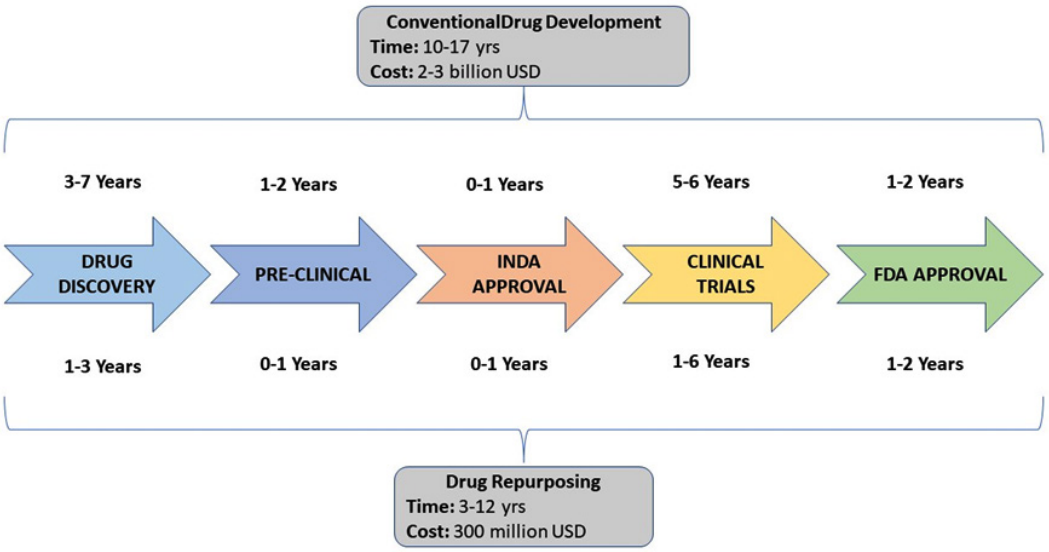

Fig. 1. The time and money comparison between the traditional medication development process and drug repurposing.

Anastrazole

Anastrazole is a drug that was used in the past to help women who could not get pregnant or who had a condition that caused many cysts in their ovaries. It is used to treat ER+ BC because it blocks the aromatase enzyme, which lowers the amount of estrogen in the body [74]. Recent research, however, alerts us to the potential for this medication to bind to ER and activate the downstream pathway of malignant development, becoming an oestrogen receptor ligand [75]. Therefore, it is crucial to do more research to better understand how anastrozole works and to show with certainty when it binds to the oestrogen receptor to develop effective

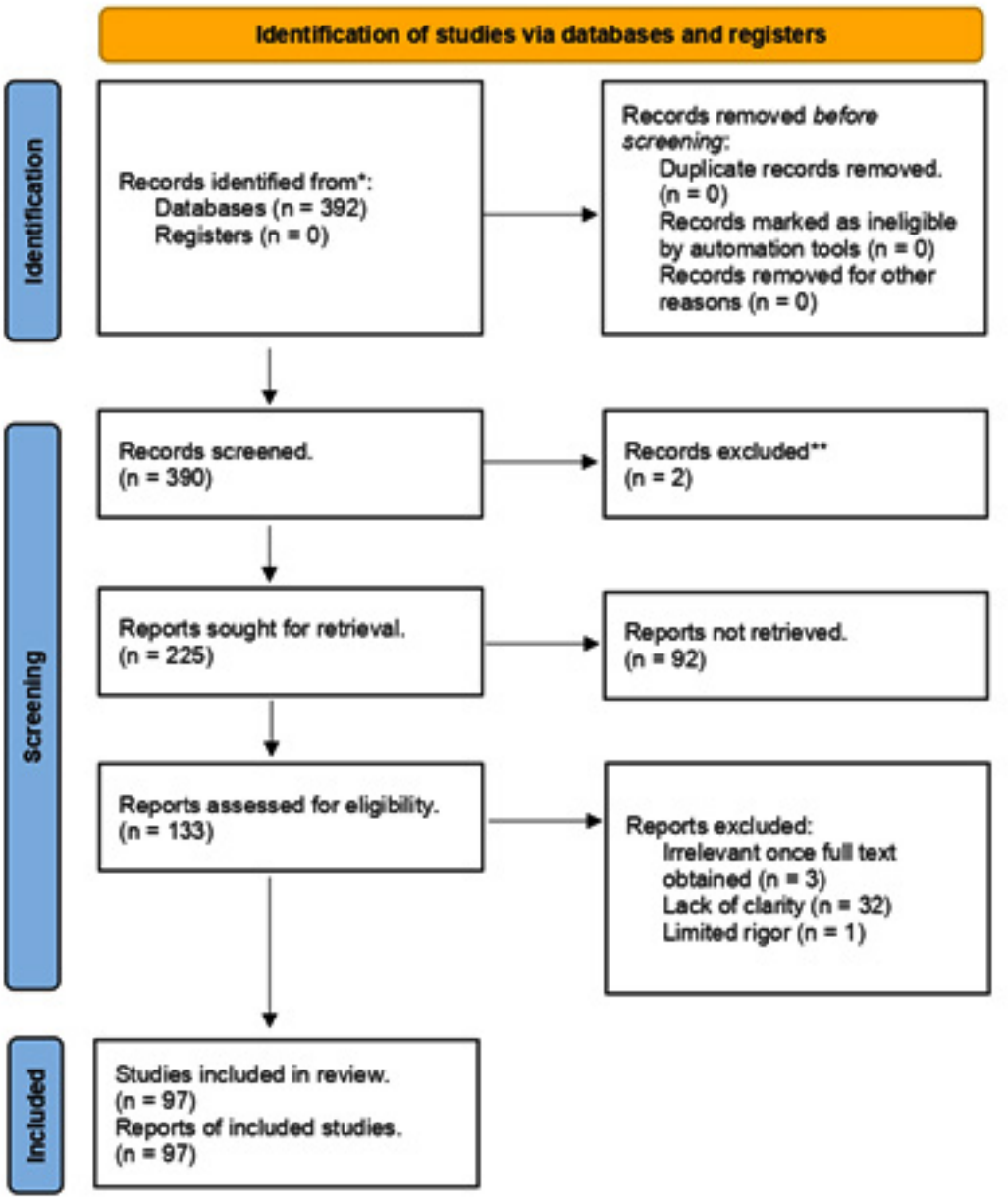

Fig. 2. PRISMA 2020 flow diagram for systematic review.

Table 1. Different drugs that have been currently evaluated for breast cancer

Name of Drug (Chemical Name)	Common Name	Drug Class	Common Side Effects
Anastrazole	Arimidex, Adova, Stazonex	Aromatase inhibitor (Phenylpropane Derivative)	Hot flashes, muscle and joint discomfort, nausea, osteoporosis, rash on the skin, and weakness
Aspirin	Ecosprin, Asprin, Loprin	NSAID's- Non-Selective COX 1&2 Inhibitors (Salicylates) (Acylsalicylic Acid Derivative)	Indigestion, a greater propensity to bleed, Nausea, stomach ache, and vomiting
Celecoxib	Zycel, Celedol, Cobix	NSAID's -Selective COX-2 Inhibitors (Pyrazole Derivative)	Symptoms of the flu, indigestion, stomach ache, Diarrhea, Edema in the legs, and flatulence
Cyclophosphamide	Endoxan N, Endoxan, Cycloxan	Alkylating agent (Nitrogen Mustard Compounds)	Fever, urine with blood, loss of hair White blood cell count decline, Vomiting, Nausea, Diarrhea
Doxorubicin (ADM)		Anthracycline Topoisomerase Inhibitor	Hives, a rash, itching, breathing difficulties, and seizures
Everolimus	Evermil, Rolimus, Rapact	Immunosuppressant- mTOR inhibitors (Macrolide Lactams)	Infection, fever, cough, exhaustion, stomatitis, otitis media, diarrhea, and upper respiratory tract illness
Fluorouracil	Flonida, Fluracil, 5FU Cbc	Antimetabolites (Pyrimidine Analog)	Weakening, vomiting, and nauseous decrease in appetite, a greater chance of infection, loss of hair Diarrhea, lower blood cells, oral ulcer Blisters on the hands or feet
Metformin	Glycomet, Glyciphage, Gluconorm	Biguanides (Biguanides Derivative)	Nausea, vomiting, a change in flavor, Diarrhea, stomach ache, reduced appetite
Nitroxoline			Nausea, headache, dizziness, anxiety, fatigue, and difficulty falling asleep
Paclitaxel	Taxonab, Intaxel, Mitotax	Antimicrotubule agents- Taxanes (Taxanes Derivatives)	Weakening, vomiting, nauseous rash, decreased blood platelets, urinary tract infection, upper respiratory tract infection Bleeding, Anemia, reduction in blood pressure, Flushing, neuropathy in the periphery loss of hair Diarrhea, White blood cell count decline
Phenfluridol	Flurilept, Penridol, Flumap	Typical Antipsychotics (Diphenylbutylpiperidine Derivatives)	Irregular voluntary motions, Constipation, tongue feeling dry increased blood prolactin levels, muscle rigidity, hypotension when standing, Sleepiness, Tremors, urinary incontinence, gaining weight
Pimozide	Atarap, Mozep, Larap	Typical Antipsychotics (Diphenylbutylpiperidine Derivatives)	Tiredness, hypoxemia when standing, tongue feeling dry irregular voluntary motions, gaining weight, increased blood prolactin levels, urinary incontinence, Constipation, muscle rigidity, strange vision, Tremor
Tamoxifen	Tamodex, Tamtero, Fineova	Selective estrogen receptor modulators (SERM)- Breast Cx (Nonsteroidal Antiestrogen)	A skin rash, hot flushes, and nausea the hair is thinning sexual dysfunction, swelling, and vaginal discharge.

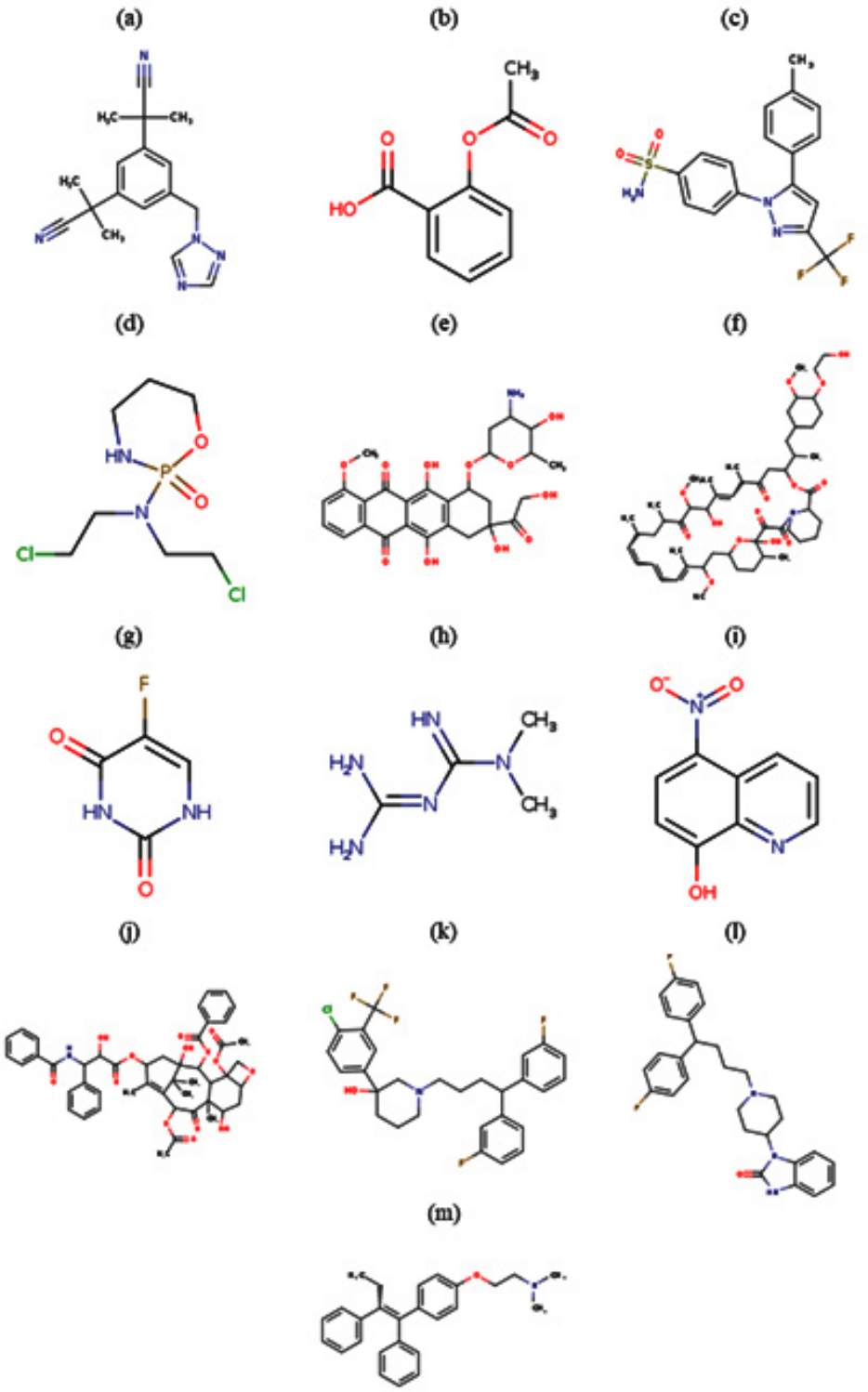

Fig. 3. Chemical structure of clinically approved drugs repurposing for breast cancer treatment. (a) Anastrozole, (b) Aspirin, (c) Celecoxib, (d) Cyclophosphamide, (e) Doxorubicin, (f) Everolimus, (g) Fluorouracil, (h) Metformin, (i) Nitroxoline, (j) Paclitaxel, (k) Penfluridol, (l) Pimozide, and (m) Tamoxifen.

Table 2. The relationship between repurposed drugs and their targeted protein classes, and the biological processes involved.

Name of Drug	Protein Classes targeted	Biological process
Anastrozole	Aromatase	Estrogen biosynthesis
	Estrogen receptor alpha	Estrogen signaling pathway
	Estrogen receptor beta	Estrogen signaling pathway
	Androgen receptor	Androgen signaling pathway
	Insulin-like growth factor-1 receptor (IGF-1R)	IGF-1 signaling pathway
	Mitogen-activated protein kinase (MAPK)	MAPK signaling pathway
	Phosphoinositide 3-kinase (PI3K)	PI3K/Akt/mTOR signaling pathway
	Mammalian target of rapamycin (mTOR)	PI3K/Akt/mTOR signaling pathway
	Cyclin-dependent kinase 4/6 (CDK4/6)	Cell cycle regulation
	Cyclin D1	Cell cycle regulation
Aspirin	COX-1	Prostaglandin synthesis
	COX-2	Prostaglandin synthesis, angiogenesis, inflammation
	NF-êB	Inflammation, cell survival, proliferation, angiogenesis
	AMPK	Energy metabolism, autophagy
	PPAR-ã	Differentiation, apoptosis
	Wnt/â-catenin	Cell proliferation, differentiation
	PI3K/Akt/mTOR	Cell survival, proliferation, angiogenesis
	STAT3	Inflammation, angiogenesis, cell survival
	P53	Cell cycle arrest, apoptosis, DNA repair
	HIF-1á	Angiogenesis, cell survival
	TGF-â	Cell differentiation, apoptosis
	NFKBIA	Inflammation, cell survival
	PTGS2	Prostaglandin synthesis, inflammation
Celecoxib	Cyclooxygenase-2 (COX-2)	Prostaglandin Pathway
	Akt	PI3K/Akt Pathway
	VEGF	Angiogenesis
	MMPs	Extracellular Matrix Remodeling
	NF-êB	Inflammation
	EGFR	EGFR Signaling Pathway
Cyclophosphamide	DNA alkylating agent	Cell cycle arrest and apoptosis
	Prodrug	Oxidative stress and DNA damage
	Alkylating agent	Inhibition of DNA synthesis and cell proliferation
	Antineoplastic agent	Induction of immunogenic cell death and anti-tumor immune response
Doxorubicin	Topoisomerase II	DNA damage and repair
	DNA intercalation	DNA damage and repair
	Free radical	Induction of apoptosis
	Iron metabolism	Induction of apoptosis
	Calcium signaling	Induction of apoptosis
	p53	Cell cycle regulation
	Bcl-2 family	Apoptosis regulation
	NF-kB	Inflammation regulation
	HER2	HER2 signaling pathway
	VEGF	Angiogenesis regulation

Everolimus	mTORC1 inhibitor	PI3K/Akt/mTOR pathway
	Ser/Thr kinase	Signal transduction
	Protein kinase	Cell cycle regulation
	Apoptosis inhibitor	Apoptosis
	Angiogenesis inhibitor	Angiogenesis
Fluorouracil	Thymidylate synthase	Pyrimidine metabolism
	Dihydropyrimidine Dehydrogenase	Pyrimidine metabolism
	Thymidine phosphorylase	Pyrimidine metabolism
	Ribonucleotide reductase	Purine and pyrimidine metabolism
	Orotate phosphoribosyltransferase	Pyrimidine metabolism
	Thymidylate phosphorylase	Pyrimidine metabolism
	Thymidine kinase	Pyrimidine metabolism
	DNA polymerase alpha	DNA replication and repair
	Tyms and FH2	Nucleotide metabolism
	5-FU enzyme complex	Nucleotide metabolism
	TS, DHFR, and TK	Pyrimidine metabolism and DNA synthesis
Metformin	AMPK	Inhibition of mTORC1, leading to reduced protein synthesis, cell growth, and proliferation
	mTORC1	Inhibition of cell proliferation and increased autophagy
	Insulin receptor	Reduction in insulin-like growth factor 1 (IGF-1) signaling and downstream effects on cell growth and survival
	PI3K/Akt/mTOR	Disruption of this pathway, which is frequently upregulated in breast cancer, leads to decreased cell proliferation and survival
	GLUT1	Reduction in glucose uptake, leading to decreased energy supply for cancer cells
Nitroxoline	Topoisomerase inhibitor	DNA replication and repair
	Anti-inflammatory agent	Inflammation
	NF-êB inhibitor	NF-êB signaling pathway
	Histone deacetylase inhibitor	Epigenetic regulation
	ROS inducer	Oxidative stress
	Iron chelator	Iron metabolism
	ERá agonist	ER signaling pathway
Paclitaxel	Microtubule stabilizers	Cell cycle arrest and apoptosis
	Tubulin	Mitotic spindle formation
	Cyclin-dependent kinase inhibitors (CDKIs)	Cell cycle regulation
	p53	DNA damage response
	Bcl-2 family proteins	Apoptosis regulation
	NF-êB	Inflammatory response regulation
	Vascular endothelial growth factor (VEGF)	Tumor angiogenesis regulation
Penfluridol	Dopamine D2 receptor antagonist	Unknown, but thought to induce apoptosis and inhibit cancer cell proliferation
	Sigma receptor agonist	Unknown, but may modulate intracellular calcium levels and affect tumor growth
	Calcium channel blocker	Unknown, but may affect calcium-dependent processes such as

		apoptosis and cell proliferation
	G protein-coupled receptor antagonist	The exact mechanism is not clear, but it may interfere with some of the pathways that help cancer cells grow and survive.
	Histone deacetylase inhibitor	Induction of cell cycle arrest, differentiation, and apoptosis
	Protein kinase C inhibitor	By altering the pathways that control how cells divide, change, and die.
	DNA topoisomerase inhibitor	Induction of DNA damage and apoptosis
	Microtubule inhibitor	Inhibition of microtubule polymerization, leading to cell cycle arrest and apoptosis
	Cholesterol biosynthesis inhibitor	By blocking the pathway that produces cholesterol, the growth of cancer cells may be slowed down or stopped.
	Glutathione S-transferase inhibitor	Modulation of cellular redox status and potential induction of apoptosis
Pimozide	Dopamine receptor antagonist	PI3K/Akt/mTOR pathway
	Calcium channel blocker	Calcium signaling pathway
	Histamine receptor antagonist	Not well-established in breast cancer
	Sigma receptor antagonist	Not well-established in breast cancer
Tamoxifen	Estrogen receptor	ER signaling pathway
	G protein-coupled receptors	MAPK/ERK signaling pathway
	Protein kinases	PI3K/Akt/mTOR signaling pathway
	Nuclear receptor co-regulators	Transcriptional regulation
	Apoptosis-related proteins	Apoptosis pathway
	Growth factor receptors	Growth factor signaling pathway
	Cyclin-dependent kinases	Cell cycle regulation
	DNA repair proteins	DNA damage response pathway

Table 3. Drugs that were tested for repurposing but did not show efficacy in the intended conditions

Name of Drug	Repurposed for	The strategy employed for repurposing	Year	Reference
Favipiravir	Coronavirus	Efforts to combat SARS-CoV-2 (In-vitro)	2020	164
Hydroxychloroquine	Coronavirus	RCTs and animal pharmacological analysis	2020	165

therapies and enhance clinical results. Some studies have found that a change in the CSMD1 gene that makes more of the CSMD1 and CYP19 proteins makes cancer cells more sensitive to anastrozole, a drug that lowers estrogen levels. Anastrozole works well for people who have the rs4646 SNP in CYP19A1, a gene that makes the CYP19 protein. It is important to know which tumors are more likely to respond to this treatment method to provide effective cancer therapy. Previous studies showed that the SNPs in CSMD1 and CYP19A1 genes could be used as indicators of how well anastrozole works [76,77].

Aspirin

Aspirin is another common medicine that has been repurposed to treat triple-negative BC [78]. When its anti-tumoral activity was discovered, aspirin's therapeutic application was further broadened. Originally intended to treat cardiovascular disorders, aspirin is an antiplatelet drug. According to certain research, consistent aspirin use lowers the incidence of the disease

[79]. It's significant to note that polymorphisms in PIK3CA have been linked to various effects of aspirin in the treatment [80]. Aspirin's ability to limit the development of cancerous cells in the breast with this gene mutation via activating the AMPK and mTORC1 inhibitory signaling pathways supplies evidence in favor of this [81]. Consequently, Henry et al. hypothesize that PI3K inhibitors and aspirin may be used in combination therapy to treat the disease. Henry and his team suggest that to make this treatment work, it is important to first group these patients based on their PI3K gene genetic profile to show who are likely to respond to this treatment [82].

Celecoxib

NSAID which is a particular COX-2 inhibitor also shows chemo-preventive potential against malignancies like colorectal and BC. Celecoxib was found to lessen the risk of the disease start and progression when taken often [83,84]. Numerous cancers, including breast, oesophageal, gastric, and liver cancers, expressed COX-2 more often. Additionally, the amount of PGE2 rose in the tumor location, which finally sparked the growth of cancer cells [85]. Additionally, it was shown that this COX-2/PGE2 induces Akt phosphorylation and aids in lowering cancer cell apoptosis [86]. On one more side, PGE2 stimulates the -catenin signaling pathway, which encourages cell mitosis and metastasis [87]. Numerous inflammatory disorders are treated with celecoxib in a big way. Numerous preclinical and clinical investigations have shown ample evidence that celecoxib improves prognosis by reducing cancer cell growth and proliferation through a variety of pathways [88]. Numerous clinical studies have showed that providing celecoxib enhances the quality and prognosis in clinical cancer patients while also preventing the development of cancer. However, it may be vital to discover which class of cancer patients it is suited for by how sensitive it is too varied populations; this must be examined [69].

By suppressing the COX-2 mediated signal axis and downstream gene targets or pathways, celecoxib may effectively restrict the spread and proliferation of cancer cells. Celecoxib's decrease of COX-2 was discovered to reduce IDO levels in BC tests, and the management of COX-2's later PGE2 also comprises preventing IDO's tryptophan synthesis (2,3-dioxygenase) (2,3-dioxygenase). Celecoxib may additionally influence the tumor microenvironment, have anti-apoptotic and anti-angiogenic actions, and aid other anti-cancer treatments to become less sensitive [89]. The suppression of Akt phosphorylation triggers the apoptotic activity, which then causes an increase in Bax levels and, finally, caspase activation to cause apoptosis [90]. Reduced VEGF levels and COX-2 suppression govern the cancer environment and help anti-angiogenic action [91]. Additionally, it has been claimed that celecoxib increases the disease sensitivity to anti-cancer treatments through the ABC pathway [92]. Celecoxib has been reported to boost the sensitivity of cancerous cells in the breast through MDR1, which oversees drug resistance, and may help in the overexpression of COX-2 [93,94]. By finding the increased methyl residues (hypermethylation) on MDR1, celecoxib decreases the production of MDR1 and limits the DNA binding element's ability to bind to transcription factors (NF-B and AP-1) (NF-B and AP-1). These transcription factors interact with MDR1, which causes drug resistance [95,96]. As a result, celecoxib creates a new opportunity for the treatment of cancer with other medications by making cancerous cells in the breast more sensitive to those medications. This gives the use of celecoxib an edge over traditional treatment.

Cyclophosphamide

An alkylating agent with a history of efficacy in immune system control is cyclophosphamide. In the tumor microenvironment, it lowers the suppressive regulatory T cells and boosts the effector T cells [74]. This medicine is being used to treat BC and other malignancies. Depending on the dosage, this medicine performs diverse activities. At lower doses, it affects immunological function; at larger quantities, it functions as an alkylating agent, producing cancer and lymphoid cell death [97]. The bioactivation of this chemotherapy drug is dependent on cytochrome P450 (CYP) enzymes. Several genes, particularly the polymorphic CYP2B6 and CYP2C19, encode these enzymes. A more detailed study is necessary to understand the roles of different variants of these genes in the response to treatment. Some of these genetic variations may result in function modification or even elimination. According to specific research, the genetic polymorphisms in the CYP2B6 (rs12721655, rs3745274, *1, *6) and

CYP2C19 (rs4244285, *1/*17/*2) genes have an influence on the drug's bioactivation and thus the efficiency of cyclophosphamide therapy. These findings suggest that cancer patients should have their genotypes checked for these gene SNPs before receiving cyclophosphamide because these variants affect how the drug is transformed into its bioactive form.

Doxorubicin (ADM)

An anti-cancer antibiotic that belongs to the anthracycline class. It was made with the use of Streptomyces peucetius var (hydroxylated congener of daunorubicin). BC, Kaposi's sarcoma, lymphoma, bladder cancer, and acute lymphocytic leukemia are among the malignancies that it has anti-cancer activity against [98]. ADM enters cells directly and is also taken up by cells via organic cation transport. SLC22A16 [99]. ADM affects tumor cells in two ways: 1) It intercalates into DNA, interfering with DNA repair by disrupting Topo-II 2) The generation of ROS damages DNA, proteins, and cell membranes [100]. The NOS3, NQO1, and XHD enzymes help doxorubicin switch back and forth between its normal and semiquinone forms. This process makes the cell produce semiquinone, which changes into doxorubicin again and lets out ROS. This ROS harms the cell by breaking down its lipids, DNA, and membrane, and triggering its self-destruction [101]. By attaching to the Sp1 site, ADM boosts the production of GCS (an enzyme that makes glucosylceramide) in breast cancer cells that have ER + receptors [102]. Doxorubicin is a better treatment than others, as many studies have shown. FTY720 helped lower the inflammation caused by the drug, making it more effective, and combining it with other drugs worked better for BC patients who were obese [103]. Patients with BC that had spread to other parts of the body had better results after getting anthracycline before the main treatment, the PLD study found [104]. According to research, combining PEGylated Liposomal Doxorubicin (PLD) with Paclitaxel and Platinum drugs works better for HER2 + patients. This type of doxorubicin is carried by liposomes, which reduce the heart damage caused by the drugs [105]. The PLD is a better drug for BC patients who need more than one treatment, because it has fewer side effects and toxicity than the current anthracycline, which can harm the heart, and it is still effective.

Everolimus

Everolimus is a medicine that has been repurposed. It was originally allowed for the treatment of renal cancer in 2009, then for the immune system's suppression during kidney transplants in 2010, and lastly for the prevention and treatment of pancreatic cancer in 2011 [74]. Everolimus is being used in the treatment of anastrozole- and letrozole-resistant metastatic BC. Everolimus displays its anti-neoplastic action via its impact on the mTOR pathway. This drug got approved by the FDA for this type of cancer in 2012. Later, it was tested with exemestane to treat HR+, HER2 advanced cancers that spread to other parts of the body and did not respond to letrozole or anastrozole. This was part of a phase III trial called "BOLERO-2", which stands for "Breast Cancer Trial of Oral Everolimus-2" [106,107]." Everolimus is processed by cytochrome enzymes, just like many other medications. More study is necessary to prove this, although some of the genes involved in its metabolism, such as the CYP3A4 (rs35599367), have been connected to a lower drug metabolic rate. Some genes, especially those related to the PI3K/AKT/mTOR pathway and the one that makes the protein transporter for the drug (ABCB1), can change how the drug is processed in the body. Some studies have found that some SNPs in these genes are linked to the side effects of everolimus, such as mucositis from ABCB1 (rs1045642), low lymphocyte count from ABCB1 (rs2032582), high blood sugar and low white blood cell count from PIK3R1 (rs10515074), and lung inflammation from RAPTOR (rs9906827) [108,109]. Therefore, to give therapies for each patient and prevent the toxicities linked to this medicine, doctors must be aware of these genetic variations.

Fluorouracil (5-FU)

5-FU is a type of heterocyclic aromatic compound that acts like the pyridine ring in DNA and RNA. It is a modified version of Uracil with a fluorine atom at the C-5 position instead of a hydrogen atom. This would be a more accurate term [110]. The US-FDA approved 5-FU as a treatment for BC patients. The disease is often treated with 5-FU. Its anti-cancer actions have been linked to numerous methods, including progression inhibition (by inhibiting the Ras/ERK pathway) and induction of apoptosis [111]. MDA-MB-231 and Tumor2 cell

lines employed in in-vitro experiments with 5-FU showed apoptotic activity and lowered levels of the H-Ras gene and its expression. Ras/ERK pathway inhibition also has an antiproliferative effect [112]. Additionally, 5-FU reduces the amount of the Rho-A gene, which lowers metastasis and apoptosis [113]. 5-FU dramatically lowered Rac1 protein expression, which is needed for cell motility, invasiveness, and anti-apoptotic activity, in Tumor2 and MDA-MB-231 cells [112]. In Tumor2, 5-FU reduced the p53 gene's expression [114]. In cancerous cells in the breast, NF-B activation is often noticed. According to research, 5-FU therapy reduced the expression of the NF-B gene, cancer cell growth, and survival [115]. According to a study, 5-FU reduced protein expression in the tumor2 cell line when compared to its equivalents. Fluorouracil has a significant advantage over currently available medications in that it reduces drug resistance in human cancer cell lines, according to several publications, where drug resistance is at its highest [115,116]. Several added studies back up these showing that fluorouracil is more effective as a treatment when NF-B expression is reduced [115]. When used in conjunction with other treatments, fluorouracil (5-FU) enhances the likelihood that tumors with medication resistance may respond [117]. Targeted treatment based on nanoparticles is used to enhance the effectiveness of 5-FU by lowering adverse effects and resistance [118]. Technology advancements have led to the creation of hydrogels (Cellulose Nanofiber-Based) coated with 5-FU, which quickly trigger pyroptosis in cancerous cells in the breast and present a new avenue for BC treatment [119]. Additionally, 5-FU has the benefit of being used by BC patients who have developed Tamoxifen resistance [120].

Metformin

A drug called N2 , N2 -dimethyl biguanide is used worldwide to treat people with type 2 diabetes [121,122]. People who took metformin for problems like obesity and diabetes had a lower risk of getting cancer, according to studies of populations [123,124]. Metformin also helps BC patients respond better and live longer with other treatments. A study that combined data from different sources found that people with DM who took metformin had up to 65% more chance of survival than those who did not use the drug [125]. Several studies look at the advantages of using metformin together with other medications to treat BC patients [126,127]. How well metformin works depends on how much metformin gets into the cell, which is controlled by OCT1 and varies in people with diabetes [128,129]. The OCT1 has in vivo anti-cancer action in cancerous cells in the breast [127]. When metformin gets into breast cancer cells through OCT1, it directly affects AMPK to maintain balance. In Triple-negative BC, metformin also stops the cell cycle, blocks the pathways that lead to cell death, and slows down the breakdown of PARP [130,131]. Metformin inhibited the mTOR, MAPK, and Akt pathways to produce its anti-apoptotic, anti-angiogenic, and antiproliferative effects [132]. Additionally, it inhibits the primary enzymes involved in the creation of cholesterol by blocking EGFR and HER 2/3. (HMGCR, HMGCS, MVD, SQLE, and LSS). It also blocks STAT3 and TGF signals, which further reduce the formation of new blood vessels, inflammation, movement, invasion, and EMT in cells [133]. Studies show that metformin reduces inflammation by lowering the levels of IL6 and TNF-, COX2, and some factors that control gene expression, such as NF-kB, STAT, Saa2 and Saa1. By reducing the expression of NF-kB, metformin can be the greatest solution for treating BC since it plays a crucial role in chemoresistance. Additionally, metformin activates SIRT1, which has many pathways for reducing inflammation and is implicated in anti-inflammatory activities [134,135]. The combination of metformin and heme was found to be effective in stopping TNBC, which is very hard to treat with existing therapies. This combo study gave us a clue on how to use metformin as an additional drug to treat cancers [136]. Shi et al., 2021 published a study showing that metformin can also suppress COX-2 expression, suggesting that it may be used in conjunction with another COX-2 inhibitor to target the COX-2 pathway. Metformin is one of the effective drugs that has advanced to the final stages of clinical trials for treating cancers of the prostate, mouth, breast, pancreas, and uterus [137]. Metformin has some benefits over the current cancer treatments, such as its stability (no change), little or no side effects, interactions with other drugs, low price, and easy availability [138].

Nitroxoline (NTX)

Chemically named 5-nitro-8-hydroxy-quinoline, this antibiotic is often used in Asian,

European, and African nations for the treatment of UTIs [139]. Because of its powerful anti-cancer properties, nitroxoline is currently garnering a lot of popularity. The initial anti-cancer action associated with nitroxoline in human bladder cancer was anti-angiogenic [140], lymphoma, glioma, leukemia, breast, bladder, pancreatic, and ovarian cancers, as well as breast, bladder, and pancreatic cancers, were among the tumors for which NTX showed potential antineoplastic effect [141,142]. According to reports, NTX decreases tumor volume in BC (60%) [143] bladder cancer growth was seen to be reduced in the orthotopic mouse model using xenografts [140]. Nitroxoline slowed down the growth, spread, and blood vessel formation of tumors in living mice that had breast cancer or fibrosarcoma models. NTX inhibits the selective and reversible cathepsin B (Cat B), which is increased in BC patients. In 2D and 3D tumor models, Cat B inhibition reduces ECM breakdown and later invasion. Nitroxoline works together with MetAP2, SIRT1, and Cat B in living organisms to prevent the formation of blood vessel-like structures by endothelial cells and greatly reduces the growth and spread of tumors [144]. According to a study, nitroxoline prevents cancer hallmarks including metastasis, angiogenesis, and invasion in in-vivo animals independent of the delivery method. Its superior pharmacokinetic profile and lack of systemic toxicity make it a more effective treatment for BC than existing regimens [144].

Paclitaxel

Another drug that has been repurposed; is paclitaxel was originally intended to treat arterial restenosis. In 1971, it experienced its first isolation from Pacific Yew. It was first used in 1992 for ovarian cancer [74]. Currently, paclitaxel is used to treat ovarian and BC as an adjuvant or neoadjuvant therapy. Its anti-tumor method involves preventing cells from going through mitosis, which lowers the pace at which cancer cells proliferate [74,145]. The genetic variability of the individuals is primarily responsible for the dispersion in the tumor response rate to paclitaxel. Some changes in the DNA of LPHN2, ROBO1, SNTG1, and GRIK1 genes may indicate that the tumor is less likely to respond to paclitaxel, according to computer-based studies. These findings are still being investigated for validation before being applied in translation [146,147].

Penfluridol (PF)/Pimozide

First-generation diphenylbutylpiperidine penfluridol is a powerful antipsychotic that was developed in 1968 by Janssen Pharmaceutical. Several types of cancer cells, such as those in the pancreas, breast, brain, and lung, can be killed by penfluridol, which works through different mechanisms. Also proved was in-vivo anti-cancer efficacy, with data proving a little alteration in animal weight and organ volume [148]. In-vitro PF treatment significantly reduced ROCK1, Rac1/2/3, Fak, Integrin 4, and Integrin 6. On therapy with penfluridol in the orthotopic model of BC, TNBC growth was reduced by 49%. Additionally, PF showed increased autophagy and apoptosis in metastatic BC and ended paclitaxel resistance [149]. Injecting penfluridol into the heart or brain of a TNBC model (4T1) reduced the spread of cancer by 90 and 72%, respectively. The creation of ROS and consequent decrease in cMyc in MDA-MB-231 and SKBR3 cells promote the anti-metastasis effect. A study found that giving PF to cells decreased their ability to withstand paclitaxel. Orthotropic apoptosis was increased in the BC model after PF treatment, which suggested a novel use for PF in Paclitaxel-resistant cancer [150]. PF antitumor action was shown in cancerous cells in the breast lines by impairing lysosomal and mitochondrial functioning [151]. PF at low doses stopped the growth of new blood vessels in living organisms and blocked the movement and formation of blood vessel-like structures of cells in the lab that were stimulated by VEGF and FGF [152]. PF at low doses (the same as those used for treating mental disorders) can reduce the formation of new blood vessels around the tumor. This can replace the current treatment that needs a high dose and has more side effects. The effects of pimozide last for up to seven days. There are no problems with taking or following the treatment, and the long-term outcomes are better than those of conventional medicines [148]. The anticancer dose may be larger than the antipsychotic dose, but the dose may still be further perfected in combination therapy. By formulation in a suitable carrier, the dosage can be reduced while potentially improving the bioavailability.

Tamoxifen (TAM)

It belongs to a class of drugs that block the effects of estrogen on the ER, forming a

stable complex that prevents ER from activating genes, stops the cell cycle at the G1 stage in breast cancer cells, and reduces their growth [153]. TAM is a medication used to treat early and advanced oestrogen receptor-positive (ER+) BC in premenopausal and postmenopausal women [154]**.** The PAX2 protein appears to be necessary for TAM to have strong anti-cancer effects. When PAX2 levels are high, the ERBB2 protein is suppressed, which causes the TAM/ER complex to exhibit antiproliferative activity [155]. In-vitro TAM boosted the expression of TGF1 and TGF2 while decreasing TGF expression [156]. Studies conducted in vivo on MCF7 xenograft mice revealed that TAM prevented BC in DMBA and NMU rats and decreased ICF-1 levels. A strong dosage of TAM in cell culture reveals BC's damaging tendency. Chronic therapy prevents carcinogenesis, which has been applied to humans when it is shown in rats [157]. In BC patient samples, it reduces proliferation and raises ER expression [156]. Tamoxifen is the most often used BC treatment because it has a 75% effectiveness rate (ER), which stabilizes cancer in around 50% of people with malignant BC who had not previously received treatment. Formulating the right carrier can supply a more effective defense against malignancies. In a cohort trial, TAM also showed promising results in males with BC, with an increase in disease-free survival (DFS) [158]. TAM lowers the incidence in women who have an elevated risk of the disease, according to the results of a five-year follow-up NSABP research. Additionally, it results in a 43% decrease in invasive BC. A further 25-year follow-up research revealed that TAM treatment was effective for patients with big, low-grade tumors who also evaluated positive for the progesterone receptor [159]. When compared to the conventional dose (20 mg), the low dose of TAM (2.5 mg) also lessens the associated adverse effects while supporting its ability to decrease tumor density [160].

Finding medications that are already being used and have also shown a link with receptors that can be a target for treating the disease were the goals of literature mining. Initially, the indicated medications were bought using the Drug Bank database [161]. It was important to figure out whether any existing pathways overlapped with the target protein classes of the existing medicines' biological processes. Results are compiled in Table 2 and were obtained using Swiss Target Prediction [162] (Supplementary file 1).

The predicted protein targets (supplementary Table 1), which belonged to different protein classes, were identified. The protein interaction networks for each drug were created using Cytoscape and the network was further analysed for protein target receptors and their associated biological pathways [163]. A few medications, including Anastrozole, Aspirin, Celecoxib, Cyclophosphamide, Doxorubicin, Everolimus, Fluorouracil, Metformin, Nitroxoline, Paclitaxel, Penfluridol, Pimozide, and Tamoxifen, were found to interact with unique protein targets.

Challenges of proposed repurposed drugs for novel applications

Drug repurposing is not always successful, several of the instances that have already been examined failed when tested for repurposing (Table 3). One aspect of all these failures in phase III seems to be common. Due to the candidates' established safety profiles, it should be less probable that these failures were caused by toxicity. Before repurposing medications, there are a variety of issues and problems that contributed to the failure of these candidates. These difficulties include organizational obstacles, patent problems, and regulatory considerations. Let's go over each of the problems with medication repurposing individually:

Regulation-Related Factors

Any drug that is repurposed must follow the regulatory standards set by regulatory bodies for any drug testing. Many repurposed drugs are evaluated according to the European Medicines Agency and undergo a common process to obtain marketing approval in all EEA member states of the European Economic Area [166]. In some cases, such as for older drugs, national approval is possible at the country level. There are different legal ways to get new therapeutic uses approved and added to the label. The main legal basis for drug applications for reprofiled drugs is Directive 2001/83/EC, including Sections 6, 8(3), 10(3), and 10(5). The researchers must provide enough pre-clinical evidence for any new indications, which can be supported by available literature references.

Patent Problems

When a patent holder's drug must be used to treat cancer, they must be given a significant

advantage. Intellectual property laws, however, prohibit the patenting of any of these alternatives. Because of the low profit potential, only charitable organizations are interested in researching these drugs. An example of this is the Repurposing Drugs in Oncology project, which is funded by drug companies in collaboration with NPO, a group of hospitals and universities that accounts for less than 5% of the total and covers about 70 drugs with 190 registered CTs [167]**.** Drugs that have been repurposed for new uses after their patents have expired may apply for a new method-of-use patent. However, this patent application process is very strict and requires a lot of evidence that the drug can treat a specific disease or condition using new, inventive dosage forms and formulations. Moreover, the main challenges to drug repurposing are patent disputes by generic drug manufacturers and market exclusivity incentives by patent holders.

Disproportionate Prescription

Theoretically, generic or reprofiled medications should be used wherever possible, and prescription medications should be provided based on scientific evidence from CT. However, by making substantial efforts in patient marketing, physician marketing, and consumer advertising, the pharmaceutical industry may have an influence on this. Because of this, patients rather than biopharma win when doctors prescribe less expensive medicines that have the same impact as more expensive medications.

The landscape of drugs used for treating breast cancer is vast and diversified, encompassing both established treatments and repurposed medications. Established drugs for breast cancer treatment typically include a range of therapies categorized into hormone-based treatments, chemotherapy, targeted therapy, and immunotherapy. Hormone-based treatments like tamoxifen, aromatase inhibitors (such as anastrozole), and selective estrogen receptor modulators (SERMs) have been cornerstones in managing hormone receptor-positive breast cancer. Chemotherapeutic agents such as anthracyclines (e.g., doxorubicin), taxanes (like paclitaxel), and antimetabolites (fluorouracil) are frequently employed for various breast cancer stages. Targeted therapies, like CDK4/6 inhibitors such as palbociclib and mTOR inhibitors like everolimus, have emerged as valuable additions to the treatment arsenal. These drugs are pivotal in targeting specific molecular pathways, controlling cell cycle progression, and inhibiting growth factors, contributing to improved outcomes in specific breast cancer subtypes. Immunotherapies are also under exploration for breast cancer, particularly in the domain of triple-negative breast cancer.

On the other hand, repurposed drugs for breast cancer treatment are medications that were initially developed and utilized for different medical conditions but have demonstrated potential efficacy in treating breast cancer. Drugs like aspirin, metformin, and nitroxoline, typically employed for different health concerns, are being reconsidered for their potential role in breast cancer management. Their repurposing arises from observations suggesting possible anti-cancer effects or supportive actions in conjunction with traditional breast cancer treatments. These repurposed drugs span various classes—ranging from NSAIDs like aspirin to antimalarials and antifungals. Their mechanisms of action often differ from the conventional breast cancer treatments, reflecting a diverse array of pathways they may influence within the cancer microenvironment. For instance, aspirin, primarily used for pain relief, shows potential in influencing inflammation and potentially impacting cancer progression.

The key distinction between established breast cancer treatments and repurposed drugs lies in their development history and primary medical indications. Established treatments undergo rigorous clinical trials and are specifically formulated for treating breast cancer, backed by substantial evidence and regulatory approval. Repurposed drugs, on the other hand, lack this direct targeting and are often used off-label or under investigation through clinical trials to assess their efficacy and safety in breast cancer. While repurposed drugs may offer the advantage of potential cost-effectiveness and established safety profiles due to their prior use, they require extensive investigation to validate their efficacy in the context of breast cancer. Both categories contribute to the evolving landscape of breast cancer treatment, with established drugs forming the cornerstone of evidence-based care, while repurposed drugs present opportunities for novel approaches and potential adjunct therapies. The efficacy, safety, and compatibility of repurposed drugs alongside

established treatments are subjects of ongoing research to ascertain their roles in optimizing breast cancer management.

CONCLUSION

The pursuit of repurposing existing drugs for breast cancer treatment presents an invaluable avenue in the realm of drug research. It offers a cost-effective and expeditious approach, significantly alleviating the burden of therapy for cancer patients. Through this process, a multitude of novel anti-breast cancer medications are being unearthed, diversifying the therapeutic arsenal. By leveraging drug repurposing, the drug development trajectory gains acceleration, promising potential in discovering cures within condensed time frames and with fewer resource allocations compared to de novo drug production. This research journey has spotlighted the promising prospect of pharmaceuticals with analogous biological and molecular mechanisms, when complementing existing therapies, showcasing encouraging effectiveness. Despite certain inherent limitations, this approach holds tremendous potential, especially when supported by in silico techniques, bolstering the identification of optimal therapeutic candidates. The integration of a comprehensive approach, involving precise protein modeling through systems biology and bioinformatics, demonstrates a high potential in formulating safer, more efficient, and economically viable chemotherapeutics for even the most severe conditions of breast cancer.

Furthermore, this pursuit necessitates a continued expansion of current pharmaceutical databases, multi-omics technologies, and bioinformatics tools through collaborative efforts among scientists, researchers, and medical professionals. This collective expansion is pivotal in fostering the development of innovative treatments, ultimately advancing the trajectory toward combatting and potentially eradicating the life-threatening grip of breast cancer. A comprehensive narrative synthesis of the findings from the selected studies is imperative. This synthesis should encapsulate a detailed depiction of the discovered drugs, their respective mechanisms of action, and their potential implications in breast cancer treatment. Additionally, such a synthesis should illuminate existing gaps in the literature, inconsistencies in findings, and areas ripe for further exploration and research. This multifaceted approach, fortified by the integration of in silico techniques and collaborative advancements, stands as a beacon of hope in the relentless pursuit of more effective, safer, and accessible treatments for breast cancer.

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Conflict of interest

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