Drug Repurposing: Potential of Antimicrobial Drugs in Breast Cancer Treatment

By

Anuradha Chakraborty
19146069

A thesis submitted to the school of pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
August 2023

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Anuradha Chakraborty

19146069

Approval

The thesis titled "Drug Repurposing: Potential of Antimicrobial Drugs in Breast Cancer Treatment" submitted by Anuradha Chakraborty, of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on August, 2023.

Supervised By:

Dr. Raushanara Akter
Professor
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

Researchers and doctors have been encouraged to repurpose currently used medications to lessen the financial burden of drug development and provide potential novel treatments because of the rising expense of drugs globally, particularly in oncology. Drug repurposing frequently causes fewer safety concerns due to the current medicines' well-established dose, safety, and toxicity profiles, which leads to faster and more successful approval of its use for new purposes. For growing resistance to the current treatments, drug repurposing represents an attractive prospect in breast cancer. It's important to note that 335 medications as repurposed drugs are now being tested in various clinical studies for their potential effects on malignancies. This review aims to provide a thorough discussion of the anti-cancer effects of antimicrobial agents and provide details on their mechanism of action. Furthermore, the challenges and potential for future development and clinical applications of current antimicrobial medications for cancer therapy are also delineated.

Keywords: Drug repurposing, antimicrobial drug, approaches, breast cancer therapy, mechanism, challenges

Dedication

This research paper is dedicated to my family who supported me to conduct this study. For the supervisor who helped me and guided me to make a final output very smoothly.

Acknowledgement

I would like to convey my heartfelt gratitude to my supervisor Dr. Raushanara Akter, Professor, School of Pharmacy for her tremendous support and assistance in the completion of my project. I would also like to thank our Dean, Professor Dr. Eva Rahman Kabir and Assistant Dean and Program Director, Professor Dr. Hasina Yasmin for their support to complete my project titled "Drug Repurposing: Potential of Antimicrobial Drugs in Breast Cancer Treatment". The completion of the project would have not been possible without their help and insights.

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List of Acronyms

BC	Breast Cancer
ReDo	Repurposing Drugs in Oncology
GIST	Gastrointestinal Stromal Tumor
BRCA	BReast CAncer Gene
PDE Inhibitor	Phosphodiesterase inhibitors
WBC	White Blood Cell
TRAIL	Tumor necrosis factor (TNF)-related apoptosis-inducing ligand
EMA	European Medicines Agency
HMG-CoA reductase	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
TNM	Tumor-Node-Metastasis
ER	Estrogen Receptor
PR+	Progesterone Receptor positive
HER2	Human Epidermal Growth Factor Receptor 2
AMPK Signal	AMP-Activated Protein Kinase Signal
mTOR	Mechanistic Target of Rapamycin
TNBC	Triple Negative Breast Cancer
ROS	Reactive Oxygen Species
CSCs	Cancer Stem Cells
EMT	Epithelial Mesenchymal Transition
SMO	Smoothened
GLI	Glioma Associated Oncogene
Hh Pathway	Hedgehog Signaling Pathway

Chapter 1: Introduction

1.1 Drug repurposing

The need for new, personalized cancer treatments has grown because of new insights into cancer diagnosis, genomic profiling, and cancer behavior. Drug repurposing is regarded as an alluring option to possibly speed up the difficult, expensive, and lengthy process of developing new cancer treatments (Roy et al., 2021). Drug repositioning, or reprofiling are two other names of repurposing procedure, which is a method for searching for new applications for an active pharmaceutical ingredient that is marketed for other therapeutic purposes (Langedijk et al., 2015; Pushpakom et al., 2018a).

To demonstrate, in the time between the 1950s and 1960s, a medication that was frequently used as a sedative to treat nausea in pregnant women, was thalidomide. But this drug was found to be the reason for severe birth defects in thousands of infants (Li & Jones, 2012). Despite its troubled history, the medication has been repurposed in recent years, and is now an approved treatment for leprosy complications and multiple myeloma (a type of blood cell cancer). Furthermore, Sunitinib is used for renal cell carcinoma, GIST, by targeting multiple kinases. Latterly, sunitinib has shown effectiveness in pancreatic neuroendocrine tumors (Li & Jones, 2012). According to these demonstrations, Drug repositioning/ repurposing is a new idea that involves using FDA-approved medications for disorders other than those for which they were originally prescribed (Langedijk et al., 2015).

A major hurdle to drug discovery is the immense cost and time required to produce novel drugs or agents (Tanoli et al., 2021). A significant number of drugs approved by FDA has decreased over the past three decades, which has increased interest in repositioning or repurposing drugs (Fiorillo et al., 2016). The focus of the current research is on cutting-edge theories and treatment options for using antifungals, anti-inflammatory, PDE inhibitors, antidiabetics,

antibiotics, antipsychotic and estrogen receptor antagonists, cardiovascular agents, Antabuse and antiparasitic as an alternative strategy for other diseases like malignancies (Kirtonia et al., 2021). Additionally, the process of development of a novel drug is time-consuming and not cheap, with little chance of success in phase III clinical trials (Roy et al., 2021). Most often, right away, discovered drugs are extremely toxic and negatively affect patients' quality of life. Globally cancer is leading causes of mortality, development of effective drugs for this deadliest disease will require a significant investment of time and money. So, drug repurposing can be an effective way for cancer treatment as previously discovered drugs have the well of pharmacokinetics and toxicology information (Kirtonia et al., 2021).

1.2 Drug repurposing in oncology

Our knowledge of the molecular causes of cancer, as well as the development of its therapy and prevention, has undergone a revolution in recent years (Schein, 2021). Over the past 20 years, the idea of personalized medicine, or targeted treatment, has expanded significantly (Li & Jones, 2012). Due to the development of effective new tailored medications, the lives of many cancer patients have been extended and improved. This method's premise is that it can treat cancer while avoiding the limitations of non-targeted therapies with minimal to no adverse effects. Sadly, despite the abundance of discovered targeted drugs, only a small number of them have the potential to be curative (Pfab et al., 2021a). The persistent incident of resistance hostile to chemotherapeutics is a substantial obstacle for pharmaceutical companies to continue searching and investing for the new lead drugs development (Pfab et al., 2021a). The development of cancer treatments with minimal adverse effects is a risky task. The cost of a novel drug development and getting into the market is over US$1 billion, and data further indicate that the gross success rate is only 10% for oncology products (Jourdan et al., 2020).

Finally, it's fascinating that more than 2000 medications have been approved globally, and that each one has an average of over six significant targets that may serve as beneficial off-targets and facilitate the development of quick, creative, safe, and reasonably priced treatments (Pfab et al., 2021a). There are undiscovered substances in the present drug supply that could have a deserved attention clinically in oncology. Recently, there have been many cases that show successful results in drug repurposing for oncology (Pfab et al., 2021a).

1.3 Role of antimicrobial drug as anticancer drugs

Immunosuppressed cancer patients are more susceptible to infection (Schein, 2021). Along with cancerous cells, important blood cells like the WBC that aid in the defense against infection are also destroyed during chemotherapy (Gonzalez-Fierro & Dueñas-González, 2021). Thus, infections are more likely to affect cancer patients. Patients often receive a combination of chemotherapeutic drugs in addition to antimicrobial agents to overcome different infections. It's interesting to note that research has frequently demonstrated that combination of antimicrobial agents and chemotherapy agents improved cancer patients' chances of surviving or their prognosis and enhanced the effect of chemotherapeutic agents (Parvathaneni et al., 2019).

Table 1: List of different classes of antimicrobial drugs (Pfab et al., 2021b)

Present different classes of antimicrobial agents	Class
Nitroxoline	Antibiotic
Ribavirin	Antiviral
Doxycycline	Antibiotic
Minocycline	Antibiotic
Ketoconazole	Antifungal
Artemisinin	Antimalarial
Ivermectin	Antiparasitic
Itraconazole	Antifungal

These different types of antimicrobial agents have an important role as a cancer therapy specially for breast cancer, colon cancer, lung cancer and some other forms of cancer. For instance, a well-known antibiotic called nitroxoline (5-nitro-8-hydroxyquinoline) is used to prevent and cure urinary tract infections (Mitrović & Kos, 2019). It's notable that combination therapy using lopinavir and ritonavir has a great ability to fight malignancy. The same combination causes apoptosis, cell viability to be downregulated, and arrest of cell cycle in cancerous cells present in the lung (Sayana & Khanlou, 2009; Xu et al., 2014). They are both antiviral drugs. Moreover, ketoconazole is an antifungal drug which is active against prostate cancer. And there is some ongoing research to evaluate the effects against breast cancer and doxycycline reduces cancer cell viability and proliferation in in vitro experiments on BC cells, and it suppresses the expression of stem cell factors (Pfab et al., 2021b).

1.4 Rationale of the study

Breast cancer is one of the most dangerous cancers in women and the main reason for mortality for female patients worldwide. For the persistent growth of resistance to drug and other deadly factors, scientists must find alternative solutions, and medication, and repurposing can be the best opportunity in oncology product development (Wang et al., 2017).

The fundamental benefit of repurposed medications is that their toxicological profiles, tolerability, pharmacokinetics, and pharmacodynamic data are already well-known and well-established (Malik et al., 2022). Furthermore, pharmacology, dose schedule, and drug interactions of existing medications are well-known. Because preclinical research and formulation are already complete, drug repurposing speeds up the transition into clinical trials while simultaneously shortening the development process and lowering expenses. Furthermore, drug repurposing frequently causes fewer safety concerns due to the current medicines' well-established dose, safety, and toxicity profiles, which leads to faster and more successful approval of its use for new purposes. That's why repurposing of drugs is a topic of particular interest, particularly in cancer (Jourdan et al., 2020). Different approaches can be utilized to find and use presently prescribed medications which can be beneficial for the treatment of cancer (Mitrović & Kos, 2019).

1.5 Aim and objectives of the study

Aim

The aim of this study is to discuss extensively about antimicrobial drugs currently undergoing various trials against breast cancer and provide an overview of their mechanism of action to understand how they work against cancer cells.

Objectives of this study are to:

- provide with the information on drug repurposing
- discuss antimicrobial agents for treating infection associated with cancer
- delineate the mechanism of antimicrobial drugs that can be potential in breast cancer therapy
- find the targets of these drugs

Chapter 2: Methodology

This review focuses on repurposing of antimicrobial drugs to treat breast cancer. Through this work I am trying to find potential antimicrobial drugs which can also be used for therapy of breast cancer. Breast cancer is one of the fatal diseases in women, which can also develop in men. And the unavailability of therapy for cancer treatment, repurposed drugs can be a blessing for cancer treatment, so for thesis writing, first I chose to do a review on this topic. Therefore, with different articles from PubMed and ScienceDirect, I search and choose which are relevant to the topic. For the articles I searched keywords like drug repurposing, breast cancer treatment and drug repurposing, development of repurposed drugs in cancer treatment, antimicrobials for cancer, different classes of medications used in cancer therapy etc. Moreover, by searching I got a good number of articles related to a topic, which around 1000 to 2500 varied from keyword to keyword. Then, from the huge number of articles, I chose several articles for my thesis writing. After that, I gathered different classes of drugs that could be a potential therapy for cancer and I chose one specific class, which is a more common option for drug repurposing without any contradictory statement. And I found some antimicrobial drugs which can be a good option for breast cancer treatment.

Chapter 3: Drug repurposing and Repurposed drugs

3.1 An overview of drug repurposing

Drug repurposing can be a promising tool in case of drug discovery and development as it takes a short period of time as well as is less expensive. A new drug discovery normally takes 10-15 years and there is less chance to develop a potential drug, especially in the case of cancer like life threatening disease (Parvathaneni et al., 2019). Thus, drug repurposing can be a blessing for different diseases where specific therapy is not available yet. Drug repurposing includes drugs that are already FDA, EMA and other regulatory bodies approved and can be indicated for other diseases (Parvathaneni et al., 2019).

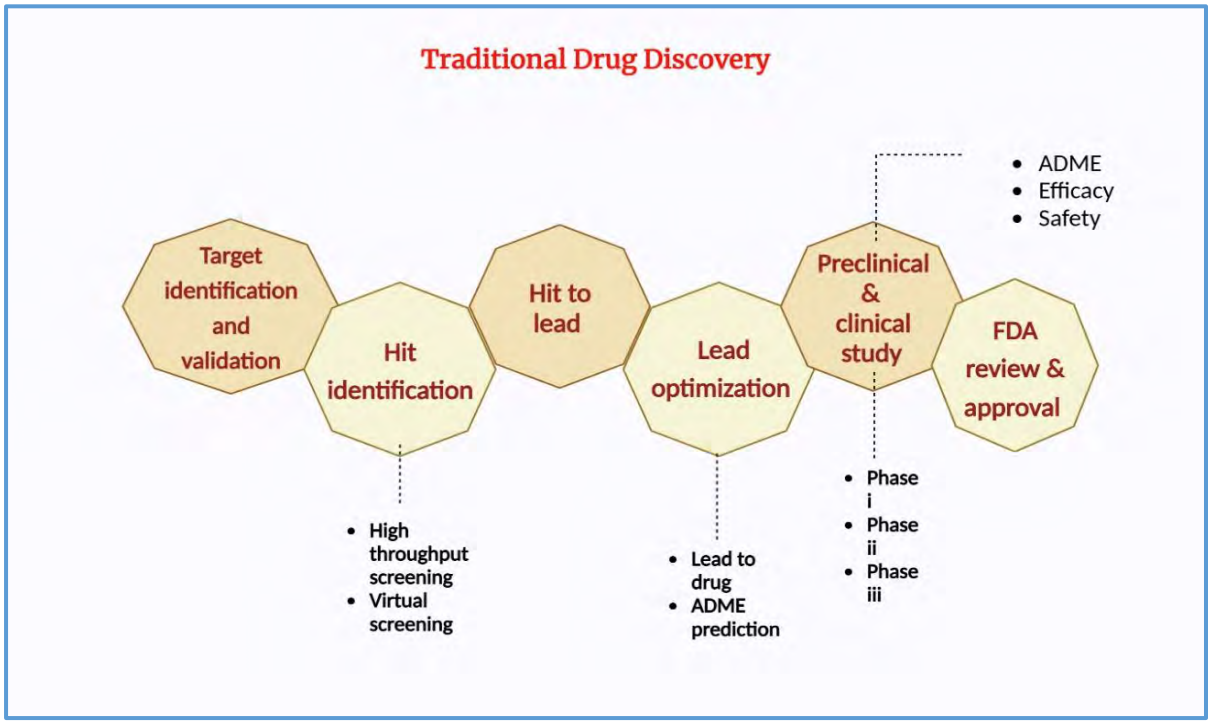

Figure 1: Process of traditional drug discovery

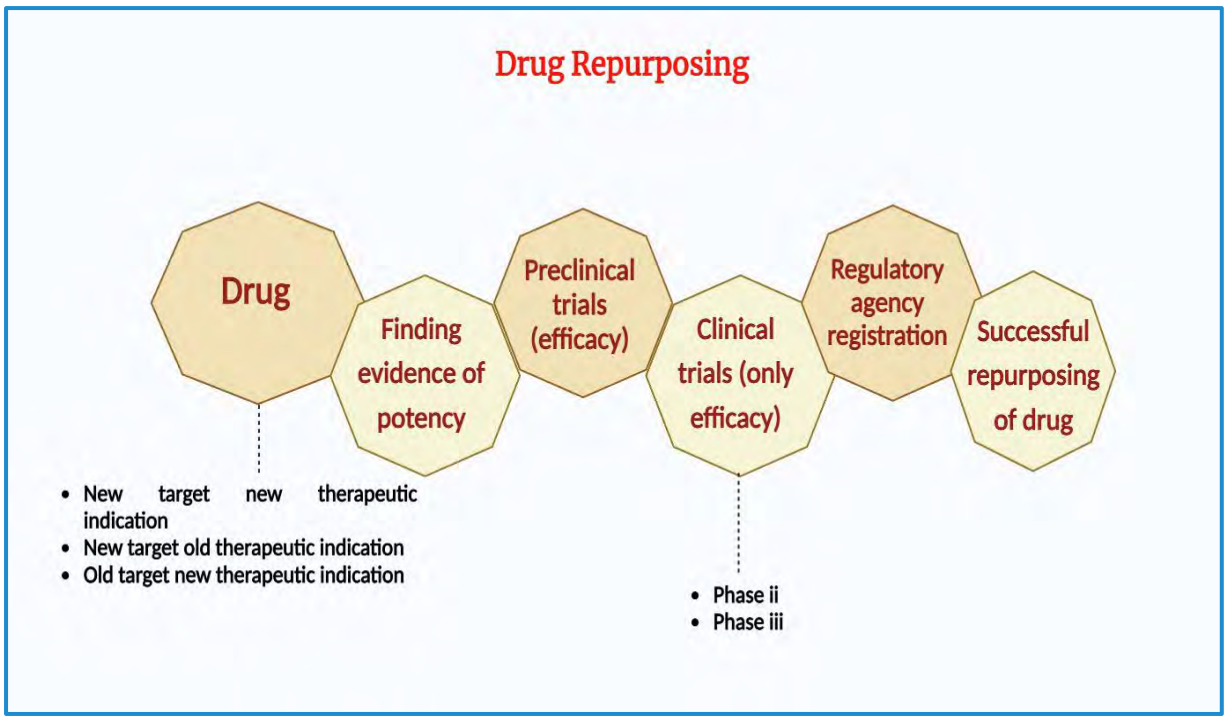

Figure 2: Process of drug repurposing

Drug repurposing can be a great tool in medical science as it has some tremendous benefits. For instance, because some autoimmune diseases, bacterial infections, and uncommon malignancies are idiopathic in nature and not inherited, they are more challenging to treat (Parvathaneni et al., 2019). When compared to lengthy traditional research and development processes, drug repurposing offers patients effective medications in a quicker and less expensive manner. Additionally, this strategy helps combat the rising costs of medication, development, cutting patients' out-of-pocket expenses and, ultimately, lowering the real cost of treatment. Although it will significantly save preclinical and phase I and II cost, a repurposed drug may have nearly the same cost for regulatory and phase III trials as a new drug. Once failures are considered, these advantages could result in less risk and quicker returns on funding for the repurposed medications development. In fact, the tariff of a repurposed medication getting into market has been estimated to be US$300 million generally (Pushpakom et al., 2018b).

As safety and efficacy data for a novel investigational molecule is not yet available, there is increased attrition during the drug discovery process, which results in more failures in terms of safety or efficacy. A repurposed molecule, on the other hand, has all the safety, preclinical, and efficacy data readily available, allowing the investigator to make an informed choice at each stage of drug development. Prior knowledge of safety, effectiveness, and the ideal administration route considerably lowers development costs and shortens the development cycle, requiring less effort to effectively launch a repositioned medicine (Parvathaneni et al., 2019).

Besides, substantial organizational, legal, and technical barriers still stand in the way of the improvement of repurposing of drugs. In this paper, an overview of drug repurposing, different classes of drugs used for breast cancer and their approaches are provided. Finally, we make recommendations that can speed up the full potential of pharmaceutical repurposing.

3.2 Advantages and disadvantages of drug repurposing

3.2.1 Advantages

Repositioning a drug has several related benefits. Particularly in some nations like the United States, they primarily simplify the processes of regulatory concerns for putting a previously approved drug on the market. This process considers previously acquired data, particularly on the safety and toxicity measures for drugs, which can significantly speed up the early stages of research for a repositioned drug, and hence is less expensive (by over 80%, according Naylor), increasing the possibility that it will be purchased (by 150% in comparison to a special medicine, per Thayer) (Jourdan et al., 2020). Additionally, not only expenses are lower but also the development period is less because of the pre-existing knowledge gleaned during phase I clinical trials, particularly pharmacokinetics and bioavailability (Pfab et al., 2021b). For instance, the development of repurposed pharmaceuticals takes only three to twelve years,

compared to the ten to seventeen years needed for conventional drug development (Pfab et al., 2021b). However, a new medical product results from any changes made to the drug's formulation, route of administration or dosage which needs an assessment again for the safety profile under the amended conditions (Kirtonia et al., 2021).

3.2.2 Disadvantages

As noted in the introduction and a few examples, drug repurposing has already seen significant results. Nevertheless, repurposing does not always work. Drug repurposing does not work for some candidates, notably in phase III trials. Especially when it is the case with the creation of wholly new pharmaceuticals, it is also typical for late-stage development to encounter some issues. However, as the safety profiles have already been featured particularly, these failures should be less likely to be toxic. However, there can be many reasons for failure in the repurposing field, such as regulatory considerations, patent considerations and organizational challenges.

Funding for clinical trials: Approving, commercializing, and widespread usage of an exploited cancer drug is no easy task. Economics is a factor that impedes development and approval of repurposed medicines (Gonzalez-Fierro & Dueñas-González, 2021). The private sector is not very interested in developing this type of drug as there are some intellectual property issues present. They strive for high profits on their investments. More than 190 drugs on the list, the majority (67%) of 72 are sponsored by universities or hospitals, and 28% are sponsored by research institutions,3% were sponsored by small pharmaceutical companies, government contributes 2%, and only 1% is contributed by large pharmaceutical companies according to the ReDo Project (Gonzalez-Fierro & Dueñas-González, 2021).

Issuing patent: There are several intellectual and legal properties which can be impediments to repurposed drugs. Another barrier that encourages medicine repurposing is enforcing patent

rights and patenting a repurposed indication because of the effect on the potential profit wished from the products that are repurposed. In the pharmaceutical markets, a newly repurposed medicinal use of an existing therapeutic molecule may be protected as it is novel and innovative (i.e., not obvious) (Pushpakom et al., 2018b). Even though they might not have completed clinical testing to prove their usefulness, prior scientific knowledge of the repurposed application may restrict the potential to gain patent protection (Malik et al., 2022). Except the patentee can distinguish their claims related to patent from those that are previously known to be in the public domain, it is applicable. To get patents for repurposed medical uses, the patentee must include information in the application demonstrating that the medicine is an effective treatment for the new indication. (Pushpakom et al., 2018b).

Furthermore, when clinical research is well-built with scientific evidence, other factors may affect the decision of medical bodies to use drugs that are repurposed. It is a matter of sorrow that some oncologists continually grumble about the exorbitant expenses of new anticancer drugs (Gonzalez-Fierro & Dueñas-González, 2021). But health professionals may be partially to blame for the phenomenon's persistence. The factor is considered that the pharmaceutical companies spends a lot of funds for advertising its goods and puts a lot of effort into getting regulatory authorities to approve new drugs (Gonzalez-Fierro & Dueñas-González, 2021). A medicine that undergoes repurposing does not experience this problem.

3.3 Approaches for drug repurposing

Before continuing to advance the prospective medication along the development pipeline, there are three main tactics, particularly in the drug repurposing process. Candidate molecule discovery, preclinical models for drug effect mechanism analysis, and phase II clinical trials for efficacy evaluation (with appropriate safety data from phase I studies carried out as part of the original indication) are these (Pushpakom et al., 2018b). These steps are proceeding by experimental and computational approaches (Pushpakom et al., 2018b).

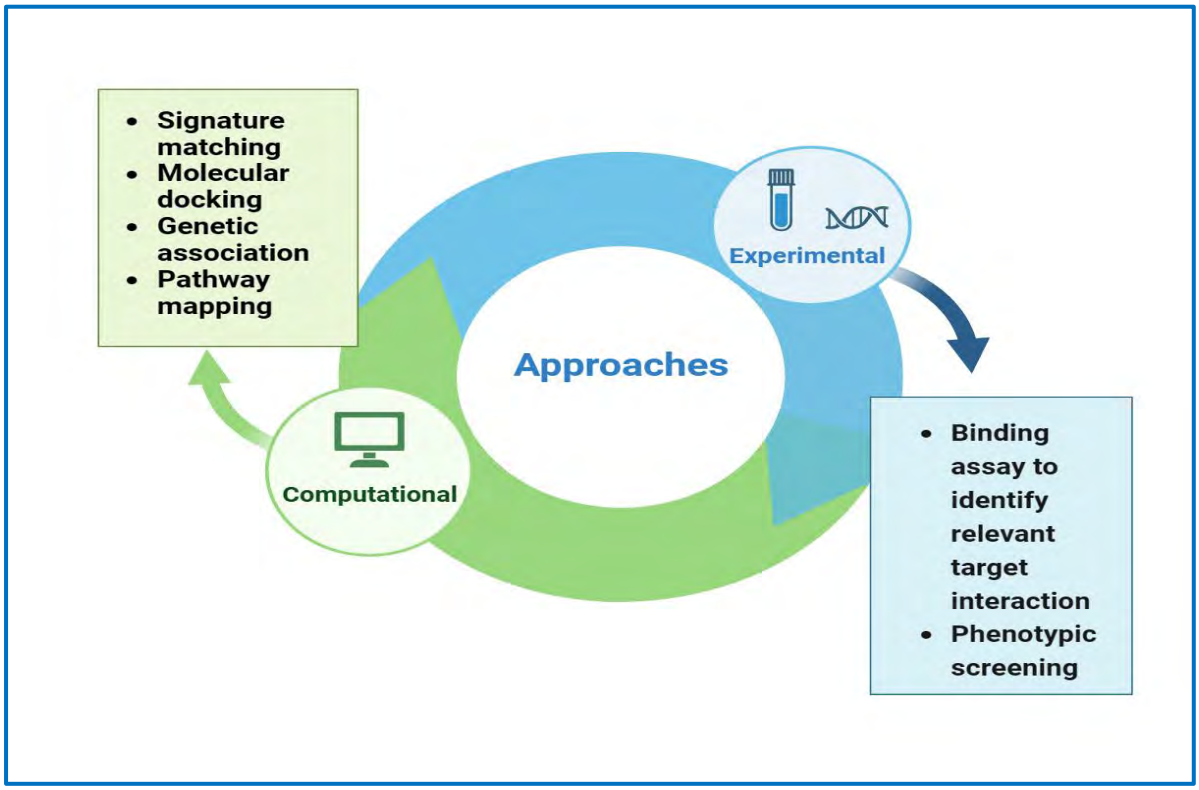

Figure 3: Approaches for drug repurposing

3.3.1 Computational approach

Computational techniques incorporate databases and tools that offer the chemical expression of cancer promoting genes to find agents for medication repurposing prospects (Kirtonia et al., 2021). Computational tools including signature matching, genetic association, molecular

docking, data mining and pathway mapping aid in the discovery of new pharmacological targets by utilizing established targets, disease biomarkers, medicines. They entail large amounts of data (such as gene expression, genotyping data, chemical structure) to match novel indications for existing medications (Fu et al., 2022).

3.3.2 Experimental approach

Data obtained by sequencing of large DNA and RNA, mass spectrometry and proteomics utilizing affinity chromatography has been employed to uncover novel binding partners for existing medications (Kirtonia et al., 2021). Thermal Stability of Cells Assay is a technique for mapping cellular targets that predicts the thermal equilibrium of targeted proteins using biophysical principles and a ligand that is the same as the present medication while maintaining the proper cellular affinity. Information on the treatment of diseases that originate in animals is also utilized to repurpose the drugs in people because of the similarity in targets (Kirtonia et al., 2021). Side effects are commonly experienced with drug regimens for specific diseases. Drug repurposing may be possible based on clinical findings from patients who report an unexpected effect or doctors who detect unusual symptoms cured by drugs (Gonzalez-Fierro & Dueñas-González, 2021).

3.4 Repurposed drugs in cancer treatment

Numerous non-oncology medications, such as antibiotics, cardiovascular drugs, antivirals, antipsychotics, anti-inflammatory drugs and other non-oncology medications that could be viable candidates for drug repurposing for cancer, are now FDA-approved or in clinical studies (Fu et al., 2022). In this review, we summarize various non-oncology drugs that have been repurposed for cancer treatment and highlight their prospective targets and molecular mechanisms.

Table 2: Investigated repurposed drug for cancer treatment (Fu et al., 2022)

Cancer type	Original indication	Repurposed drug	Mechanism
Breast cancer	Angiotensin receptor blocker	Olmesartan	Blocking RAF leads to apoptosis and cytotoxicity.
	Antimicrobial drug	Mebendazole	Cell cycle arrest in G2/M phase
	HMG-CoA reductase inhibitors (statins)	Atorvastatin	Through Apoptosis and autophagy. It reduces radiotherapy toxicity.
	Antimicrobial drug	Artemisinin	Caspase dependent apoptosis is shown.
	Antimicrobial drug	Doxycycline	RANK signaling, TGF-ß signaling, beta-catenin signaling, stimulation of AMPK, inhibition of the mammalian target of rapamycin (mTOR), ß-adrenergic signaling, stimulation of M1 and M2 melatonergic receptors, and prevention of eIF4E phosphorylation are all targets or processes that they each block.
	Anti-psychotic drug	Quetiapine	
	For idiopathic pulmonary fibrosis	Pirfenidone	
	Antibiotic	Rifabutin	
	Anti diabetic	Metformin	
	Beta blocker	Propranolol	
	NSAIDs	Aspirin	Block of cox 2 and leads to mutagenesis, inhibition of cell division.
Ovarian cancer	Antibiotic	Tigecycline	Targets HIFs, MYC, AMPK-mediated mTOR,
	Antiretroviral drug	Ritonavir	Ritonavir inhibits migration and invasion, triggers apoptosis, and stops AKT signaling.
	Statin	Lovastatin	Under clinical trial
Glioblastoma	Antimalarial	Quinacrine	Through apoptosis and autophagy
	Antimicrobial	Ketoconazole	Decrease glycolytic metabolism

	For rheumatoid arthritis	Auranofin	Auranofin inhibits thioredoxin reductase (TrxR). TrxR inhibition, particularly in cancers, causes an increase in cellular oxidative stress and initiates apoptosis.
	NSAIDs	Celecoxib	Celecoxib might stop the development of tumor cells by blocking some of the enzymes necessary for cell proliferation.
	For Alzheimer's disease	Donepezil	By cell mitotic arrest
	Alzheimer's disease	Memantine	Autophagy
	Antipsychotic drug	Chlorpromazine	regulates the cell cycle, cancer growth, and metastasis, among other functions, and has an impact on several molecular oncogenic targets through a variety of routes.
	For OCD	Clomipramine	Cell death
	Antidiabetic	Rosiglitazone	Stops cell proliferation by G2/M phase arrest.
Lung cancer	Antimicrobial drug	Albendazole	By VEGF and HIF-1a-dependent glycolysis inhibition
	To treat various infections (tapeworm, roundworm)	Niclosamide	A potent STAT3 inhibitor can reduce the nuclear localization of STAT3 in radioresistant lung cancer cells.
	Antidiabetic drug	Pioglitazone	Through apoptosis
	Antidepressant	Imipramine	Cell death
	Antimicrobial drug	Itraconazole	Apoptosis
Colon cancer	For bacterial infection	Ciprofloxacin	MDR reversal through ABCB1 efflux inhibition
	NSAIDs	Aspirin	Blocked of cox 2 and leads to mutagenesis, inhibition of cell division.
Colorectal cancer	Diabetic nephropathy, hypertension	Captopril	Cell proliferation is inhibited by apoptosis.

Chapter 4: Breast cancer and drug repurposing

4.1 Breast Cancer

The death rate from cardiovascular disease and pneumonia decreased over the past 50 years, resulting from novel treatments and measures of prevention depended on a complete understanding of the causes and pathogenesis. Cancer-related deaths have barely changed during this time span. As a result, history has reached a turning point when the number of cancer deaths will soon exceed cardiovascular disease more. For this sense, BC has the unfortunate distinction of now being the top cause of death in women all over the world (Chodosh, 2010). BC develops in the epithelium cells present in the glandular tissue of the breast, according to the WHO. The development of cancer is typically contained to the duct, where it has a minimal chance of spreading and frequently shows no symptoms (Breast *Cancer*, n.d.).

Among all forms of cancer, this is the most common form that is found in females, but the development of breast cancer in a male is also occurs. This case is rare in male due to their anatomic differences compared to females. Compared to the male, females have well-developed breast tissue though they both have a breast. For the formation of functional units of the breasts, the female breast has some lobules of glandular tissue about 15 to 20 in number. A lactiferous duct is responsible for drainage of these lobules and this duct opens on the nipple. Each duct enlarges deep to the areola to create a lactiferous sinus where milk can accumulate. Different levels of an adipose tissue and fibrous connective tissue hold the lobules together and provide support. Most of the breast volume in the non-lactational state is made up of these stromal components (Omene & Tiersten, 2010).

At birth male and female both have similarities in their anatomy of breast. They consist of a small number of ducts called rudimentary ducts which are mainly brunched and associated

beneath the nipple-areola complex. They vanished during adolescence so development stops in males. The lactiferous ducts in females continue to expand and branch out in addition to an increase in adipose and stromal tissue. This is the reason behind a progressive enlargement of breasts. The terminal ducts eventually give rise to saccular buds, which later grow into secretory glands during pregnancy. When lactation stops, there is glandular atrophy, and the stromal elements of the breast once more make up most of the breast (Omene & Tiersten, 2010).

Table 3: Common risk factors of breast cancer in male and female (Omene & Tiersten, 2010)

<table>
<tr><th colspan="2">Risk factors in Male</th><th colspan="2">Risk factors in female</th></tr>
<tr><td>Genetic factors</td><td>Mutation of BRCA2 and BRCA1 (BRCA2>> BRCA1). PALB2.CHEK2, androgen receptors mutation (possible).</td><td colspan="2">Genetic factors (mutation of BRCA1 and BRCA2)</td></tr>
<tr><td colspan="2">Alteration of ratio of estrogen to androgen</td><td>Hormonal and reproductive disbalance</td><td>Early menarche (first menstrual cycle), low parity, late menopause. Higher level of endogenous estrogen.</td></tr>
<tr><td colspan="2">Due to extra X- chromosome (Klinefelter's syndrome)</td><td colspan="2">Food contains high energy, alcohol consumption</td></tr>
<tr><td colspan="2">Exogenous use of estrogen for treatment of prostate cancer</td><td colspan="2">Pregnancy related hormonal imbalance (due to lack of ER and Progesterone receptor)</td></tr>
<tr><td colspan="2">Obesity (lack of exercise)</td><td colspan="2">obesity</td></tr>
<tr><td colspan="2">Chronic liver disease (possible)</td><td colspan="2">Late first birth</td></tr>
</table>

The average age of presentation for male breast cancer is between 60 and 65, ten years later than that of female breast cancer. The non-tender, palpable lump that is frequently located in

the middle (70–90%) is the primary symptom in most patients. Early signs of nipple involvement in male breast cancer patients include retraction, discharge, and ulceration. Serosanguineous or bloody male breast discharge is virtually always malignant in nature and should always be investigated by biopsy. A benign papillary adenoma is the most common cause of bleeding flow from the female breast. A clinically suggestive axillary adenopathy in 40–55 percent of male patients at the time of diagnosis indicates metastatic illness (Omene & Tiersten, 2010). Bilateral breast cancer, which is thought to occur between 1.4 and 1.9% of the time, is much less common in men than in women. It is most likely because men lack lobular differentiation because lobular malignancies commonly present as bilateral illness and multicentric disease. There is a slight inclination toward left-sided illness as opposed to right-sided illness, much like in women (Omene & Tiersten, 2010).

4.2 Staging of breast cancer and their prevalence worldwide

Breast cancer was staged with tumor-node-metastasis (TNM) approach, which was recently amended by the American Joint Committee on Cancer (AJCC) (Teichgraeber et al., 2021). Each patient's TNM status is assessed for them individually and correlates to a particular stage. This data significantly plays a role in determining a patient's prognosis and treatment plan (Jeruss et al., 2008; Teichgraeber et al., 2021). Before any surgical intervention, breast cancer patients will fall into a clinical stage based on physical examination, radiological investigations, and biopsy findings (Jeruss et al., 2008). Pathologic data obtained after surgical tumor elimination as well as lymph nodes (regional) indicate the condition of BC. A pathologist assesses the tissue to determine the size of tumors and the lymph node involvement (Jeruss et al., 2008).

According to AJCC 8th edition, the system of breast cancer staging falls under two categories: anatomic and prognostic (Teichgraeber et al., 2021). The TNM categories define the anatomic

stage of cancer. Recommends performing a physical examination with history, ultrasound and bilateral mammography as needed, pathological review, and hormone receptor tests to determine the anatomic stage recommended by The National Comprehensive Cancer Network (NCCN) (Teichgraeber et al., 2021). The biomarker status (ER, PR, HER2), tumor grade and genomic panel results are used in the staging process. A clinical prognostic stage applies to every patient's cancer status since it creates a baseline and guides the beginning of treatment. Additionally, independent of the treatment (first surgery with adjuvant therapy and NAC), this system aids in comparisons among all patients (Teichgraeber et al., 2021).

The AJCC 8th edition staging system requires that the expression status of HER2, also PR and ER receptor status, be determined in all invasive carcinomas whenever possible (Jeruss et al., 2008). Tamoxifen and other endocrine medications have slowed the progression of ER-positive and PR-positive cancers. Additionally, advancements in breast cancer genomics have enabled profiling of prognosis based on the expression of thousands of gene combinations in tumor cells (Teichgraeber et al., 2021). Depending on hormone receptor status and gene expression patterns, the primary subtypes include luminal A-like, HER2-enriched, luminal B-like and basal-like (triple-negative) (Teichgraeber et al., 2021).

The burden of breast cancer incidence and death is fast increasing all over the world; this reflects both population growth and changes in the prevalence and spreading of breast cancer risk factors (Chodosh, 2010).

Worldwide, there will be 2.3 million new cases of female breast cancer in 2020, and the disease will claim the lives of roughly 685,000 people. Australia, New Zealand, Northern America, Western Europe and Northern Europe had the highest incidence rates, which is more than 80 per 100,000 females, and Eastern and Middle Africa, Central America, and South-Central Asia had the lowest rates (40 per 100,000). Western Africa, Micronesia/Polynesia and Melanesia

had the highest mortality rates (>20 per 100,000), while rates in most other geographical areas varied between 10 and 20. The global burden remains concentrated in women aged 50 and older in case of breast cancer. However, the age distribution of cases and mortality varied significantly across geographical regions, with 43% of incidence and 49% of mortality occurring at postmenopausal ages in Middle Africa and in Northern America, as well as Western and Northern Europe, postmenopausal women account for more than 80% of cases and 90% of fatalities. The age distribution of cases and deaths, on the other hand, varied significantly across geographical regions, with 43% of incidence and 49% of mortality occurring at postmenopausal ages in Middle Africa and over 80% of cases and 90% of deaths occurring at postmenopausal ages in Northern America, Western and Northern Europe, and Northern Africa (Arnold et al., 2022a).

Besides, the recently estimated rate of 2023 is 300,590, with a mortality of 43,700 in the US (American Cancer Society 17.07.2023). Breast cancer is still the most usual and deadly cancer in Bangladesh for females. It has become a hidden burden, accounting for 69% of female deaths. Breast cancer at a rate of 22.5 per 100,000 females of all ages in Bangladesh; among Bangladeshi women aged 15-44, breast cancer has the highest prevalence (19.3 per 100,000) compared to any other type of cancer (Anisur Rahman Forazy Begum Rabeya Khatun Chowdhury Nursing College, 2015).

From a study, researchers found that by 2040, the number of newly diagnosed breast cancers will increase by more than 40%, and will reach 3 million cases. Similarly, mortality from BC will rise by more than 50%, from 685,000 in 2020 to 1 million in 2040 (Arnold et al., 2022b).

4.3 Resistance to current breast cancer treatments

Genetic amplification hastens the occurrence of therapeutic resistance. Cancer cells can grow more resilient and aggressive with this technique. Every systemic chemotherapy regimen targets a subset of cancer cells that acquire resistance to therapy, decreasing the likelihood that additional therapies will be successful (Gonzalez-Angulo et al., 2007).

Systemic treatment refers to treatment that includes the application of cytotoxic, immunotherapeutic agents as well as hormonal. They are mainly applied in adjuvant, neoadjuvant, and metastatic treatment systems (Gonzalez-Angulo et al., 2007).

90% of initial breast tumors and 50% of metastases typically respond well to systemic medicines when treatment first begins (Jeruss et al., 2008). And shows decreased serological tumor markers, improved symptoms, and low tumor volume. However, advancement takes place after variable amounts of time. Some cases reveal that some patients will resist therapy at this time. To overcome resistance to individual medications, combinations of non-cross-resistant regimens have been used. However, cancers continue to develop resistance because of these combinations. It is incorrect to blame therapeutic failure on a single factor because carcinogenesis has many facets (Gonzalez-Angulo et al., 2007).

4.4 Drugs used in breast cancer and the role of pharmaceutical companies in repurposing field

Drugs that are repurposed for different cancer treatments are discussed in table 1. Agents that have the potential for repurposing for BC treatment can be used alone or in combination with traditional therapeutic agents (Liao et al., 2021). Combination therapies improve anti-cancer drug efficacy by targeting distinct critical pathways, reducing resistance of the drug (Liao et al., 2021). Additionally, the drug combination beneficially reduces the dosage of each drug

separately, prevents harmful effects on healthy cells, and triggers cytotoxic effects on cancer cells to ensure maximal efficacy with the least amount of toxicity.

Antidiabetic agents: To assure life and expansion, cancer cells, particularly breast cancer cells, employ aerobic glycolysis as their principal source of energy rather than oxidative phosphorylation (Zhou et al., 2020). The "Warburg effect" promotes the intake and assimilation of nutrients required for neoplasia (De & Kuppusamy, 2020). Breast cancer cells frequently use mechanisms to boost glucose absorption and utilization to give subsequent drop in ATP generation (Zhou et al., 2020).

Breast cancer cells are immortal due to changes in their metabolism (De & Kuppusamy, 2020). Some research has focused on turning on as well as off the cell metabolism, which causes malignant cells to get hungry (Zhou et al., 2020). The study used anti-diabetic medicines to specifically target the proteins that pump this critical nutrient into tumor cells and search for the potential treatment of breast carcinomas. They reduce glucose absorption, activate the AMPK signal, and thus block the mTOR pathway (De & Kuppusamy, 2020).

Antimicrobial drug: As mentioned in chapter 1 that antimicrobial drug has a potential effect as an anti-cancer drug, it also plays significant role as breast cancer therapy.

Anti-inflammatory drug: Numerous anti-inflammatory substances, such as NSAIDs and dietary phytochemicals, have been identified in pre-clinical and clinical studies as potential cancer chemoprevention agents, including those for breast cancer (Gadi & Shetty, 2022). In almost 40% of cases of breast cancer and ductal carcinoma (pre-invasive) in situ lesions, the overexpression of COX-2 was the main reason (Gadi & Shetty, 2022). These findings are related to aggressive breast cancer characteristics such as ER/PR negativity, large tumor size and HER-2 overexpression. Anti-inflammatory drugs block COX, thus inhibiting prostaglandin synthesis and nuclear factor-B-mediated signaling (Malik et al., 2022).

Cardiovascular drug: FDA-approved medications that are potential treatments for cardiovascular diseases have been investigated in several preclinical trials and show an anti-cancer effect (Fu et al., 2022). Glycosides like digoxigenin, cast-off is potential for patients with a high risk of heart failure and to decrease heart rate, also can be potential for anti-cancer effects (Kirtonia et al., 2021). Digitalis is a drug used as a cardiovascular drug that has effects on the breast cancer treatment which was reported in 1980. Patients with Digitalis have shown lower death rates (Kirtonia et al., 2021). And propranolol, a non-selective beta-adrenergic antagonist, has an anti-cancer effect. It reduces tumor angiogenesis and shows immunostimulatory action (Gales et al., 2022).

Table 4: List of different classes of drugs that are repurposed for breast cancer therapy (Costa et al., 2020)

Drug class	**Drug name**		**Type of breast cancer**
Antidiabetic drug	Dapagliflozin (SGLT-2 inhibitor)		Not specified
	Alpha-Lipoic Acid		Not specified
	Epalrestat		Basal-like breast cancer
	Glibenclamide		Not specified
	Glipizide		Metastatic
	Metformin		ER+ TNBC
	Pioglitazone		Metastatic
Antimicrobial drug	Antimalarial	Amodiaquine, Artesunate	Metastatic, TNBC and HER2- enriched breast
	Antibiotic	Azithromycin, Clarithromycin	ER
	Antifungal	Clotrimazole, Itraconazole	TNBC
	Antiparasitic	Ivermectin, Mebendazole	Stem like cell, TNBC

	Antiviral	Oseltamivir, Ribavirin	Metastatic Luminal- B, TNBC
Anti-inflammatory drug	Celecoxib		Not specified
	Indomethacin		Not specified
	Naproxen		Not specified
	piroxicam		Not specified
Cardiovascular drug	Amiloride		During operation of breast cancer and metastatic
	Amlodipine		Metastatic TNBC
	Atenolol		TNBC and HER2+ BC
	Bepridil		TNBC
	Captopril		Metastatic
Antiulcerants	Cimetidine		ER+ invasive ductal carcinoma
	Ranitidine		Metastatic
Lipid lowering drug	Simvastatin		Invasive basal-like
Selective estrogen receptor modulators	Bazedoxifene		TNBC and hormone receptor breast cancer
Diuretics	Ethacrynic Acid		HER2+
SSRIs	Fluoxetine		TNBC
Antipsychotics	Haloperidol		Not specified

In drug repurposing, pharmaceutical corporations play a significant role. While they share a particular strategy for drug discovery by investigating new applications for a field of specialty, existing medications, the emphasis, capabilities, financial structures and incentives vary substantially.

Pharmaceutical companies are well-positioned to adopt a systematic strategy to repurposing to boost the likelihood of success in candidate identification due to their core competencies, such

as clinical development, paired with their all-encompassing responsibility to provide effective pharmaceuticals to patients. Pharmaceutical businesses have various advantages within this general framework, particularly in case of data access and clinical improvement (Cha et al., 2018). Moreover, translational research, cross-disciplinary teams consisting of biostatistics, and clinical elements will be required in pharmaceutical corporations to systematically review and enhance the algorithms and procedures behind drug repurposing (Cha et al., 2018). Secondly, the commercial side, which includes incentives to make an authorizing ecosystem and support the chain value to develop such drugs. Big pharma companies provide significant strengths and knowledge about repurposing (Cha et al., 2018). The firms bring extensive medication development capabilities and a thorough understanding of regulatory, intellectual property, and commercial issues (Cha et al., 2018).

Chapter 5: Potential of antimicrobial drugs in breast cancer treatment and their mechanism of action

Only a handful of cells within a tumor have self-renewing capabilities, making them resistant to standard treatment and responsible for tumor maintenance, genesis and spread (Peiris-Pagès et al., 2015). These cells are tumor-initiating cells (TICs) (Peiris-Pagès et al., 2015). Recently some antimicrobials are repurposing for BC therapy. For example, itraconazole, doxycycline, artemisinin, telaprevir, ribavirin, bedaquiline, levofloxacin etc.

5.1 Antibiotics

Bedaquiline is an antimicrobial medication approved by FDA for multidrug-resistant pulmonary tuberculosis (TB) (Goulooze et al., 2015). Bedaquiline is a first-class diarylquinoline chemical that prevents bacterial ATP synthase mechanistically as well as exerts potent action against both drug-resistant and drug-sensitive tuberculosis (Fiorillo et al., 2016).

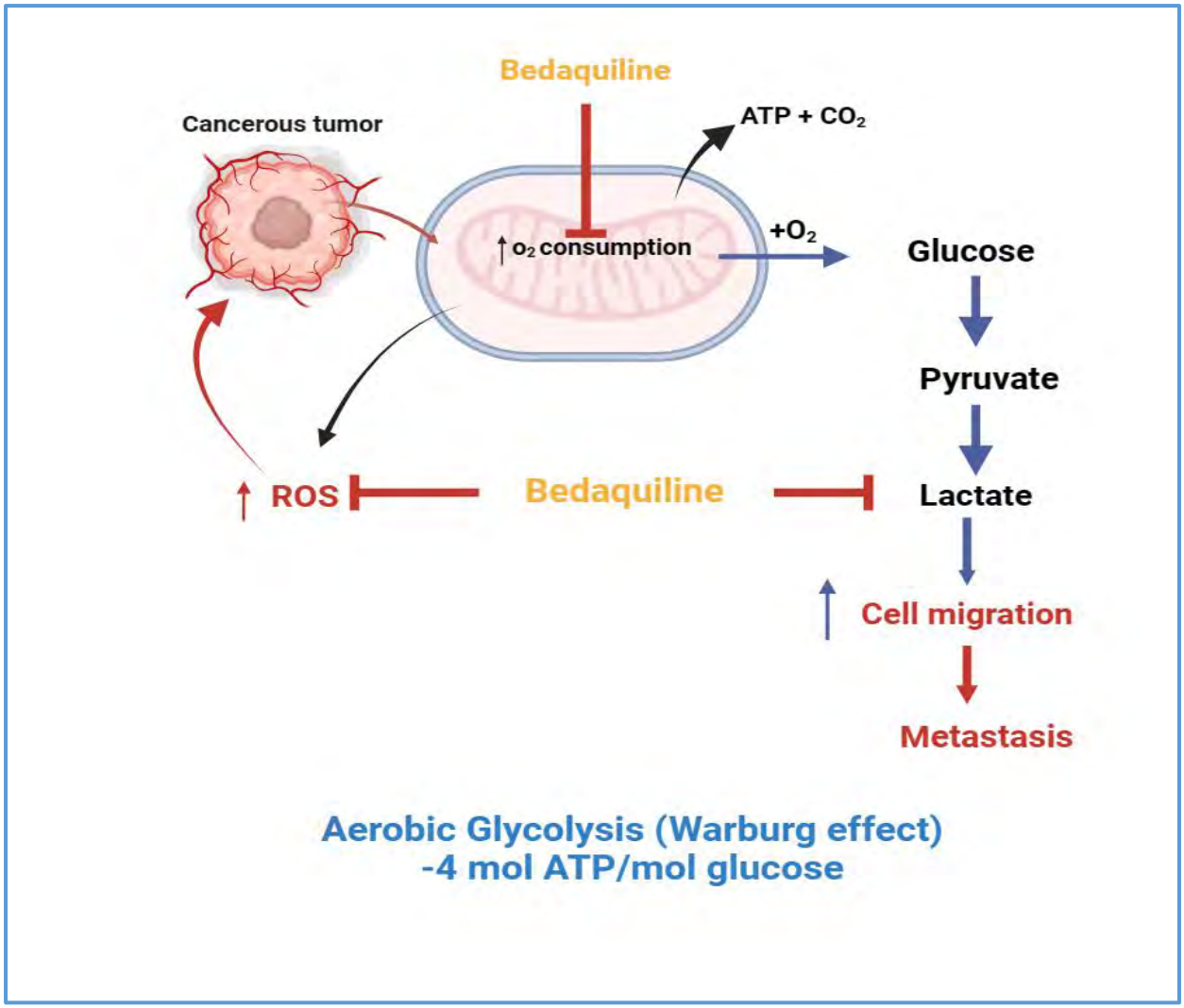

Figure 3: Mechanism of Bedaquiline as breast cancer therapy

Bedaquiline can be a potential drug to repurpose by targeting metabolism of mitochondria in BC cells. Aerobic glycolysis is metabolic adaptation in malignant cells. Thus, focusing on the function of glucose metabolism could be a promising treatment method for BC (Z. Wu et al., 2019). Regardless of the abundance of oxygen available, tumor cells primarily use glycolysis for energy production processes and have higher glycolysis rates. The Warburg effect is the name given to this aerobic glycolysis phenotype (Z. Wu et al., 2019). Bedaquiline significantly slows oxygen consumption and ATP synthesis. Thus, Bedaquiline administration reduces aerobic glycolysis (the Warburg effect). In this situation, bedaquiline decreased mitochondrial membrane potential while increasing mitochondrial bulk and total ROS production. According

to several experimental research, ROS functions as a tumor-suppressing or tumor-promoting agent, depending on its production level (Sahoo et al., 2022). High levels of ROS production can cause DNA damage and result in proliferation (Frattaruolo et al., 2020). They are also responsible for reducing lactate which is converted by pyruvate (glycolysis) (Feron, 2009; Hirschhaeuser et al., 2011). Lactate induces cell migration and develops cancer (Hirschhaeuser et al., 2011). They also create radio resistance (Feron, 2009). Most importantly, bedaquiline suppressed CSCs proliferation with an IC50 of 1 μm as evaluated by the mammosphere experiment (Goulooze et al., 2015).

Additionally, evidence from experiments indicates that BC develops from breast cancer stem cells (BCSCs), and mitochondrial biogenesis is necessary for survival and CSC anchorage-independent clonal proliferation, making mitochondria a prospective target for novel therapeutic strategies (Peiris-Pagès et al., 2015). The reduction of mitochondrial biogenesis is a major known side effect of the doxycycline approved by FDA. Doxycycline can reduce the proliferation and viability of BCSCs and BC cells, as well as the efficiency of mammosphere migration, formation and invasion of breast cancer cells. Doxycycline therapy dramatically reduced the expression of stem cell factors Nanog, Oct4, Sox2 and CD44 (Peiris-Pagès et al., 2015). Furthermore, doxycycline down-regulates the autophagy markers LC-3BI and LC-3BII way, implying that inhibition of autophagy may be responsible for some of the reported effects on EMT, proliferation and stem cell markers (Peiris-Pagès et al., 2015).

5.2 Antifungal drug

Itraconazole (ITZ), a widely used antifungal medication, recently validated in preclinical and clinical testing as an anti-cancer therapy (H. T. Wu et al., 2022). ITZ works as an antifungal agent by inhibiting ergosterol synthesis, and it is necessary for fungal cell membrane integrity. ITZ is an effective and safe long-term prophylactic for fungal infections in

immunocompromised malignant patients with neutropenia due to its antifungal properties (H. T. Wu et al., 2022).

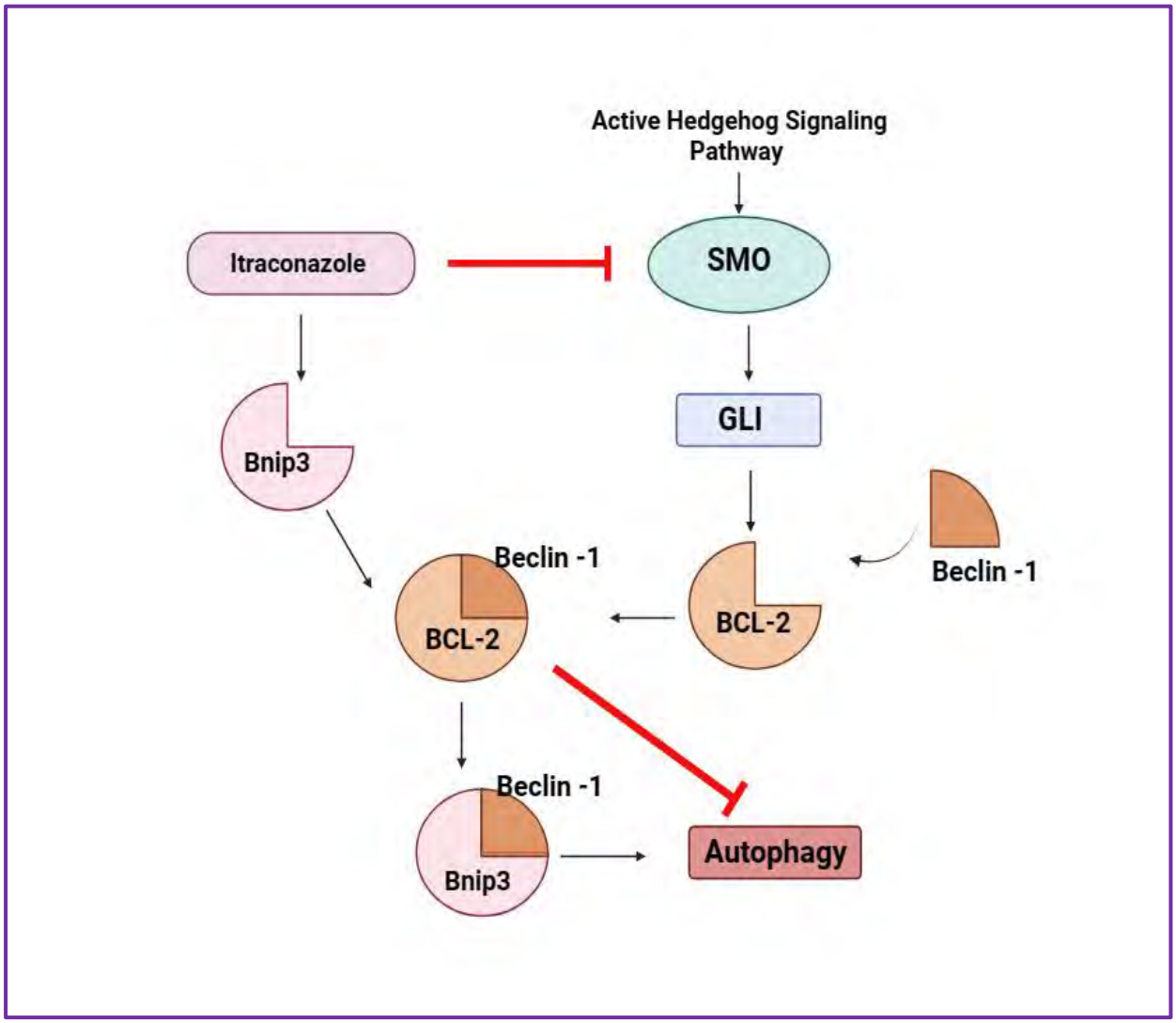

Figure 4: Mechanism of action of Itraconazole. Itraconazole induces autophagy. When the Hh pathway is activated, SMO releases trapped GLI, which enters the nucleus and induces transcription of the target gene BCL-2. BCL-2 interacts with Beclin-1's domain BH3 to generate a compound that inhibits autophagy. Itraconazole targets SMO and works as an inhibitor, reducing the number of GLI while increasing the number of Bnip3. Finally, Bnip3 replaces BCL-2 in the Beclin-1/BCL-2 binding complex, which promotes autophagy (Wei et al., 2020).

Although the Hh signaling system is a vital regulator of cell proliferation, embryonic development and differentiation, evidence suggests that abnormal Hh signaling activity is connected to cancer (Wang et al., 2017; Wei et al., 2020). Hh pathway components such as SHH, Gli1, PTCH1, Smo and Gli2 are abnormally expressed in tissue of tumor, indicating that inhibiting the hedgehog signaling pathway may hold promise for prevention of breast cancer (TNBC) (Wang et al., 2017). The Hh pathway's target genes include genes related to proliferation like cyclin-D1 and genes related to apoptosis like BCL-2. An abnormally activated Hh pathway in malignancies causes smoothened (SMO) release, this then facilitates GLI's separation from cytoplasmic inhibitory protein (Wang et al., 2017). GLI then penetrates the nucleus, where it eventually causes either the transcription of genes related to growth or apoptosis. In a nutshell, itraconazole blocks transcription of the BCL-2 and cyclin-D1 genes while also inhibiting GLI release. Finally, it increases cell death and suppresses tumor cell proliferation. Itraconazole is also responsible for raising cyclin-dependent kinase inhibitors (p21 and p27) in malignancies, indicating that itraconazole slows the growth of cells (Wang et al., 2017).

5.3 Antiviral drug

Maraviroc is a novel antiviral family called CCR5 antagonists. Chemokines have an important role in the progression and development of breast cancer (Xu et al., 2014). Recent research has identified CCL5, a chemokine ligand which is secreted by tumor cells or draws mesenchymal stromal cells to the tumor (Xu et al., 2014).

The chemokine receptor 5 (CCR5) axis is the important part in the progression and genesis of BC. Activation of the CCR5 receptor of breast cancer cells is responsible for their invasiveness and acts as a catalyst for metastasis (Sayana & Khanlou, 2009).

The mechanisms that regulate how breast cancer cells are stimulated to express CCL5 are activated by the activator protein-1 (AP-1) (Velasco-Velázquez et al., 2014). CCL5 expression is caused through the AKT/NF-B, JNK, and MAPK kinase pathways. These pathways respond to microenvironmental signals; for example, IL-6 circumstances increase CCL5 expression. In chromatin immunoprecipitation tests, c-Jun the transcription factor directly combines to the CCL5 which acts as promoter, inducing CCL5 and stem cell factor (SCF) expression (Velasco-Velázquez et al., 2014). In ErbB2 mammary tumor cells, CCL5 controls migration, whereas SCF results in the establishment of a stem-like phenotype (Velasco-Velázquez et al., 2014).

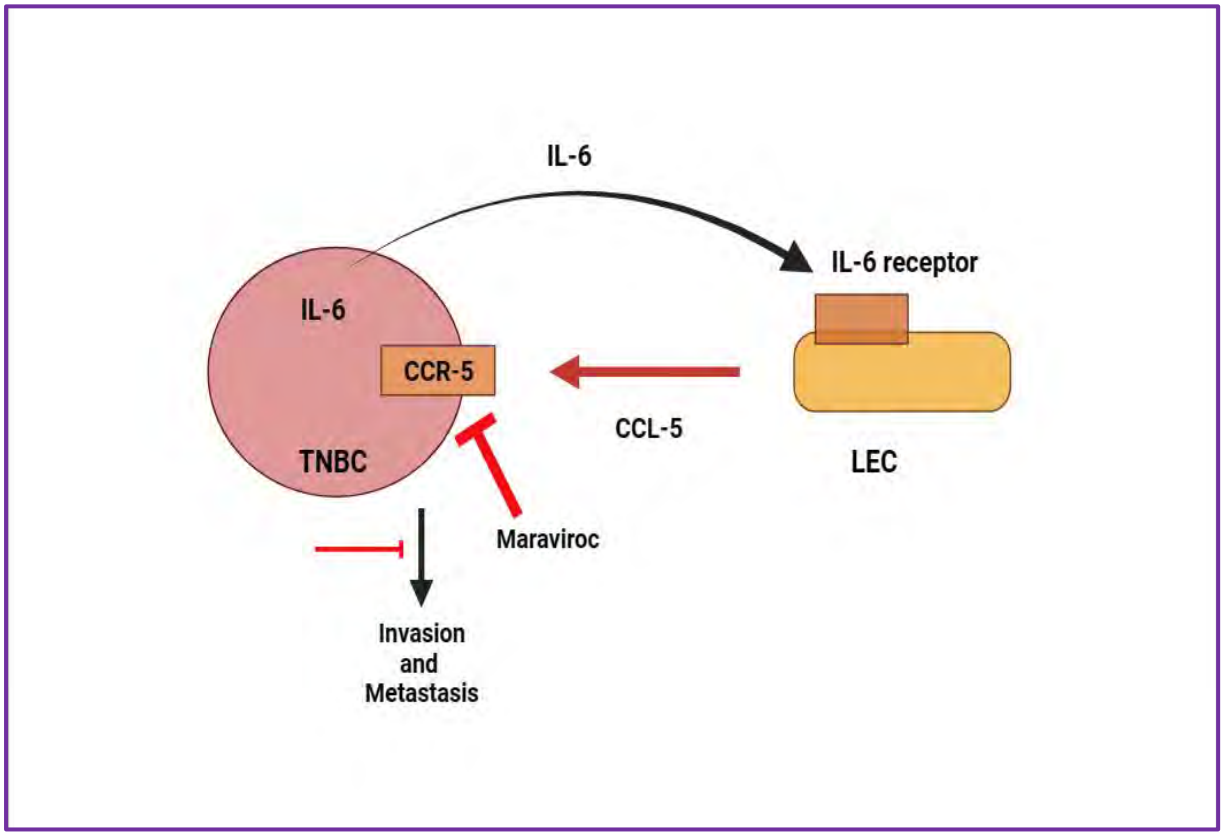

Figure 5: Mechanism of action of Maraviroc in the treatment of TNBC

CCR5 suppression in breast cancer might decrease malignant cells' ability to react to CCL5 produced by autocrine sources (Velasco-Velázquez et al., 2014). As a result, researchers

investigated the possibility that CCR5 antagonists could diminish breast cancer cell invasion and metastasis. Maraviroc inhibited decreased basal breast cancer cell invasion and ligand-stimulated intracellular calcium increase, demonstrating that CCR5 in breast cancer cells responds to pharmacological inhibitions (Velasco-Velázquez et al., 2014).

Chapter 6: Future of drug repurposing in breast cancer treatment

As repurposing of drugs is one of the cheapest and finest approaches for therapy of cancer, it is well established in academia and appreciated by scientists as well as pharmaceutical companies (Kirtonia et al., 2021). For repurposing of drugs there are some recommendations which can facilitate the process largely.

Better integrative systems for data analysis are first and foremost needed. The advantages of large data and how it can help with repurposing opportunity discovery are obvious. Advanced analysis technologies are important for clinical trials, reducing manual curation need, helps in integration of omics data (Pushpakom et al., 2018b). Moreover, this is important for getting more refined analyzed data given by non-experts. Second, the industry's preclinical and clinical compounds need to be easier to access. There should be enough collection of compounds for development. Third, more information from phase II-IV clinical trials financed by the industry must be made public. For studies that have been discontinued, this would enable scientists from the outside to sift the data for novel insights that might offer promise for repurposing (Pushpakom et al., 2018b). Researching more recent safety hazards related to drugs that have been repurposed is also crucial. Fifth, more funding options are required for drug repurposing operations in general, including easing compound availability, funding of appropriate technologies and sharing of drug libraries that are repurposed. These can help in the drug repurposing process for great acceptance (Pushpakom et al., 2018b).

For forecasting a drug's efficacy, mode of action, and safety to repurpose it for use in other disorders, such as cancer modern pharmacogenomics and high-throughput drug screening methods (Kirtonia et al., 2021). Drug repurposing brings up an entirely novel field for the study of already-approved medications and may offer higher chances for prompt therapy.

Chapter 7: Conclusion

To conclude, drug repurposing can be a best alternative to the medication research procedure for cancer due to savings of billions of dollars. With the alarming rise in cancer diagnoses and the obstacles and failures of conventional treatment, new approaches to treat this dreadful disease are necessary. Reassessing a drug's efficacy for cancer therapy outside of its intended medical usage is based on a prior understanding of its biological effects on targets of the disease. To a greater extent this helps in drug development due to their investigated safety profile, as toxicity studies are done over repeated manner, which reduce the likelihood of failure due to adverse toxicology. Before investigating off-site targets in clinical trials, understanding of the biological background of that off-target and its effects on the individual disease are crucial. Considering the high cost of anticancer drug development, it is a burden on the global healthcare system. So, identifying anticancer properties in approved drugs, which are frequently more affordable, is a best option for the treatment of cancer, even in impoverished nations. Overall, this study highlights some antimicrobial medicines and their potential to be employed in the future either alone or in combination with chemotherapy as the treatment of breast cancer and they are Bedaquiline, Itraconazole, Maraviroc, Artesunate, Ribavirin. However, only a few non-cancer medications are licensed, and a good number of non- cancer drugs are undergoing preclinical and clinical tests to treat breast cancer or other forms of cancer.

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