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Review

Exploring the multi-drug resistance (MDR) inhibition property of Sildenafil: phosphodiesterase 5 as a therapeutic target and a potential player in reversing MDR for a successful breast cancer treatment

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Abstract: In recent years, there has been an increase in both the incidence and mortality of breast cancer. Globally, breast cancer is ranked as the main root of cancer-related death in women. Multidrug resistance (MDR) is identified as a primary cause of treatment failure in anticancer chemotherapy. This makes multidrug resistance an interesting therapeutic target in breast cancer. Therefore, elucidation of the molecular mechanisms involved in chemoresistance is essential. Phosphodiesterase 5 (PDE5) cross-talks with nitric oxide/cyclic guanosine monophosphate (NO/cGMP), Wnt/β-catenin, and PI3K/Akt signaling pathways to upregulate the expression of ABC transporters and increase cGMP efflux. This enhances multidrug resistance and impacts cellular processes such as proliferation, apoptosis, and angiogenesis. Thus, further research on the identification of possible factors in the reversal of MDR in breast cancer is necessary. Sildenafil is a selective phosphodiesterase type 5 inhibitor that is commonly utilized as first-line therapy in treating erectile dysfunction. Its safety profile and tolerability have encouraged researchers to develop an interest in further investigations into its beneficial uses, especially its chemo-preventive activity in managing breast cancer. In this review, we critically examined the central role played by PDE5 in activating several pathways involved in MDR in breast cancer. Given that sildenafil is a selective PDE5 inhibitor, we provide insight into its

modulatory effects and interactions with signaling pathways targeted by PDE5 to overcome MDR in breast cancer.

Keywords: sildenafil; breast cancer; chemoresistance; signaling pathway

1. Introduction

Breast cancer is the primary cause of cancer-related mortality among women and represents a significant worldwide health concern [1]. It is also the most diagnosed cancer in the world [2]. There are predictions of increasing prevalence in the future due to the westernization of lifestyles, dietary patterns [3] and reproductive-related determinants [4], limited success with current therapies, delay in diagnosis and treatment availability, and increase in the cost of new anti-cancer drugs, which has caused drawbacks in meeting the medical needs of cancer patients [5], especially in developing countries. Further, the prolonged and costly process of developing new drugs interferes with drug discovery and clinical implementation. The rise of resistance to current therapies has positioned drug repurposing as a process that might produce some lead candidates that may be promising to treat breast cancer [6]. It is common knowledge that MDR significantly and negatively affects the clinical outcomes of cytotoxic anticancer therapies used conventionally by targeting molecular pathways involved in cancer cell functions and survival approaches. Therefore, there is a rising interest in repurposing approved drugs for other diseases to address the need for effective breast cancer treatments. Finding medication substitutes to combat the rise in drug resistance will help better manage the disease's spread.

Sildenafil, commonly termed Viagra, was originally developed for the treatment of anti-hypertension and angina pectoris. However, sildenafil was discovered to cause penile erections during phase II clinical trials. Despite, its repurposing for treating erectile dysfunction [7], Sildenafil's ability as a PDE-5-inhibitor for smooth muscle relaxation by increasing the inflow of blood has been discovered to be useful for the enhancement of drug accumulation and increase in the preferred targeting of drugs in diseased tissues such as tumors [8]. The uncovering of its molecular mechanisms of enhancing drug availability to counter MDR during breast cancer treatment will offer more insight into the need for its repurposing for breast cancer treatment.

Recent years have seen a rise in reports of drug resistance in different tumors to well-established treatments, as well as the discovery of new treatments with fewer or no side effects for cancer patients. These factors have drawn attention to medication repurposing in oncology.

2. Breast cancer

One in eight deaths worldwide is attributed to cancer, a disease that develops because of alterations in a cell's genome's DNA sequence [9]. Being one of the most common cancers among women worldwide, breast cancer is a major issue. According to [10], breast cancer is classified as a tissue cancer that mostly affects the interior layers of milk glands, lobules, and ducts. It is described as a diverse illness concerning pathology, clinical course, and image features. Breast cancer has been defined by the World Health Organisation (WHO) as a heterogeneous illness based on histology. Different clinical outcomes and behaviors have been observed for several disease sub-types [11].

Breast cancer may be roughly classified into three kinds based on the extent of invasion. They might be intrusive, non-invasive, or different [12]. Breast cancer, in its non-invasive or pre-invasive stage, is defined as epithelial neoplasia limited to the breast's duct or lobule; on the other hand, the invasive type of the disease indicates that cancer cells have penetrated the basement membrane and spread from the ductolobular system to the surrounding stroma. Variants have been found in invasive breast tumors from a histology perspective. The two most frequent types of invasive breast cancers are invasive ductal and invasive lobular carcinoma, with invasive ductal accounting for around 80% of all cases [13]. Most clinically proven in situ breast cancers are ductal carcinoma, which may act as a trigger for the emergence of invasive breast cancer [14].

Most cases of breast cancer usually occur with no traces of family history [15]. Environmental and non-genetic factors shared among relations could also predispose individuals to acquire breast cancer [16]. However, the environmental factors seem to be more readily under control when compared with the genetic factors [17]. Other risk factors include diet, smoking, depression, and stress [18].

According to [19], breast cancer may develop later in life because of several acquired somatic mutations or be linked to a person's first- or second-degree relatives. A mutation in autosomal dominant causes a genetic predisposition that accounts for 5–10% of breast cancer cases. Two major kinds of genetic variations might predispose someone to breast cancer: One is a loss of function mutation in the tumor suppressor gene, which, when inherited, accounts for 70% of the risk of breast cancer development in women before the age of 70 [20], snowballing into unrestricted cell growth and division with a failure in the DNA repair mechanism; the second is a gain of function mutation in the proto-oncogene.

There are different forms of breast carcinoma. Steroid hormone receptors (HRs) have been found as significant prognostic factors for breast cancer [21]. Breast cancer cells with HRs expressing estrogen (ER), progesterone (PR), or both are referred to as ER-positive (ER +), PR-positive (PR +), or ER/PR positive (ER + /PR +) breast cancers, respectively. Most breast carcinomas are ER +, of which more than half are both ER + /PR +, while only about 2% are reported to be solely PR + . Triple-negative breast cancer (TNBC) are cancerous cells lacking ER and PR with little or no expression of human epidermal growth receptor 2 (HER2). Accumulating evidence showed that about 10–15% of all breast carcinomas are TNBC [22]. The tumor suppressors BRCA1 and BRCA2, which participate in genome stability and repair pathways like mismatch repair, inter-strand DNA crosslink repair, transcription control, stabilization of the DNA replication fork, and participation in DNA damage checkpoints [23], are among the genes that have been linked to hereditary breast cancer. Mutations in these genes have been linked to around 25% of hereditary breast cancers [24]. Up to the age of 80, those who have BRCA1 or BRCA2 gene mutations are very susceptible to developing breast cancer [25]. Triple-negative breast cancer with a basal-like phenotype and high proliferation rate is caused by a mutation in the BRCA1 gene, whereas individuals with a mutation in the BRCA2 gene are more likely to develop ER and/or PR-positive breast cancer [26]. In addition to BRCA1 and BRCA2, uncommon gene abnormalities have also been linked to an increased risk of developing breast cancer. These moderately penetrant genes include CHEK2, BRIP-1, PALB2, or ATM [27]. In contrast, the high penetrant genes include PTEN (phosphatase and tensin homolog [28] and STK11 (serine/threonine kinase 11) [29]. The others include TPK53, phosphoinositide 3-kinase (PIK3), MDM2, RB, and HER2 [12]. The tumor suppressor gene TP53 is crucial for senescence, apoptosis, DNA repair, and cell cycle regulation. It also contributes to preserving genomic stability [30]. The oncogene known as the tumor suppressor gene p53 was first identified in 1979 [31]. The human p53

gene is on 17p13 with a molecular weight of 53 kDa and a length of 20 kb. It has 10 exons and 11 introns, and more than 200 single nucleotide polymorphisms (SNPs) have been found in both coding and non-coding sections of the gene. According to [32], p53 mutations result in genetically unstable cells that cannot control cell proliferation. This leads to ineffective DNA repair, which increases the risk of neoplasia because of chronic genomic damage. According to [33], the emergence of lumps, compactness of dimples, redness, and pain are some of the typical symptoms linked to the start of breast cancer.

3. Multidrug resistance in cancer cells

3.1. Mechanisms of actions

3.1.1. Activation of DNA repair pathways

Another way that tumor cells might develop resistance to anticancer medications is via their capacity to repair DNA damage (Figure 1). To effectively repair DNA damage caused by crosslinking and platinum-based medications, DNA repair endonuclease XPF and DNA excision repair protein ERCC1 are actively engaged in and crucial to the nucleotide excision repair (NER) pathway [34]. Research has shown a noteworthy association between the overexpression of the XPF and ERCC-1 proteins and the emergence of resistance in cisplatin-treated cancer cells [35].

Moreover, decreased activity of the DNA mismatch repair (MMR) pathway causes increased damage tolerance, which might result in increased mutagenicity and chemoresistance. It is known that ataxia telangiectasia and the Rad3-related protein ATR kinase are involved in controlling the DDR process. Its inhibition has been shown to increase certain cancer cells' susceptibility to DNA-damaging chemicals, such as compounds based on platinum, *in vitro*. RAD51 is another protein involved in the homologous recombination (HR) pathway in DNA repair that oversees DNA double-strand break repair. It attaches to ssDNA and exchanges breaks in DNA strands to promote HR repair. Multiple myeloma cells have been shown to overexpress it, and its increased HR has been associated with chemoresistance and poor patient survival.

The TLS pathway is another important process for restoring interstrand DNA cross-links (ICLs). Cancer cells with mutations in TLS DNA polymerase Rev1 alter TLS activity, which helps the proliferating cells survive by increasing their resistance to DNA damage during replication.

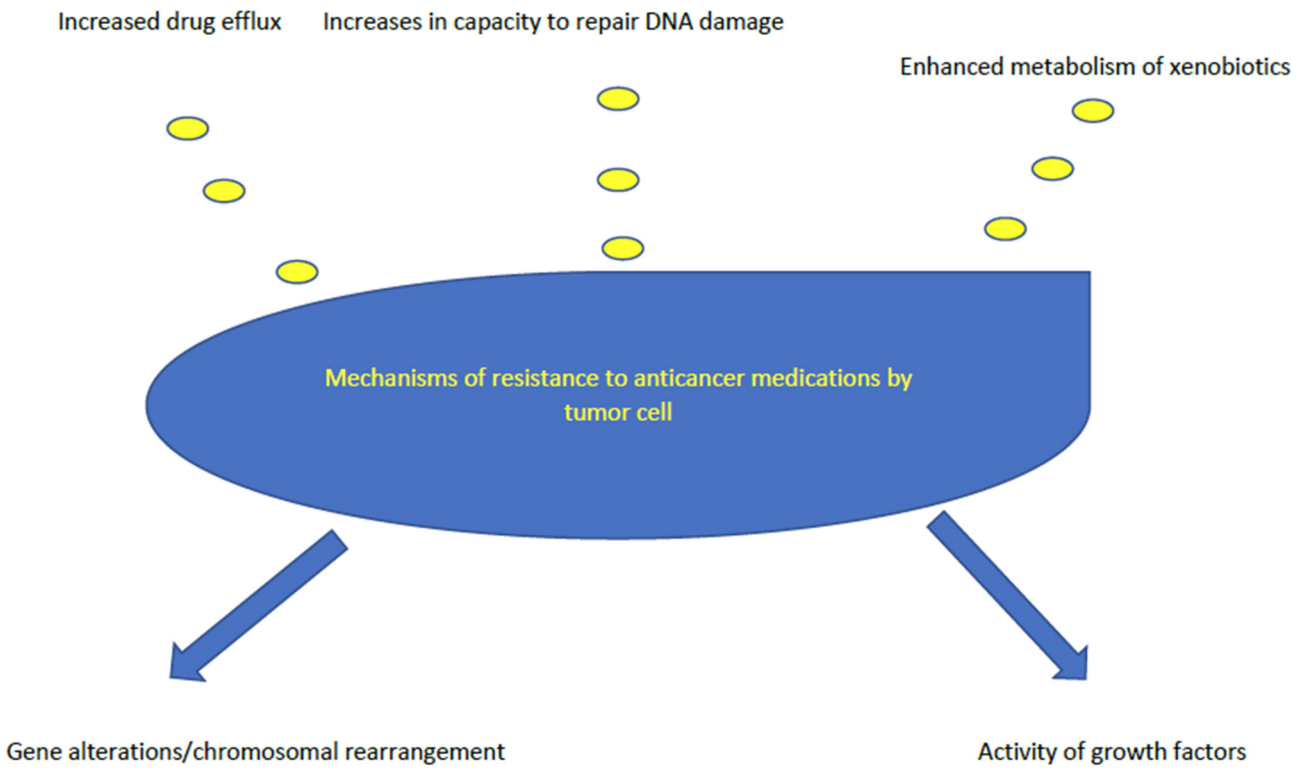

Figure 1. Mechanisms of multidrug resistance in cancer cells.

3.1.2. Genetic factors

One of the major reasons why chemotherapy treatments do not work is recognized to be gene alterations. Numerous investigations have proposed that drug-sensitive genes disappearing or biochemical pathways changing often due to chromosomal rearrangements or loss during mitosis are critical components of chemotherapeutic drug resistance (Figure 2).

According to [36], the TP53 gene is crucial for protecting organisms against the development of tumors and neoplastic transformation. In addition to regulating the cell cycle and inducing apoptosis or G1 arrest, this tumor suppressor is also responsible for maintaining cellular homeostasis and genomic integrity, achieved via the coordination of effector pathways and the organization of various activities. One of the most well-known indicators of carcinogenesis is the presence of TP53 gene alterations, often seen in cancer cells. The TP53 pathway's protective function may be negatively impacted by the initiation of chemoresistance, invasion, and metastasis brought on by missense mutations in the TP53 gene, regularly seen in human malignancies. Anticancer medications normally cause DNA damage by activating TP53, which results in cell death. As a result, cancer cells that lack TP53 function would be able to replicate regardless of the kind or degree of DNA damage, rendering them immune to genotoxic medications [37].

Tumor cell gene mutations often result in changes to the cells' reaction to target molecules, making the cells resistant to the medication. The altered gene is still active, but it can no longer bind to the medication because of modifications to its stereochemical structure. Antiestrogen therapy for breast cancer is a well-known example of this mechanism of resistance, where individuals who originally responded appropriately to tamoxifen treatment eventually lose their sensitivity to an

endocrine manipulation. The progressive depletion of estrogen receptors in mutant cells causes this unresponsiveness [38].

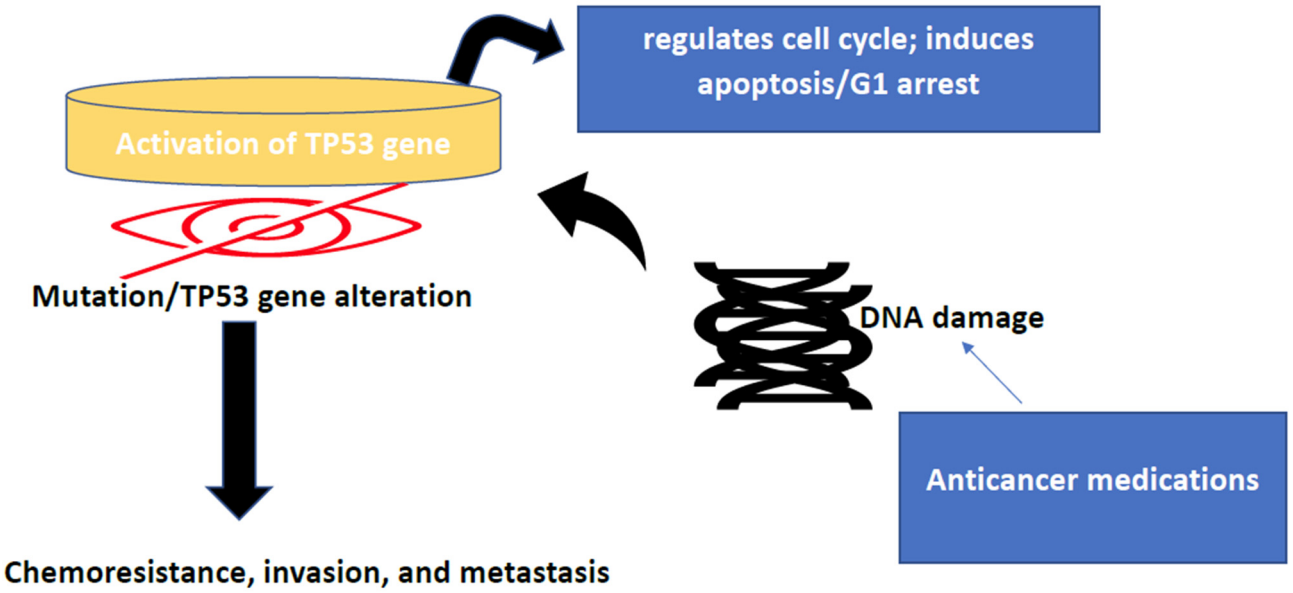

Figure 2. Mutation and MDR.

3.1.3. Growth factors

Multidrug-resistant cancer cells, when compared to drug-sensitive tumor cells, have been shown to produce more growth factors, including interleukin (IL)-1, IL-4, IL-6, and IL-8 [39]. Research [39] has shown a robust association between MDR of gastric cancer cells and IL-6 activity in cancer-associated fibroblasts found in the tumor stroma. The application of tocilizumab, an anti-IL-6 receptor monoclonal antibody, prevented the chromatin assembly factor-1 (CAF)-mediated inhibition of apoptosis, which can increase the responsiveness of gastric cancer cells to anticancer agents. It was shown that IL-6 is a CAF-specific secretory protein, conferring chemoresistance by paracrine signaling in gastric cancer cells. The activation of the Ras mitogen-activated protein kinase/ERK kinase/extracellular signal-regulated kinases (Ras/MEK/ERK) and phosphoinositide 3-kinase AKT (PI3K/Akt) signaling pathways, the overexpression of MDR-related genes, such as ABCB1, and the activation of caspase-3 and apoptosis inhibitory proteins (XIAP, Bcl-xL, and Bcl-2) have been connected to the increased expression of IL-8 seen in ovarian cancer cells [40]. This provides support for the idea that regulating IL-8 expression might be a helpful therapy approach for metastatic ovarian cancer. According to studies demonstrating a high correlation between proliferation and the activity of fibroblast growth factors (FGFs), such as FG2, FGF9, and FGF10, Song S et al. [41] established the significance of FGFs in the development of cancer, which is resistant to chemotherapy. Additionally, it has been discovered that elevated levels of extracellular matrix (ECM) and protein kinase C [42,43] in breast tumor cells are linked to the cells' resistance to chemotherapy by encouraging invasion and metastasis, particularly for matrix metalloproteinases (MMPs), such as MMP-2, -9, -11, and -14, which break down matrix proteins. Furthermore, it has been demonstrated that stromal cells, such as adipocytes, cancer-associated fibroblasts, and tumor-associated macrophages (TAMs), are connected

to the development of tumors by forming a network of vessels that feeds the tumor mass and enables TAMs to secrete vascular endothelial growth factor A (VEGF-A), which leads to tumor invasion [43].

3.1.4. Enhanced drug efflux

P-glycoprotein (P-gp)/ATP-binding cassette subfamily B member 1 (ABCB1) and breast cancer resistance protein (BCRP), which are found in the cell membrane, are examples of ATP-binding cassette proteins that help control the distribution, absorption, and excretion of many kinds of chemical substances. They may impede drug delivery, reducing the drug's bioavailability and intracellular concentration, since they defend against cell death from high intracellular drug concentration [44]. Chemotherapeutic medicines' ability to penetrate target areas is decreased when P-gp is highly expressed on the surface of endothelial cells [45,46]. Anticancer medications that are physically and functionally unrelated may be removed from cancer cells via P-gp and BCRP, which lowers bioaccumulation [47]. In patients with multiple myeloma, acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, and metastatic breast cancer, overexpression of P-gp and BCRP has been associated with poor clinical response and MDR [47]. Additionally, it has been observed that P-gp inhibits the tumor necrosis factor, which contributes to cancer cells' MDR-related mechanisms of apoptosis, including caspase- and TRAIL-mediated pathways, as well as the efflux of intracellular chemotherapeutic drugs [48].

3.1.5. Increased activity of detoxifying enzymes through antioxidative stress-related pathways

3.1.5.1. Kelch-like ECH-associated protein 1 (Keap1) and nuclear factor erythroid 2-related factor signaling pathway

Cells act via the oxidative stress response when intracellular ROS production becomes excessive [49]. ROS has a variety of effects on how genes are expressed in cells. The Keap1-Nrf2 pathway is a well-known method of cell resistance to ROS. This mechanism increases the number of antioxidants in the cell and rewires its metabolism to create more glutathione and other compounds by triggering the transcription of many cytoprotective genes. These actions may aid the cell in fending off ROS-induced cell damage. An essential function of the Keap1-Nrf2 signaling pathway is cell adaptability and protection against oxidative stress. Nuclear factor erythroid 2-related factor 2 (Nrf2) and Kelch-like ECH-associated protein 1 (Keap1) are the two primary components of the signaling pathway [50]. Under normal physiological conditions, Keap1 interacts with Cullin 3 (Cul3) to create an E3 ligase complex that triggers Nrf2 ubiquitination. This, in turn, causes Nrf2 to be targeted, degraded, and inactivated by the 26S proteasome [51]. This may stop the Keap-Nrf2 signaling pathway from being activated.

However, when chemotherapy medicines raise the amount of ROS in cells, Nrf2 may be activated by dissociating from Keap1 during chemoresistance. The mechanism entails the oxidation of cysteine residues in Keap1, which causes Keap1 to separate from Nrf2 and slow down the rate at which Nfr2 breaks down. It has been shown that the three functionally significant cysteines that control Keap1-Nrf2 activation are Cys151, Cys273, and Cys288. While a subset of Nrf2 activators targets Cys151, Cys273 and Cys288 are known to be vitally necessary for the inhibition of Keap1 by Nrf2 under normal circumstances. Other proteins with an ETGE amino acid motif that are implicated in

Nrf2 regulation under stressful conditions include dipeptidyl peptidase 3, protein kinase B (PKB/AKT), protein kinase C extracellular-regulated protein kinases, transcriptional factor EB, protein kinase-like endoplasmic reticulum kinase, and acetyltransferase p300. When Nrf2 separates from Keap1, it becomes activated and moves to the nucleus, promoting oxidative stress adaption. It interacts with one of the small MAF (sMAF) proteins after translocation into the nucleus to produce the Nrf2-sMAF heterodimer, which is crucial for inducing the expression of cytoprotective genes and causing cancer cells to become resistant to chemotherapy. It attaches to cytoprotective genes known as the antioxidant response element [52]. The most common method by which Nrf2 is known to increase cancer cells' resistance to oxidative stress is by binding the Nrf2-sMAF heterodimer, which has been proposed to mostly lead to increased antioxidant levels and reprogramming metabolism [53].

3.1.5.2. MAPK/JNK signaling pathway

Due to their conjugating activity, glutathione-S-transferases (GSTs) are enzymes linked to resistance to various anticancer medications in a wide range of malignancies. Their expression levels in cancer cells are often high when compared to normal cells [54]. This overexpression could contribute to an elevated detoxification of anticancer drugs [55]. In addition, GSTs have also been observed to be involved in synergistic interactions with efflux pumps. Following the conjugation process, efflux transporters, such as MRP1 and P-glycoprotein, which are members of the superfamily of ATP-binding cassette transporters, actively transport the so-called GS-conjugates out of cells [56]. Therefore, overexpression of GST and efflux pumps may confer high resistance to the cytotoxic action of certain anticancer medicines.

By inhibiting the JNK signaling pathway, GSTs may potentially impart multidrug resistance via a non-catalytic method. This is an occurrence that keeps the tumor cells safe. The activity of members of the mitogen-activated protein kinase (MAPK) family is regulated by GSTs, which have been identified as modulators of signal transduction pathways involved in cell survival and death [42]. Specifically, GSTP1-1 may shield cancer cells from signals of apoptosis by directly interacting with other proteins to inhibit c-Jun N-terminal kinase (JNK), a component of the MAPK cascade, in a non-catalytic manner [57]. The complex may separate in response to various extracellular stimuli, and JNK may then phosphorylate c-Jun, a transcription factor component of activator protein-1. Consequently, AP-1-dependent target genes that are involved in DNA repair, cell division, and apoptosis are induced [58]. When GSTP1-1 is in its monomeric state, it binds to both c-Jun and JNK to create a heterotrimeric complex that prevents JNK from phosphorylating c-Jun. When the enzyme separates from JNK, GSTP1-1 dimerizes. Moreover, GSTP1-1 can bind to and block TRAF2, an upstream JNK activator, preventing the MAPK/JNK signaling cascade from occurring at many different levels [59]. Further, GST activities and their effects on some antineoplastic agents which could invariably contribute to the resistance of drugs during cancer chemotherapy are described below:

Cisplatin

Cisplatin is one of the most efficacious antineoplastic drugs but with several side effects. It intercalates with DNA to form adducts such as crosslinks between DNA and proteins, which may initiate signal transduction pathways that result in apoptosis [60]. On the other hand, this anti-cancer medication may be bound and rendered inactive by reduced glutathione (GSH) [61]. Its thiol group is

highly concentrated when cisplatin is present, which reduces the drug's bioavailability. Its non-enzymatic conjugation to cisplatin, which GSTs may catalyze, significantly increases drug resistance [62].

Dichloroacetate

A byproduct of water chlorination, dichloroacetate (DCA) treats illnesses, including hyperproliferative conditions and hereditary mitochondrial diseases [63]. Dichloroacetate is metabolized by a bifunctional enzyme known as GST of the zeta class (GSTZ1-1); this enzyme dechlorinates the compound to glyoxylate, which renders it inactive and confers resistance to DCA therapy [64]. It has recently been shown that aberrant control of GSTZ1-1 expression in cancer cells may affect DCA metabolism, which may change the response to treatment [64].

3.1.5.3. PI3K-AKT pathway

ROS are well-known and regarded as one of the major mediators of chemotoxicity, which results in the death of cancer cells. Some chemotherapy drugs can upregulate their intracellular levels to a threshold that can trigger tumor cell death; a prooxidant therapy that is being utilized to treat patients, which can eventually give rise to chemoresistance [65]. One important reducing agent for antioxidant defense mechanisms is NADPH. It provides tumor cells with defense against ROS toxicity. The oxidative PPP pathways and ME- and IDH-dependent NADPH synthesis increase its cytosolic pool. Thus, the ongoing production of ROS during chemotherapy triggers the PI3K-AKT and Keap1-Nrf2 pathways. These signaling pathways have a role in the increase of the expression of certain PPP enzymes as well as the control of several downstream antioxidative actions. The PI3K-AKT pathway also promotes the development of IDH and ME, which helps to liberate NADPH from NADP+ via the middle effector SREBP.

These activated antioxidant pathways not only increase NADPH synthesis but also raise antioxidant levels to inhibit ROS formation. Activating the PI3K-AKT or Keap1-Nrf2 signaling pathway in response to elevated ROS levels confers chemoresistance in cancer cells by enabling them to tolerate ROS production induced by prooxidant treatment. It has been discovered that these two signaling pathways contain inhibitors, which may provide therapeutic options for reducing chemoresistance. These include delicaflavone, a potent inhibitor of the PI3K-AKT signaling pathway, trigonelline, an effective inhibitor of Nrf2, to overcome oxaliplatin resistance in colon cancer cells [66]. Halofuginone was reported to be one of these. For chemotherapeutic sensitivity, the Keap1-Nrf2 and PI3K-AKT pathways should be considered.

3.2. Multidrug resistance in breast cancer cells

Exposure to a chemotherapeutic agent may predispose cancer cells to develop resistance to many medications that are physically and functionally unrelated, but they can also exhibit cross-resistance to these treatments, a phenomenon known as MDR in cancer cells [67,68]. According to the researchers in [69], intrinsic or acquired MDR continues to be a major obstacle to effective chemotherapy, which may lead to the return of malignant tumors and, in the end, relapse or death. Resistance to chemotherapy is a major issue in the treatment of breast cancer, as many cancers that were originally

receptive to treatment relapse and become resistant to anticancer drugs with different structures and modes of action. Numerouspathways may cause drug resistance. Reductions in intracellular drug concentrations may be caused by an increase in the activity of ATP-dependent efflux pumps, such as P-gp, ABCB1, multidrug resistance protein 1 (MRP-1, ABCC1), and ABCG2, which are mediated by the ABC transporters superfamily of proteins [70]. Clinical agents that are most often associated with this kind of resistance include paclitaxel, vinblastine, daunorubicin, doxorubicin, and vincristine [71].

Resistance may also result from decreased cellular drug absorption. Nutrient transporters may bind to medications that are soluble in water. As a result, the cell may experience bioaccumulation. This mechanism mediates resistance, which is often present in medications like cisplatin, 8-azaguanine, and 5-fluorouracil [72]. Other causes of drug resistance include activation of DNA repair pathways and increased activity of detoxifying enzymes such as cytochrome P450 mixed function oxidases. Furthermore, alterations in the cell cycle mechanisms that activate checkpoints and prevent the initiation of apoptosis, or malignant transformation-related defective apoptotic pathways [73], can also result in resistance [74]. Drug targets that have changed, inadequate drug penetration, and altered prodrug activation capabilities are other factors contributing to drug resistance.

The contribution of PDE5 to multidrug resistance has been noted in the downregulation of the cGMP pool and a decrease in protein kinase-G, a downstream effector of cGMP [75]. The process involves hydrolyzation of the 3′,5′-phosphodiester bond in the second messenger molecule cGMP to an inactive 5′-GMP by PDE5. PDE5 is allosterically activated by the increased level of cGMP via cGMP binding to its regulatory domain, resulting in enhanced activity of the PDE5 catalytic domain, and subsequently, bringing the intracellular cGMP concentration to the basal levels. The reduction in cGMP level is due to its degradation and efflux by PDE5 [76]. Multidrug-resistant proteins mediate the increased degradation and efflux of cGMP. This action leads to multidrug resistance in breast cancer cells. The degradation of cGMP by PDE5 plays an important role in the rapid termination of relaxation in smooth muscle of blood vessels [77]. Therefore, the modulatory effect of PDE5 inhibitors can impact many signaling pathways associated with breast cancer cell growth and survival and enhance blood flow to tumors by regulating the vascular endothelial growth factor expression, thereby improving drug delivery of therapeutic agents [78] through blood flow in breast tumors, resulting in an improvement in the delivery of chemotherapeutic drugs.

4. Protection of sildenafil against multidrug resistance in breast cancer

Increasing scientific and clinical interest in targeting phosphodiesterase (PDE) using pharmacological agents to modulate their effects in pathologic cases is emerging. PDEs have a great influence on the intracellular concentration of second messengers, cAMP, and cGMP via activation and inhibition [79]. Studies have shown their high expression in bladder and breast cancers [80] and there are indications that PDE inhibitors (PDEIs) may serve or be useful as antitumor compounds when used alone or synergistically [79].

4.1. Mechanisms of protection of sildenafil

4.1.1. PDE5 inhibition by sildenafil: the interactions with NO/cGMP and Wnt/β-catenin signaling pathways

Research has shown that the cGMP signaling system regulates some malignancies, including breast cancer [81]. It is known that cyclic GMP-dependent protein kinase is activated by cGMP. Moreover, the apoptotic mechanism in breast cancer is the activation of protein kinase [82]. As a result, PDE5 inhibition promotes the build-up of cGMP and inhibits the breakdown of cyclic adenosine monophosphate (cAMP), which may be advantageous for the treatment of breast cancer. According to an observation by the researchers in [20], the MDA-MB-231 and ZR-75-1 cell lines have higher PDE5 levels, and sildenafil (1μM) was shown to be a powerful inhibitor of cGMP breakdown in both cell lines. Additionally, the researchers showed that PDE5 inhibition promoted apoptosis and decreased cell proliferation via various ways, including sildenafil therapy. To explain these effects, attenuation of β-catenin-mediated transcription has been proposed. Jedlitschky et al. [83] reported a connection between the removal of cGMP and ABC transporters, demonstrating that sildenafil functions by raising intracellular cGMP concentrations, while the multidrug resistance protein isoform MRP5 (ABCC5) promotes the cellular efflux of cGMP. Sildenafil exhibits a dual function by preventing PDE5 from degrading cGMP and its exportation by ABCC5.

The PDE5 inhibition by sildenafil interacts with NO/cGMP, Wnt/β-catenin, and PI3K/Akt signaling pathways (Figure 3). Phosphodiesterase 5 normally degrades cGMP, reducing nitric oxide's effects. Sildenafil acts by blocking PDE5, enabling cGMP levels to remain elevated. This activates protein kinase G, which can downregulate ABC transporters' expression and reduce cGMP efflux. This prolongs vasodilation, improves blood flow, and enhances NO bioavailability. Other cellular processes impacted are proliferation, apoptosis, and angiogenesis [84]. The relaxation of the smooth muscle of blood vessels and increasing blood flow to tumors improve the delivery of chemotherapy drugs such as doxorubicin [85]. The build-up of cGMP caused by PDE5 inhibition by sildenafil shares crosstalk with Wnt/β-catenin. cGMP modulates the activity of GSK-3β (glycogen synthase kinase 3 beta), a key regulator of the Wnt/β-catenin pathway involved in phosphorylating β-catenin and targeting it for degradation. Elevated cGMP levels inhibit GSK-3β, leading to β-catenin stabilization. This interplay has been documented to preferentially reduce the metastatic potential by altering cancer stem cell activity in a mouse model of breast cancer [86]. Targeting this pathway by therapeutic agents has been proposed to be applicable in preventing and managing breast cancer [87].

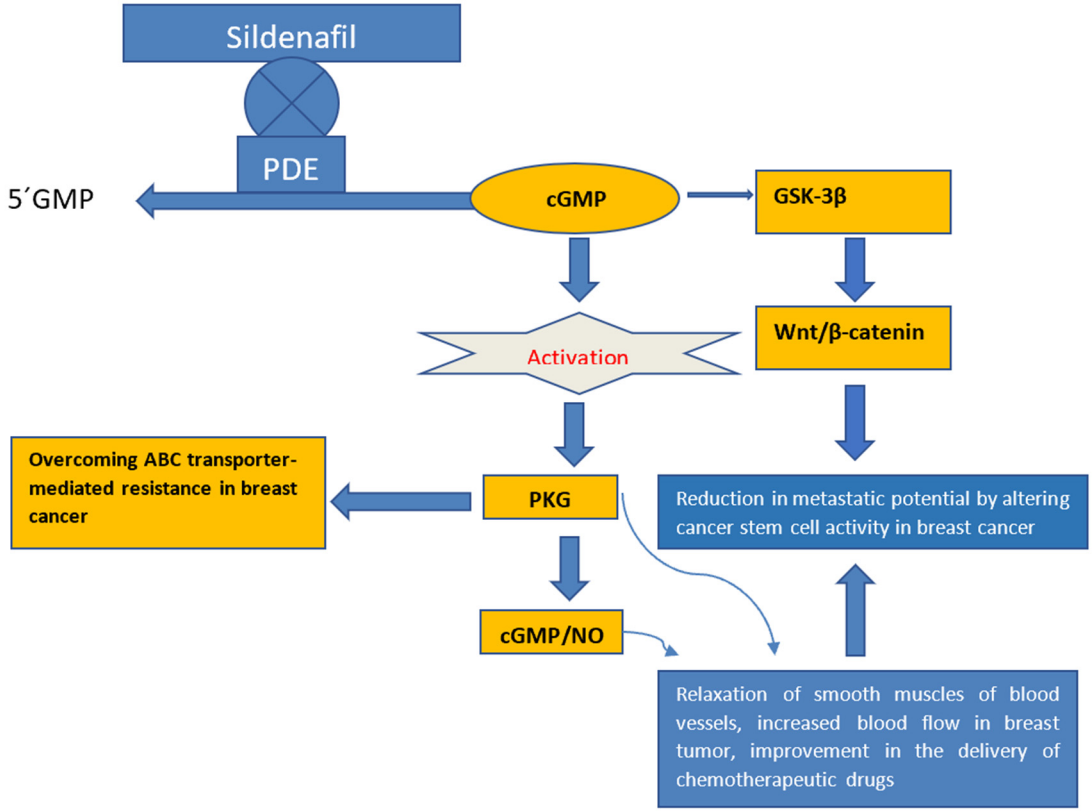

Figure 3. Phosphodiesterase 5: a crucial drug target for reversing MDR in breast cancer.

4.1.2. Sildenafil's role in multidrug resistance: the interplay between ABC transporters' utilization of cGMP and PDE5 inhibition

ATP-binding cassette transporters are a family of transmembrane proteins that play a critical role in the efflux of various substances, including drugs, from cells. They use energy sourced from ATP hydrolysis to actively transport substrates across cellular membranes, which contributes remarkably to MDR [88]. MDR is a common challenge in cancer treatment and infectious diseases, as it diminishes the intracellular concentration of therapeutic agents, reducing their efficiency [89]. ABC transporters are classified into seven subfamilies (ABCA to ABCG) based on sequence homology and structural organization. Among these, specific members are prominently associated with drug resistance.

ABCB1 typically known as P-glycoprotein (P-gp), is a prominent member of the ABC transporter family. It is a transmembrane protein that plays a significant role in cellular detoxification by actively effluxing xenobiotics and endogenous substances out of cells. While its physiological role involves protecting tissues from toxic substances, ABCB1 is also implicated in multidrug resistance (MDR), a significant challenge in cancer chemotherapy [90]. ABCB1 functions as an ATP-dependent efflux pump. It binds to various substrates, including chemotherapeutic drugs, and uses energy from ATP hydrolysis to transport the molecules across the plasma membrane. This diminishes the intracellular concentration of drugs and limits their ability to interact with their molecular targets within cancer cells [91]. One of the most striking features of ABCB1 is its broad substrate specificity, which includes many chemotherapeutic agents. These drugs stabilize microtubules and prevent their depolymerization. DNA intercalating agents and topoisomerase inhibitors such as anthracyclines are among the most

widely used chemotherapeutics. However, ABCB1 overexpression significantly lowers their cytotoxic effects [92].

The overexpression of ABCB1 is shown in various cancers, including breast, ovarian, colorectal, lung, and leukemia. It is often associated with resistance to first-line chemotherapeutic agents and poor clinical outcomes. Tumors with elevated ABCB1 activity can thrive even with high-dose chemotherapy regimens, making them particularly difficult to treat [93]. Moreover, ABCB1 is highly expressed in cancer stem cells (CSCs), a subpopulation within tumors responsible for recurrence, metastasis, and therapy resistance. This expression further complicates treatment as CSCs can repopulate tumors even after chemotherapy, contributing to relapse [94].

Considerable measures have been directed at overcoming ABCB1-mediated drug resistance [95]. Sildenafil has emerged as a promising candidate for reversing ABCB1-mediated resistance. The inhibition of the efflux activity of ABCB1 by sildenafil increases the intracellular retention of drugs like paclitaxel and doxorubicin, enhancing their therapeutic efficacy [96]. Recent studies have demonstrated that sildenafil can inhibit ABCB1 by targeting its ATPase activity, reducing drug efflux. In preclinical breast cancer models, sildenafil has been shown to sensitize resistant cells to doxorubicin and paclitaxel, leading to enhanced drug accumulation and apoptosis. This makes sildenafil a compelling adjuvant therapy in cancers, where ABCB1 plays a significant role in MDR [97].

The ABCC subfamily, encompassing multidrug resistance-associated proteins, plays a key role in mediating MDR. ABCC4 overexpression has been linked to poor therapeutic outcomes in drug-resistant cancers. It effluxes various chemotherapeutic agents, including nucleoside analogs like 6-mercaptopurine and cytarabine, essential drugs in cancer and antiviral therapies. This action by ABCC4 reduces their cytotoxic potential, allowing the malignant cells to evade apoptosis and continue proliferating. Additionally, ABCC4 transports cyclic nucleotides and signaling molecules like prostaglandins, which modulate inflammatory responses and tumor progression, further complicating cancer treatment [88].

ABCC5 is a key mediator of drug resistance, actively exporting chemotherapeutic agents like 5-fluorouracil (5-FU) and other nucleoside analogs. This function decreases the intracellular concentrations of the drugs, undermining their efficacy and empowering cancer cells to evade apoptosis. Moreover, its efflux of signaling molecules such as cGMP and cAMP further disrupts pro-apoptotic pathways and supports tumor survival and proliferation [98]. ABCG2 actively effluxes drugs such as topoisomerase inhibitors, anthracyclines, and tyrosine kinase inhibitors, making it a formidable barrier in the fight against cancer. By transporting these agents out of cancer cells, ABCG2 enables tumors to survive and proliferate despite aggressive therapies. Additionally, ABCG2 mediates the transport of signaling molecules like porphyrins and flavonoids, which can further influence cancer cell behavior by modulating intracellular signaling pathways [99].

Sildenafil can inhibit ABC transporters' activities, effectively modulating their efflux activity and enhancing the intracellular retention of therapeutic agents through the various signaling pathways discussed below (Figure 4).

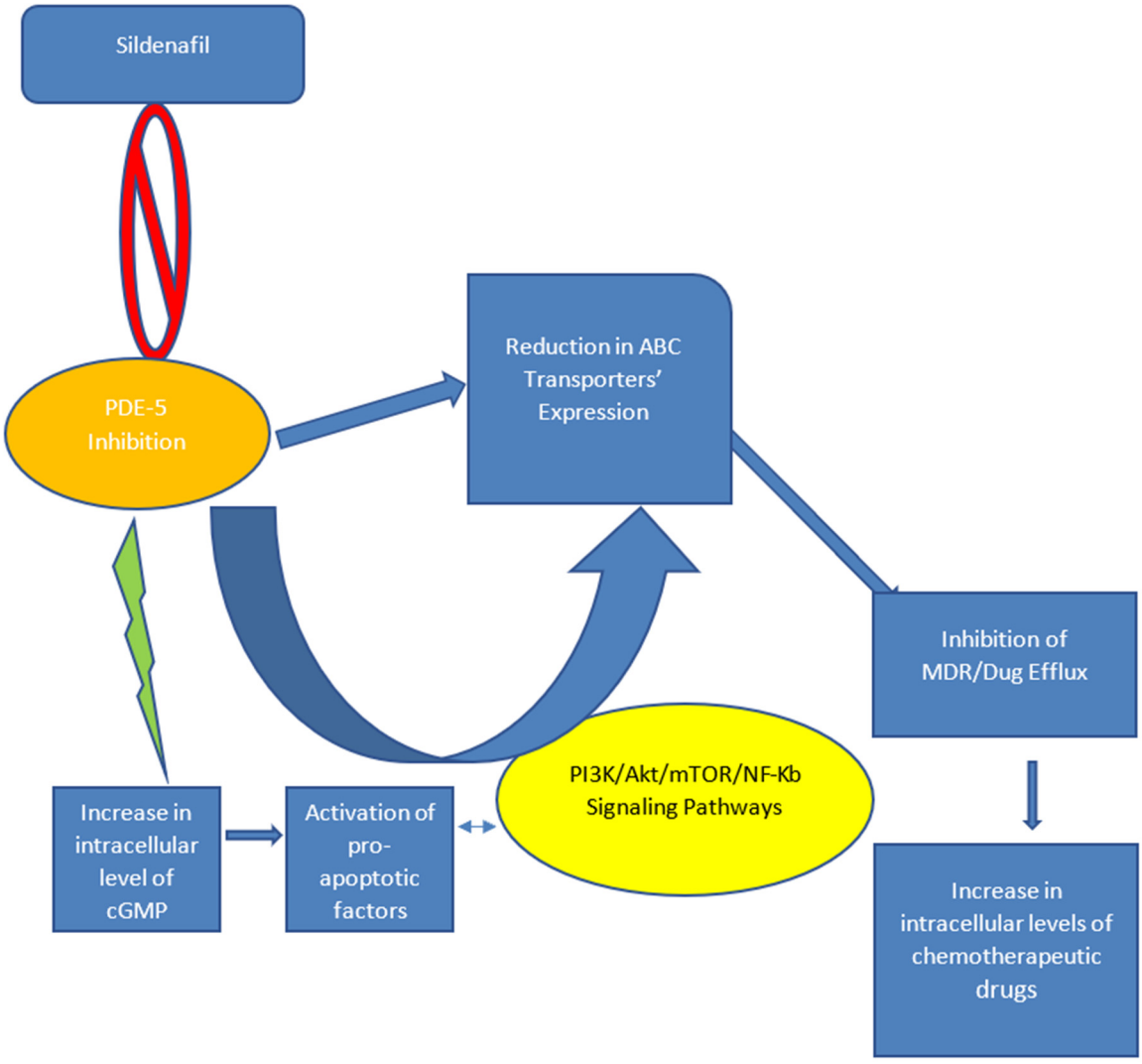

Figure 4. PDE5 inhibition as a central measure of overcoming MDR by sildenafil in breast cancer.

4.1.2.1. ATP hydrolysis inhibition pathway

Sildenafil inhibits the ATPase activity of ABC transporters (ABCB1, ABCC4, ABCC5, and ABCG2), reducing their ability to utilize ATP to pump drugs out of cancer cells actively. This disrupts the energy-dependent efflux process, increases intracellular drug retention, and enhances cytotoxicity [100]. Sildenafil's inhibition of ABCG2 extends beyond drug retention. It also affects the transport of signaling molecules, including porphyrins, which are involved in cellular processes such as oxidative stress and apoptotic regulation. By disrupting the efflux of these molecules, sildenafil enhances pro-apoptotic signaling pathways, contributing to cancer cell death and improving therapeutic outcomes [101].

Sildenafil's inhibitory action on the ATPase activity of ABCC4 reduces the energy required for the transporter to function. This disruption leads to the intracellular accumulation of therapeutic agents, such as nucleoside analogs, enhancing their cytotoxic effects against cancer cells [102]. Furthermore, sildenafil's inhibition of ABCC4 efflux prevents the export of cyclic nucleotides, particularly cGMP, which sildenafil naturally elevates by inhibiting PDE5. The increased intracellular cGMP levels

activate protein kinase G (PKG), a pro-apoptotic signaling pathway, contributing to cancer cell death [103].

Sildenafil interferes with ATP hydrolysis and effectively reduces the ABCC5 transporter's ability to efflux chemotherapeutic drugs and cyclic nucleotides, resulting in their intracellular accumulation. This action amplifies the cytotoxic effects of nucleoside analogs, such as 5-FU, by maintaining higher intracellular drug concentrations, which are essential for disrupting DNA synthesis and inducing apoptosis in cancer cells [104].

4.1.2.2. Modulation of signaling pathways

The phosphatidylinositol-3-kinase and the mammalian target of the rapamycin (mTOR) signaling pathway are essential for cell proliferation and survival. The PI3K/Akt/mTOR pathway promotes the development of drug resistance by activating ABC transporter overexpression in several cancers, including breast cancer, which may induce drug efflux [105]. The PI3K pathway activates lipid kinases by binding to growth factor receptors such as epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR), by utilizing an adaptor protein that binds with p110 and p85 to activate PI3K [106]. The activated PI3K pathway converts phosphatidyl 3,4-bisphosphate (PIP2) into secondary messenger 3,4,5-triphosphate (PIP3). Activated PIP3 binds to phosphoinositide-dependent kinase-2 (PDK2), phosphorylating and activating Akt kinase [107] Activated Akt kinase then translocates from the cytoplasm to the nucleus, activating downstream genes such as *mTOR and NF-κB*. These proteins are actively involved in drug resistance by enhancing the expression of ABC transporters. Sildenafil inhibits these ABC transporters and affects downstream signaling pathways such as PI3K/Akt/mTOR, MAPK, and NF-Kb [108]. PI3K/Akt/mTOR signaling pathway is one of the most frequently disrupted pathways in malignancies, making it a target pathway of interest for treatment. These pathways mediate cell survival, drug resistance, and apoptotic regulation. Their disruption sensitizes cancer cells to chemotherapy and reduces resistance.

4.1.2.3. Apoptotic pathway activation

The increase in intracellular levels of pro-apoptotic molecules such as caspase-3 and Bax and a decrease in anti-apoptotic factors such as Bcl-2 by sildenafil can enhance apoptotic signaling. This promotes cancer cell death, further overcoming resistance mechanisms mediated by ABC transporters.

4.1.3. Increase in permeation retention

Relaxing the smooth muscle modifies the permeability of the vascular endothelium, increasing blood flow and potentially improving blood flow in both normal and diseased tissues, including inflammatory and tumorous tissues. Blood flow enhancements can improve medication accumulation and promote preferred drug targeting in sick tissues, such as tumors. It has been shown that sildenafil is one kind of PDE5 inhibitor that affects blood vessel smooth muscle layers, resulting in vasodilation in tissues expressing the particular isoenzyme [8]. The combination of sildenafil and doxorubicin in tumor tissues enhanced doxorubicin concentration by 2.7-fold and improved anti-cancer action against breast cancer by 4.7-fold [109]. According to [110], sildenafil works by increasing the permeability of

tumor capillaries, which improves permeation retention. The steady-state volume of distribution (105 L) and quick absorption of sildenafil, which reaches a peak plasma concentration in an hour and has a half-life of three to four hours, is shown by the drug's pharmacokinetics. This shows that the drug's capacity to attach to tissues and distribute within them, as reported by [111], is advantageous for its usage as an anti-cancer agent. Furthermore, Zhang et al. [112] suggested that tumor acidity is an additional element that can release PDE5 inhibitors selectively and increase their concentration in cancer tissues. This is a tactic that has been shown to enhance medication accumulation as well as anti-cancer action. These findings point to the possibility that sildenafil as a PDE5 inhibitor may improve the delivery of anti-cancer drugs via increased permeation retention.

4.2. Interactions of sildenafil with drug molecules in breast cancer treatment: the synergistic effects in MDR reversal

4.2.1. Sildenafil and doxorubicin

Doxorubicin is a commonly used anthracycline in breast cancer treatment. Its effectiveness is often compromised due to the overexpression of ABC transporters, which facilitate its efflux thereby reducing its cytotoxic efficacy [113,114]. Studies have demonstrated that sildenafil inhibits ABCB1-mediated efflux, leading to increased intracellular retention of doxorubicin and enhanced cytotoxic effects. A clear demonstration of improved cytotoxic activity of co-therapy of doxorubicin and sildenafil has been noted with an improved clinical response and patient survival rate while ameliorating doxorubicin's toxic side effects [75]. Also, *in vitro* potentiation of doxorubicin cytotoxicity by sildenafil in a panel of breast cancer cell lines, and an *in vivo* reduction in tumor growth rate in a 4T1 breast cancer model has been documented [75].

4.2.2. Sildenafil and crizotinib

The cytotoxicity of sildenafil and crizotinib on MCF-7 human breast cancer cell lines has been studied. *In vitro* cytotoxicity assays with crizotinib alone displayed 22% cellular viability, compared to a reduction to 10% upon co-administration of sildenafil. It was reported as a 2.2-fold decrease in cell viability after 48 hrs treatment. This has been attributed to the inhibitory effect of sildenafil on ABC efflux transporters, hence overcoming cancer cell resistance and promoting their apoptosis [115].

4.2.3. Sildenafil and cisplatin

Evidence revealed that sildenafil and cisplatin showed a significant decrease in tumor volume in mice bearing breast cancer tumor compared to the control, as shown in Table 1. After treatment with the combination therapy, an investigation of the local tissue microenvironment showed an increase in caspase-3 levels which can decrease MDR. There was a considerable reduction in tumor necrosis factor-α contents, angiogenin, and vascular endothelial growth factor expression [116]. *In vitro* studies entailing the potentiation of the antitumor activity of co-therapy of cisplatin with sildenafil on MCF-7 human breast cancer cells showed a dose-dependent cytotoxic effect of sildenafil illustrating its potentiation effect on the chemotherapeutic agent [116].

4.2.4. Sildenafil and celecoxib

The researchers in [117] found that the combination of sildenafil with celecoxib was cytotoxic *in vitro* in breast cell lines. *In vivo*, athymic mice bearing BT474 breast cancer tumors were treated with sildenafil (5 mg/kg/day), and celecoxib (10 mg/kg/day) or a combination for 5 days. The combination showed significantly lower tumor growth volume compared to single drug treatment.

Table 1. Studies on the effect of sildenafil on breast cancer.

Type of study	Tumor model	Therapy	Therapeutic effect/mechanism of action	References
In vitro	MCF-7 human breast cancer cells	Cisplatin + sildenafil	Dose-dependent cytotoxic effect of sildenafil, showing its potentiation effect on the chemotherapeutic agent	[116]
In vitro	MCF-7 and MDA-MB-468 human breast cancer cells	Sildenafil (50, 100 μM) plus cisplatin (15 μM and 22 μM)	Tumor cell sensitization to cisplatin, rise of ROS accumulation into the extracellular environment, increased apoptosis via activation of caspase 3 and BAX, and decreased Bcl-2	[118]
In vitro	MCF-7 human breast cancer cell lines	Sildenafil/crizotinib loaded poly (ethylene glycol)-poly (DL-lactic acid) (PEG-PLA) polymeric micelles	2.2-fold decrease in cell viability, after treatment for 48 hrs	[115]
In vivo	Female BalB/c mice inoculated with 4T1 murine mammary carcinoma cells	Sildenafil (1–100 μM) + doxorubicin (1 μM)	Significant reduction of tumor growth with a 2.7-fold rise in drug concentrations when compared to DOX alone	[119]
In vivo	Inoculation of ehrlich ascites carcinoma cells in Swiss albino female mice	Sildenafil (5 mg/kg/d) + cisplatin (7.5 mg/kg) on the 12th day after EAC cells inoculation - sildenafil (5, 12.5, 25, and 50 μg/mL) + cisplatin (5, 12.5, 25, and 50 μg/mL)	Remarkable reduction in tumor volume in mice bearing breast cancer tumor when compared to the control group. Therapy showed an increase in caspase-3 levels with a considerable decrease in tumor necrosis factor-α contents, angiogenin, and vascular endothelial growth factor expression. Sildenafil potentiated cisplatin antitumor activity	[116]

Continued on next page

Type of study	Tumor model	Therapy	Therapeutic effect/mechanism of action	References
In vitro	BT549 breast cancer cell	Sildenafil (0.5 μM) + Celecoxib (1 μM) + FTY720 (~50 nM)	Suppression of anti-apoptotic ERK, AKT, p70 S6K, mTOR, NFκB, activation of JNK, p38 MAPK, ceramide-mediated CD95 activation	[120]
In vitro	MDA-MB-231 human breast cancer cells	Sildenafil (10–50 μM) + HSP90 inhibitor, PU-H71 (50 nM)	Decreased HSP90 expression, degradation of PKD2 and increased apoptosis	[121]

5. Conclusions and future perspective

The side effect known as MDR severely restricts the effectiveness of clinical chemotherapy in the treatment of cancer. The use of cancer models for experimental drug resistance has contributed to the recognition of some of the underlying mechanisms associated with the development of MDR. Many researchers conducting clinical studies have tried to overcome medication resistance, but the results have not been encouraging. Preventing the development of drug resistance is, thus, an important and very valuable tactic in the treatment of cancer. Delaying or preventing the development of drug resistance might be a helpful strategy to boost chemotherapy's efficacy and increase cancer patients' clinical outcomes.

The mechanisms by which sildenafil guards against multidrug resistance in breast cancer have been emphasized in this review. Its pharmacokinetics demonstrated its capacity to bind tissues and its stable distribution into tissues, which are advantageous for its usage as an anti-cancer drug. Additionally, it strategically inhibits PDE5 by docking at the catalytic site of PDE5, which stops the hydrolysis of the phosphodiester bond in cGMP. These may be related to the molecular synergy between sildenafil and anticancer medications that have been shown to provide positive results for *in vitro* breast cancer therapy. These results have strengthened the case for formally recommending repurposing to improve sildenafil's suitability as a medication option for the treatment of breast cancer.

Author contributions

Anne A. Adeyanju, Wonderful B. Adebagbo, Olorunfemi R. Molehin and Omolola R. Oyenihi: conceptualization, writing—original draft preparation, review and editing. All authors have read and agreed to the published version of the manuscript.

Use of AI tools declaration

The authors declare they have not used artificial intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no conflict of interest.

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