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Tamoxifen: The Past, Present, and Future of A Previous Orphan Drug

Ghadier Matariek, John Oluwafemi Teibo, Kholoud Elsamman, Titilade Kehinde Ayandeyi Teibo, David Idowu Olatunji, Amira Matareek, Olabode Ebenezer Omotoso, and Ahmed Nasr

ABSTRACT

Tamoxifen, a non-steroidal selective estrogen receptor modulator is a widely used drug for the prevention and breast cancer treatment. It binds to the hormone-receptors to prevent the binding of the cancer cells in the breast to the hormones they need for growth. It undergoes metabolic activation which converts it to an active metabolite (endoxifen and afimoxifene) by the action of cytochromeP450 isoforms CYP2C9, CYP2D6, CYP3A4.

Notable among its side effects include hot flashes, weight loss, endometrial and uterine cancer, irregular periods, stroke, abnormal fetal development in pregnant women and others discussed in our review. Other than breast cancer, medicinal potential of tamoxifen has been probed in several therapeutic targets. The outcome has shown great promise in managing osteoporosis, infertility, advanced gliomas, lung and liver cancer, among many others. The major drawbacks on the use of tamoxifen have been centered on its resistance and associated side effects. Some of the notable future direction of tamoxifen is centered on overcoming its resistance as well as repurposing of tamoxifen in wider cancer settings.

Targeting LEM4 as a biomarker for predicting tamoxifen resistance in ER-positive breast cancer could be a viable research area in the future to overcome tamoxifen resistance.

Keywords: Anti-neoplastic agents, breast cancer, resistance, selective estrogen receptor modulator, tamoxifen.

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G. Matariek
Faculty of Pharmacy, Mansoura University, Egypt.
(e-mail: ghadiermatariek@gmail.com)
J. O. Teibo*
Department of Biochemistry and Immunology, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Sao Paulo, Brazil.
(e-mail: johnteibo@usp.br)
K. Elsamman
Biochemistry and Nutrition Department, Faculty of Women for Science, Ain Shams University, 11566, Cairo, Egypt.
(e-mail: 29911050200347@std.women.asu.edu.eg)
T. K. A. Teibo
Department of Maternal-Infant and Public Health Nursing, College of Nursing, Ribeirão Preto University of São Paulo Ribeirão Preto, SP-Brazil.
(e-mail: tayandeyi@usp.br)
D. I. Olatunji
Nigeria Centre for Disease Control, Nigeria.
(e-mail: davidi.olatunji@ncdc.gov.ng)
A. Matareek
Faculty of Pharmacy, Mansoura University, Egypt.
(e-mail: amiramatareek99@gmail.com)
O. E. Omotoso
Cancer Research and Molecular Biology Laboratories, Department of Biochemistry, University of Ibadan, Ibadan, Nigeria.
(e-mail; olabodeomotoso@gmail.com)
A. Nasr
Faculty of Veterinary Medicine, Mansoura University, Egypt.
(e-mail: ahmednasr725@std.mans.edu.eg)

****Corresponding Author***

I. Introduction

Tamoxifen [trans-1-(4-b-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene] (Fig. 1), used in the Breast cancer therapy and prevention is one of the World Health Organization's (WHO) list of essential medicine [1].

Tamoxifen is a non-steroidal selective estrogen receptor modulator (SERM). It is used to treat pre- and post-menopausal breast cancers where it acts by competitively

displacing estrogen; the natural ligand for the estrogen receptor in and by preventing the ligating of the receptor with the co-activator in a bid to prevent downstream signaling and proliferation in breast tissue [2].

Since 1998, upon its approval by the FDA, it has been used to treat millions of individuals with hormone-positive breast cancer globally playing the dual role of prevention and treatment, which is estimated to be taken for five years. Hormone receptor-positive breast cancers need either estrogen or progesterone (or both) hormone to grow. Tamoxifen binds to the hormone-receptors to inhibit the binding of cancer cells in the breast to the hormones they need for growth. Tamoxifen is the oldest and most prescribed SERM. In the year 2017, it was identified as one of the most prescribed drugs with over 1 million prescriptions in the United States of America. It undergoes metabolic activation which converts it to an active metabolite (endoxifen and afimoxifene) by the action of cytochromeP450 isoforms CYP2C9, CYP2D6, CYP3A4 [2], [3].

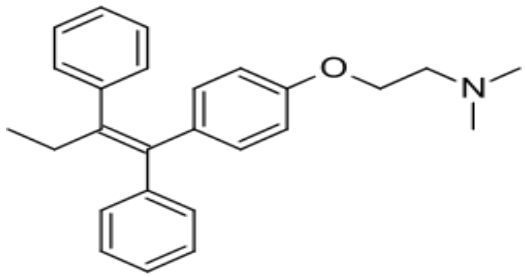

Fig. 1. Structure of Tamoxifen.

It is available as tablet or oral solution which some of the notable side effects includes its partial agonist effect on the endometrium tissue thereby enhancing cell proliferation linking it to endometrium cancer. Other side effects are blood clot, hot flashes, irregular period, cardiovascular and metabolic effects as well as hepatotoxicity. The possibility of contraindication during breastfeeding or pregnancy has been a major concern, recent report [2] identified evidence is limited and that counselling during pregnancy would go long way to remedy the pre-conceived relationship.

On the other hand, tamoxifen has shown to be effective in lowering cholesterol levels, halting post-menopausal bone loss and in psychiatric diseases such as bipolar disorder, where its therapeutic effect may be independent of estrogen receptor interaction [4]. Recent research [5] indicates there is potential of tamoxifen usage in wider cancer setting upon repurposing.

In this review, we discussed the history and synthesis of tamoxifen as well as highlight the appraisal in the treatment of diseases. We also presented the mechanism of action and well as the side effects and mechanisms of resistance. From this we concluded and provide future directions on the use and research on tamoxifen.

II. Literature

A. Tamoxifen History

Tamoxifen, firstly identified as compound ICI-46,474, was synthesized by Dora Richardson in 1962 when she was making triphenylethylene derivatives as a part of a project aiming at developing a contraceptive pill at Imperial Clinical Industries (ICI) Pharmaceuticals Division (now AstraZeneca), Dr. A.L. Walpole who was the leader of the team, was interested in carcinogenesis, cytotoxic chemotherapy, and endocrinology. Harper & Walpole in 1967 managed to identify trans-isomer of a substituted ICI-46,474. They found that ICI-46,474 functioned as a partial estrogen agonist/antagonist in the immature rat without raising desmosterol levels which were thought to cause cataract in young women. However, the next development of tamoxifen was not favored by the company as ICI Pharmaceutical Division, was not a part of the cancer treatment market, hence, the drug could not get the patent in the USA. Though the project was saved due to Walpole's enthusiasm, to defend his work, Tamoxifen was developed by Walpole as a palliative treatment for advanced breast cancer in a small market for a small population [6], [7].

Turning from cutting some or all parts of the breasts to treat breast cancer, tamoxifen had provided FDA promising results to get its approval to treat breast cancer in 1977. This turning point was credited to many clinical trials in the 1970s that confirm the effectiveness of the drug**.** The initial trial had only recruited a few hundred women, then the next trial engaged over 3,100 women of all ages with different ages, the study revealed that tamoxifen for two years after treatment with surgery and radiation, improved 10-20 % more women over 50 survive disease-free, prevent tumors from growing larger in 22 % of patients, and eradicated tumors in four percent. In 1985 a published paper in The Lancet identified that tamoxifen decreased death rates by 34 % for patients of different ages [7]**.** The protective effect of tamoxifen for high-risk women was proved through randomized placebo-controlled clinical trials in the United States in 1992. Tamoxifen reduced breast cancer incidence by 50% in the treatment group compared to the placebo group; additionally, postmenopausal women were found to have questioned side effects such as endometrial cancer and blood clots. In 1998 eventually the FDA approved tamoxifen to lower breast cancer risk in both premenopausal and postmenopausal women [6], [8]**.**

B. Tamoxifen Synthesis

The structure of tamoxifen was derived from antiestrogens; ethamoxytriphetol, chlorotrianisene and diethylstilbestrol-like estrogens. Tamoxifen differs structurally from raloxifene but is structurally related to other triphenylethylene derivatives: ospemifene, clomifene, toremifene and nafoxidine [9].

Desoxybenzoin substitution is considered the chief component for tamoxifen synthesis through alkanol preparation in standard conditions and olefinic linkage produced during elimination reaction in acidic media [10].

Construction of tamoxifen and its derivatives basic skeleton are done through two general methods includes formation of double bonds by corresponding tertiary alcohol dehydration or two aromatic ketones reductive coupling. The presence of transition metal catalysts such as nickel, titanium, and palladium species during early synthetic stages allows ethylene moieties to be formed and olefins to be coupled with metalated aromatics to make desirable olefin substiles [11].

The complete synthesis of tamoxifen can be performed in several steps. Friedal- Craft acylation where anisole reacts with phenylacetic acid in the presence of acylating agent which is a mixture of PCl5 / SnCl4 yielding keton. Keton is being treated with sodium hydride (NaH) in alkylation reaction removing acidic protons to produce enolate ion. These ions can be isolated as sodium enolate of keton by the addition of ethyl iodide resulting in formation of compound D that serve as intermediate compound during synthesis process [2]. The phenol in the dimethyl formaide "DMF" is then removed using lithium ethanthiolate, which aids in the removal of the methyl group and the replacement of it with H to generate the hydroxyl group. The product is alkylated using 2- dimethyl aminoethyl chloride, with the OH group on the phenyl ring being the most convenient site for this procedure. Tertiary alcohol is formed after treating compound with Grignard reagents " phMgBr". Finally, dehydration process occurs to get final product "tamoxifen" by the aid of methanoic hydrogen chloride producing mixture of both cis and trans isomers [11].

To separate tamoxifen isomers, researchers utilized silica gel thin layer chromatography with benzene or triethylamine as the developing solvent at a 9:1 ratio. The ratio produced from this process is approximately 1:1 cis and trans. Analysis has proved that the Z (trans) isomer was more mobile than the E (cis) isomer. Also, fractional crystallization process may be used to separate isomers and obtain the main functional form of tamoxifen [11].

C. Appraisal of Treatment Effects/Success

Studies have been conducted on tamoxifen following its failure in 1970s as postcoital contraceptives. Nowadays, Tamoxifen is commonly used as an adjuvant therapy for people with ductal carcinoma and early-stage invasive breast cancer. Scientists have shown its efficacy in advanced breast cancer diseases [12]. In this advanced stage cancer, tamoxifen is the most potent treatment strategy employed. Tamoxifen has been employed to reduce the incidence of breast cancer in high-risk women. Both the Bowel's Project Cancer Prevention Trials as well as the Nation Surgical Adjuvant Breast Cancer study showed that using tamoxifen on women with high danger for breast cancer lowered the occurrence of breast cancer [8]. Tamoxifen is also the gold standard of care for the prevention of recurrence and treatment of estrogen receptor-positive breast cancer in premenopausal and postmenopausal women. Administration of adjuvant tamoxifen for up to 5 years to women in this category, showed 31 % decrease in the yearly breast cancer death rate, without taking into consideration chemotherapy use, patient age (less than 50 – 70 years and above), as well as status of progesterone receptor [13].

Tamoxifen has been known to be potent in women who have passed the menopause stage, and who cannot bear the use of aromatase inhibitors. Scientists have also found that it is the most potent treatment strategy for men with breast cancer [12]. Here, because up to 90 % male breast cancer cases are estrogen receptor positive, just as in women, tamoxifen is used as the standard adjuvant therapy. A study reveal that men administered adjuvant tamoxifen showed better disease-free and overall survival rates [14]. Another research team showed that in 39 male breast cancer patients with stage 2 and 3 cancers, the 5-year survival rate after management with adjuvant tamoxifen was 61 %, signifying considerable advantage [15]. Early studies have shown that tamoxifen is generally used for five years as adjuvant therapy, depending on the health condition of the patient. However, recently other trials have found that taking tamoxifen for ten years is more beneficial than 5 years [16]. The Adjuvant Tamoxifen – To offer more? (aTTom) trial as well as the Adjuvant Tamoxifen: Longer Against Short (ATLAS) trial which recruited 6,953 and 6,846 women respectively, provided further proofs that using tamoxifen for more than 5 years is advantageous. The result from these studies reveals decreased breast cancer mortality by about 25 % [16].

Tamoxifen served as the main hormonal-based therapy in breast cancer treatment especially in metastatic and adjuvant conditions for sometimes [6]. It continues to be one of the main choices for treatment that extends recurrence-free as well as overall survival [13]. However, lately, scientist has raised interest in the possibility for tamoxifen generating effect in new "off-targets" across several malignancies, exploring other strategies besides the anti-estrogen mechanism. Some potential targets across several malignancies other than breast cancer have been explored with tamoxifen when used as adjunct therapy. The effect of tamoxifen in some malignancies are here described: In 15 patients with advanced lung cancer, tamoxifen alone and in combination with cisplatin caused no harm, indicating tolerance and effectiveness [17]. Tamoxifen was coupled with cisplatin, epirubicin, and ifosfamide as an adjuvant drug in a 25-patient cohort with lung cancer, however only 20% of patients reacted partially after two therapy sessions. The median time to illness progression was 4.9 months longer, while the median survival time was 7.7 months [18]. In one trial, 27 patients with locally advanced pancreatic disease were treated with tamoxifen plus gemcitabine, and clinical improvements were seen in 59 percent of the patients [19]. Over a 4.5-month period, 11 percent of the patients responded somewhat, while 48 percent demonstrated disease stability and an overall good safety profile [19]. In addition, tamoxifen in conjunction with cyclophosphamide, 5-FU, and leucovorin was used to treat 50 patients with advanced pancreatic cancer [20].

Hormone refractory prostate cancer has been explored to determine the possible benefits of tamoxifen. The combination of leucovorin, doxorubicin and tamoxifen in 17 patients showed good response in 11 patients evidenced by decreased PSA level (for about 6 weeks) and better life quality (in 13 patients) demonstrated by decreased overall analgesia intake [21]. More so, in malignant glioma patients, administration of high dose tamoxifen resulted in radiological regression and stoppage of disease progression [22]. Study here show tamoxifen was well tolerated and could be utilized as adjuvant therapy for aggressive disorders as well as radiosensitizers [22]. Tamoxifen also showed efficacy in raising temozolomide's efficacy in the treatment of recurring malignant gliomas [22]. Lastly, administration of tamoxifen in combination with octreotide on inoperable liver cancer patients resulted in complete response (4/39), stable disease (9/39) and disease progression (4/39) [23].

TABLE I: EVIDENCE OF TREATMENT EFFECT AND SUCCESSES OF TAMOXIFEN IN PRIMARY MALIGNANCIES BESIDES BREAST CANCER

Primary cancer	Evidence	Reference
Lung	Tamoxifen was adequately tolerated when administered separately as well as in combination with cisplatin and verapamil.	[17]
	Tamoxifen was used in conjunction with cisplatin, epirubicin and ifosfamide in 25 patient's cohort with Lung cancer - only 20% of patients responded partially after two treatment rounds. The median time to illness progression was 4.9 months longer, while the median survival time was 7.7 months.	[18] [19]
Pancreas	Tamoxifen when combined with Gemcitabine against the metastatic disease resulted in partial response (11%), stable disease (48%), and disease progression (41%) Tamoxifen, when combined with cyclophosphamide, leucovorin, 5-FU resulted in partial response (14%), stable disease (64%), and disease progression (22%)	[20]
Prostate	The combination of leucovorin, doxorubicin and tamoxifen in 17 patients showed good response in 11 patients evidenced by decreased PSA level (for about 6 weeks) and better life quality (in 13 patients)	[21]
Glioma	Daily administration of tamoxifen increased Temozolomide effectiveness in patients who have recurrence. Tamoxifen when combined with IV Carboplatin resulted in partial response (15%), stable disease (52%), and disease progression (33%)	[29] [30]
Colorectal	Tamoxifen when combined with doxorubicin and dexverapamil resulted in stable disease (4/15)	[31]
Liver	Administration of tamoxifen in combination with ocretide resulted in elevated median survival time (3/12) and percentage of complete response as compared with chemotherapy which is standard.	[23]
Skin	As compared to standard chemotherapy alone, administration of combination of tamoxifen and chemotherapy resulted in better overall response (3/11 complete response complete response)	[32]

Lately, the medicinal potential of tamoxifen has been probed in several therapeutic targets, and the outcome has shown great promise. Tamoxifen has been used to treat a variety of cancers (Table I), as well as several disorders unrelated to cancer. This drug has been employed in the treatment of retroperitoneal fibrosis as well as infertility, gynecomastia and idiopathic sclerosing mesenteritis with positive effects [24], [25]. It has been shown to have advantageous effect in the treatment of osteoporosis and has been found to lower the occurrence of cardiovascular diseases [26], [27]. Further, it has been investigated in the treatment of Riedel's thyroiditis, McCune-Albright syndrome, and bipolar disorder [4], [28].

D. Mode of Action

Hormonal therapy shows high efficacy in both adjuvant and metastatic disease. This makes it necessary for patients with positive hormone receptor (ERα) breast neoplasms. Tamoxifen is considered the most active adjuvant hormonal treatment in pre-menopausal and post-menopausal women where they respond to tamoxifen greatly because it depends mainly on ER and PR percent in breast cancer cells [2], [16], [33].

Tamoxifen has an agonist impact on the bones, liver, and cardiovascular system, where it lowers total cholesterol and LDL cholesterol [2], as well as it has an antagonist effect in the uterus and breast cells, or mixed one depending on species type, target gene, and organ [34]. For example, in breast tissue, tamoxifen regulates signal transduction pathways related to estrogen-responsive genes where it competes with estrogen for binding to its receptors inhibiting estrogen through its activation of co-repressor nuclear receptor co-receptor, retinoid silencing mediator, and thyroid hormone recruitment to ER target gene [33]. Tamoxifen engages the co-activator steroid receptor co-activator-1 [SRC-1] that is amplified in breast cancer-1 (AIBC1) and CREP-binding protein to the ER target gene in endometrial cells instead of a co-repressor. These are done through its competition with estradiol at its binding site. In bone cells, tamoxifen encourages estrogen binding to its receptors, so it exerts estrogen agonist effect and prevents injury with osteoporosis. especially, in postmenopausal women [2].

Tamoxifen mechanism in cells is a complex process with several and clear well-defined actions [33]. Tamoxifen binds to the estrogen receptor and inhibit estrogen multiplication action on epithelial mammary tissues through its binding to cytoplasmic antiestrogenic receptors; increasing the level of intracellular drug and sex hormones that binds to globulin leading to decrease in the free estrogen that diffuse into tumor cells inducing their proliferation (Fig. 2). Consequently, it serves as a selective estrogen receptor modulator [2], [34], [35].

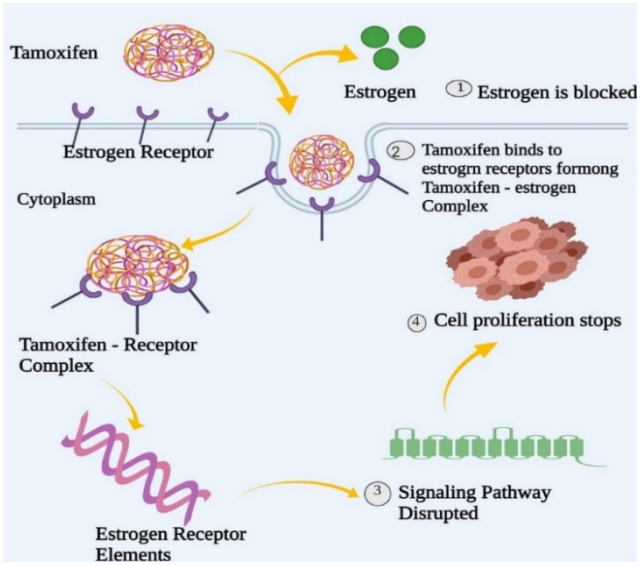

Fig. 2. Mechanism of action of Tamoxifen.

It was suggested that the anti-proliferation action of tamoxifen lies in its induction to cytokine transforming growth factors (TGF-α and TGF-β) synthesis that serves as a negative autocrine regulatory molecule. Nevertheless, it has been shown that tamoxifen induces synthesis of TAG-B in cells that do not contain estrogen such as fetal fibroblast [35].

Also, some immunohistochemical studies [36] assumed that Tamoxifen stimulates transforming growth factor B

(TGF-B) production (TGF-B) proposing that tamoxifen has both paracrine and autocrine action, increase natural killer cells, and decrease insulin-like growth factor that is considered a cancer cell mitogen. Tamoxifen can be activated by endocrine, paracrine, and autocrine routes to stimulate cancer cell growth. It also modifies the hormonal regulation of cancerous cell kinetics [5]. Tamoxifen inhibits protein kinase C that is thought to prevent DNA synthesis through inducing apoptosis in estrogen receptor-positive cells [35]. Another theory for tamoxifen's apoptotic action is that it is caused by a rise in calcium ion concentrations in the cell and mitochondria approximately 3-fold after induction of tumor TGF- B [35].

E. Tamoxifen in Combination with Simvastatin

Statins have a vital role as hypolipidemic agents, so they are used in disorders that required lowering cholesterol and triglycerides levels such as coronary diseases and atherosclerosis through 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) inhibition [37]. Hypercholesterolemia is a potential risk factor for the development of several types of cancers in particular breast cancer [38], so using statins especially simvastatin as hypocholesterolemic agents showed a promising result in breast cancer management [39], [40].

Because of the hopeful benefits of simvastatin in breast cancer control and tamoxifen as the pioneering drug in breast cancer treatment [13], a preclinical trial was launched to assess the effectiveness of combining tamoxifen and simvastatin in T47D, an estrogen receptor-positive (ER+) breast cancer cell line, and Ehrlich solid tumor-bearing mice [41]. the results of this combination involved an enhancement in the effectiveness towards ER+ breast cancer through reduction of oxidative stress markers, glucose uptake, matrix metalloproteinase 2&9 (MMP 2&9), and vascular endothelial growth factor (VEGF) in the cell line. In addition, this combination induced cell apoptosis through apoptotic markers Bax/BCL-2, caspase 3, and decreased protein expression of nuclear factor kappa B (NF-KB), and tumor necrosis alpha (TNF-α) as well [41]. Those results are compatible with the results of another study that exhibited tumor growth inhibition when both tamoxifen and simvastatin were combined, besides induction of tamoxifen resistance (TamR) cell apoptosis [41].

F. Tamoxifen in Combination with Chemotherapy

In the treatment of breast cancer, the advantages of tamoxifen and chemotherapy are observable [13], so clinical trials were initiated to assess their combination in improving the breast cancer condition in pre-menopause patients with node positive and ER+ tumors. the results of this combination revealed minor enhancement in the breast cancer state of the pre-menopause young patients with the same effect if tamoxifen was taken without chemotherapy and better effect than administration of chemotherapy alone [13]. This little effect of the combined therapy converted into no effect, while increasing the risk of edema and hot flashes [13], [42].

On the other hand, in breast cancer post-menopause patients with node-positive and ER+, the concurrent administration of tamoxifen and chemotherapy (Cyclophosphamide, Methotrexate, Fluorouracil, Vincristine, and Prednisone) showed no significant efficacy over taking tamoxifen or chemotherapy alone. However, this combination according to other trials led to an improvement in overall survival with superior activity than giving tamoxifen or chemotherapy alone [42], [43]. In another two trials, one for investigating the combination's effectiveness in patients with node-negative breast cancer and ER-positive tumors and the other for ER-negative (ER-) in post-menopause patients, the results included a reduction in the recurrence rate in the combined group compared to tamoxifen or chemotherapy groups with no difference in the overall survival rate [13], [42].

G. Tamoxifen Side Effects

Tamoxifen has adverse effect on the stomach. An animal model (mice) was administered tamoxifen treatment with a single dose ≥3 mg/20 g of body weight. The therapy caused apoptosis in over 90% of stomach parietal cells and metaplasia of the chief zymogenic cells within three days. However, the parietal cells returned to nearly normal after three weeks post-treatment [44].

Further, though rare, vasculitis has been identified as another adverse effect of tamoxifen use, especially in pre-menopausal women. A 45-year-old woman who had modified radical mastectomy and received tamoxifen treatment for 6 months, was later diagnosed with vasculitis, yet with using dapson, symptoms relieve for 3 weeks. Vasculitis appeared again when dapson use had stopped. Vasculitis and cholestasis during tamoxifen treatment were also detected in another case with a 53-year-old patient, but after stopping tamoxifen use, the toxicity was reversed [45].

Endometrial pathologies are one of the side effects of tamoxifen treatment. Overall, 106 studies with postmenopausal tamoxifen exposure, endometrial polyps were observed with a high rate of malignancy that is considered the most common endometrial pathology [46]. Also, malignant mixed mesodermal tumors, endometrial cancer, sarcoma, and endometrial hyperplasia were noticed. Another study aims to investigate the rate of malignancy in endometrial polyps that retrieved from tamoxifen-treated postmenopausal women. After six months of tamoxifen treatment, it was observed that only 2 (0.3) of 67 endometrial polyps recovered [47].

As tamoxifen could pass the blood-brain barrier, it has pharmacological effects on brain health, cognition, and mood in breast cancer patients. Tamoxifen else has effects related to psychiatric disorders, such as bipolar disorder. In another study that compares the effect of Aromatase inhibitors (AIs) and Tamoxifen on cardiovascular safety for patients with postmenopausal breast cancer. In terms of the following hemorrhagic stroke, ischemia, and acute coronary syndrome (ACS), tamoxifen has lower effects than (AIs) on cardiovascular events [48].

Although tamoxifen is recommended for young women with hormone-sensitive breast cancer, it is not recommended for pregnant women. In a study that included 167 pregnant who received tamoxifen, 21 of them show abnormal fetal development [2]. Additionally, tamoxifen was observed to cause respiratory dysfunction like cough, pneumonia, and lung injury [49].

H. Mechanism of Tamoxifen Resistance

One of the greatest obstacles to tamoxifen's success has

One of the greatest obstacles to tamoxifen's success has been resistance to the drug., mechanistic studies into this reveals some pathways that are involved in this resistance mechanisms. They are inhibition of receptor tyrosine kinase (RTK), cell cycle regulators and EMT-like phenomena, activation of ERα36 and inhibiting protective autophagy [50].

I. Receptor Tyrosine Kinase Role in Tamoxifen Resistance

High p-AKT expression is associated with a bad prognosis and inhibiting AKT expression can help activate cells that are resistant to treatments [51]. Also, PI3K/AKT pathway activation isn't simply connected with tamoxifen resistance. According to ongoing research, activation of the PI3K/AKT pathway allows Tamoxifen-resistant (TAM-R) cells to establish drug resistance to DNA-damaging chemotherapy by upregulating BARD1 and BRCA1 [52], indicating that the PI3K/AKT pathway is particularly important in the treatment of breast cancer.

Tamoxifen resistance has been shown to be exacerbated by the MAPK/ERK pathway [53], while Overexpression of VEGF in drug-resistant cells causes MAPK to become more activated. Unexpectedly, the utilization of VEGF inhibitors has not been effective in the treatment of resistance to tamoxifen [54], which may likewise be linked to drug resistance's complex network. There is still no proof that VEGF relates to Tamoxifen resistance. In like manner, Tamoxifen resistance is hypothesized to be linked to EGFR. Downregulation of miR-186-3p expression by tamoxifen, which prompts more upregulation of the outflow of EREG, a downstream target of miR-186-3p. At that stage, EREG stimulates EGFR significantly, improving glycolysis and triggering tamoxifen resistance. Recent report shows that the NOGO-B receptor adds to the passage of RAS, which improves Transduction of the EGF signal, bringing about a lessening in p53 expression and progression of tamoxifen resistance [55].

Tamoxifen resistance has been linked to ERα36 [56], and by upregulating EGFR, ERα36 reduces the susceptibility of breast cancer cells to tamoxifen. In TAM-R cells, EGFR expression and basal phosphorylation of ERK are increased. By removing ERα36, it is possible to slow down the EGFR/ERK signaling pathway [57]. Be that as it may, Lapatinib suppresses not only the phosphorylation of EFGR and HER2, but also the expression of ERα36 [56]. Surprisingly, crosstalk between HER2 and ERK has been found to aid in the enhancement of drug resistance [58].

IGFR has also been linked to tamoxifen resistance, according to some research. IGF-1R inhibition Reduces tamoxifen sensitivity in cells, which could be attributed to IGF-1R low expression inhibiting FoxO1 expression [59]. IGF1R signaling, on the other hand, may be advantageous in the advancement of tamoxifen resistance in some situations. Tamoxifen resistance is induced by P21-activated kinase 2 (PAK2), and by increasing PAK2 outflow that enables the IGF1R to accelerate the progression of tamoxifen resistance [60].

J. Enzymes and Transcription Factors Roles in Tamoxifen Resistance

Endocrine resistance has been linked to the transcription factor SOX9 [61]. SOX9 in TAM-R cells can be deacetylated and nuclear localized thanks to Histone Deacetylase 5 (HDAC5), a member of the HDAC family whose primary job is to remove acetyl groups. The C-MYC/HDAC5/SOX9 pivot has been connected to tamoxifen resistance. MYC is also implicated in the onset of HDAC5 transcription [61].

HDAC1, a member of the HDAC family, has been associated to tamoxifen resistance as well. TAM-R cells had considerably higher RBP2 expression than in tamoxifen-sensitive cells. IGF1R activation is triggered by the RBP2–ER–NRIP1–HDAC1 complex. The PI3K/AKT pathway has been discovered as a link between RBP and tamoxifen resistance. RBP triggers the PI3K/AKT pathway by increasing IGF1R-HER2 receptor crosstalk, resulting in medication resistance [48]. Surprisingly, it has also been discovered that HDAC stimulates the expression of ER66 and AKT, and HDAC inhibitors diminish the quantity of AKT by lowering its mRNA stability [62].

Estrogen Binds to ER66 in the cytoplasm, which suppresses cancer growth. Tamoxifen has a negative effect on ER66. However, it has been established that Tamoxifen use is linked to increased expression of ER36, SPhk1 (sphingosine kinase 1), and S1P (sphingosine-1-phosphate), which activates downstream signaling pathways and leads to drug resistance [63] but inhibiting ER36 is useful in restoring tamoxifen sensitivity in breast cancer cells [63].

The arginine methyltransferase PRMT2 (HRMT1L1) belongs to the arginine methyltransferase family that inhibits signaling pathways such as ER36, PI3K, MAPK, and others in breast cancer cells, preventing them from becoming resistant to tamoxifen [64].

Instead of HIF-1, a transcription factor linked to disease progression called Spalt-like transcription factor 2 (SALL2) boosts tamoxifen sensitivity in breast cancer cells, while ER is downregulated when SALL2 is silenced [65]. This demonstrates that tamoxifen is a potential endocrine therapeutic option for people with ER-positive breast cancer. Regardless, ER expression is strongly linked to the tolerability of tamoxifen treatment in ER-positive breast cancer patients. Various transcription factors limit the affectability of breast cancer cells to tamoxifen by directing ER through distinct components. Furthermore, the expression of glutathione S-transferase mu 3 is regulated by ER (GSTM3) to protect drug-resistant cells from cytotoxicity produced by drug treatment [66].

The ER–c-Src–HER2 complex has been shown to play a key role in the resistance of tamoxifen [57], c-Cbl, on the other hand, inverts tamoxifen resistance by inhibiting the ER–c-Src–HER2 complex. To counteract drug resistance, most drugs appear to interact with the RTK pathway. Furthermore, a few enzymes can be utilized to predict breast cancer endocrine medication sensitivity. According to prior research [67], ASPH expression was increased in tamoxifen-resistant cells, and the overexpression was mediated by the PI3K and MAPK pathways. The results were critical, as cells with high ASPH expression were more susceptible to tamoxifen than those with low ASPH expression [67].

In breast cancer cells, aspartate-b-hydroxylase (ASPH) may also predict tamoxifen sensitivity [67]. Reference [68] have revealed that tamoxifen ineffectiveness is linked to the transcription factor OCT 4, and that its level can be utilized to predict breast cancer cell sensitivity to the treatment.

K. The Association between Cell Cycle Regulators and Tamoxifen Resistance: The Role of LEM4

Tamoxifen has little effect on the cell cycle when given to cells alone [69]. Tamoxifen resistance in breast cancer cells is dependent on the expression of cyclin D1 and cyclin E, according to previous study. Tamoxifen inhibits the expression of cyclin D1, a protein that supports the advancement of the G1–S stage and is found in drug-resistant cells [70]. Researchers have proposed several approaches to address medicine resistance in view of these systems, including the cyclin-subordinate kinase (CDK) 4/6 inhibitors palbociclib and ribociclib [71].

LEM4 (LEM structural protein) increases cyclin D1 transcription via ligand-free receptor initiation, which is significantly expressed in breast cancer-resistant cells. LEM4 also collaborates with CDK 4/6 and Rb to speed up the transition from G1 to S [55]. Tamoxifen's inhibitory effect on the progression of breast cancer cells from the G1 to the S stage is reduced by LEM4. The presence of LEM4 enables ligand-free activation of the estrogen receptor in the presence of tamoxifen [55].

Reference [65] also established a relationship between tamoxifen resistance and cell division cycle related 8 (CDCA8). On drug-resistant cells, it has a considerable effect. After the CACA8 gene was deleted, the number of drug-resistant cells in the G1 stage increased, but tamoxifen resistance reduced. When Spy1 is confined to CDK, it interferes with ERK phosphorylation; a rise in its level has been connected to the resistance of tamoxifen [72].

III. Conclusion

Overcoming resistance to tamoxifen, as well as repurposing tamoxifen in other cancer contexts, are two of the most important future directions for the drug. To elaborateLEM4 is thought to be a biological measure for predicting tamoxifen resistance in ER-positive breast cancer and targeting LEM4 could be a viable research route in the future to overcome tamoxifen resistance [50].

Although aspirin (ASA) has been used to treat several cancers, including rectal cancer, lung cancer, pancreatic cancer, and breast cancer [73], [74], it is unclear whether it increases patient survival. The usage of aspirin, on the other hand, appears to be useful in the fight against tamoxifen resistance. The expression of cyclin D1 was lowered when tamoxifen was coupled with ASA, and the number of cells captured in the G0/G1 stage enhanced. Tamoxifen resistance in ER-positive breast cancer cells can be overcome by combining ASA with tamoxifen [69].

DpC, a new thiosemicarbazone, was synthesized by [75]. They discovered that When DpC and tamoxifen were combined, cyclin D1 was lowered, p27 was elevated, and breast cancer cell growth was inhibited, which could be useful in overcoming tamoxifen medication resistance. A growing variety of approaches have been investigated to overcome tamoxifen resistance. ASA reduces drug resistance not only by impeding G0/G1 stage safe cells, but also by preventing the phosphorylation of AKT [69]. Phosphodiesterase 4D (PDE4D) can inhibit cAMP and downstream signaling channels, making cells resistant to tamoxifen. However, after taking aspirin, the amount of cAMP in the cells increases as well as the degree of phosphorylation of AKT decreases [76].

It has also been established that NF-B is connected to tamoxifen resistance. Aspirin inhibited the activation of NF-B signaling, which helped cells overcome their resistance to specific therapeutic medicines, according to [77]. By all accounts, aspirin is a viable method for combating tamoxifen resistance, and it is necessary to continue breast cancer treatment. ASA in combination with tamoxifen, as well as proteasome inhibitors (PIs) in combination with endocrine therapy, have been shown to be effective in sensitizing tamoxifen-resistant cells [69].

To overcome medication resistance, restraining kinases in the RTK pathway is also considered a viable option. Gefitinib, perifosine, and GnRH-I and GnRH-II analogues, for example, have been used to inhibit AKT expression [78]. The bile corrosive chenodeoxycholic corrosive (CDCA) was identified by [79] to activate the farnesoid X receptor (FXR) and block the expression of HER2. Quercetin has also been demonstrated to improve tamoxifen sensitivity by preventing ER overexpression and HER-2 downregulation [56].

The combination of tamoxifen and gefitinib accelerated drug-resistant cells' apoptosis. Gefitinib prevented EGFR from downregulating ER and partially restored tamoxifen sensitivity in cells [80]. Surprisingly, Gefitinib has no influence on the behavior of breast cancer-resistant cells, whereas neratinib, another EGFR inhibitor, inhibited the EGFR and HER2 signaling pathways and caused death in healthy cells [81]. furthermore, by downregulating EGFR, dichloroacetate can overcome tamoxifen resistance [82]. As a result, greater study into EGFR inhibitors' effects on tamoxifen-resistant cells is required.

Pin1, a peptidyl-prolyl isomerase that activates E2F-4, contributes to medication resistance. Pin1 inhibitor all-trans retinoic acid (ATRA) lowers cell drug resistance by inhibiting the ERK 1/2 and AKT pathways [83]. Inhibiting epithelial–mesenchymal transition (EMT)-like processes can also be used to overcome drug resistance. Resveratrol can repress EMT by decreasing TGF- and overcome tamoxifen resistance, despite LDHA's capacity to prevent EMT-like phenomena. Surprisingly, EGFR activation is also connected to EMT-like aggregate change, suggesting that suppressing EMT may aid in the treatment of tamoxifen resistance [84].

Reference [5] published a study that looked at the use of tamoxifen in various malignancies, including lung, pancreas, prostate, glioma, colorectal, liver, skin, head and neck, leukemia, gastric and bladder cancers, with some pre-clinical data confirming its anti-cancer activity. Similar biochemical pathways have been implicated in the sensitivity to cisplatin in the HN5 and HN6 cell lines of head and neck squamous cell cancer, like studies in ovarian cancer [85]. Regardless of p53 status, tamoxifen therapy triggered G1 arrest, with up-regulation of the CDK inhibitors p21, p27, and p15., as well as an increase in hypo-phosphorylated active retinoblastoma protein levels. Tamoxifen therapy significantly increased sensitivity to cisplatin-induced apoptosis, but this was not due to suppression of PKC activity in these cells. Reference [86] investigated the interaction of cisplatin and tamoxifen in human head and neck cancer cell lines UM-SCC-10B and UM-SCC-5 *in vitro*. The development of cisplatin resistance

in the UM-SCC-10B cells was slowed in the presence of tamoxifen. This finding, however, was not confirmed in the second cell line. Tamoxifen elevates cytosolic free Ca(2þ) concentrations in human oral cancer cell lines [87]. Quercetin and tamoxifen inhibit the laryngeal cancer cell lines Hep2 and CO-K3, keeping the cells in the G2/M phase of the cell cycle and causing apoptosis [88].

Tamoxifen inhibits the synthesis of C6-glucosylceramide and C6-sphingomyelin from C6-ceramide in the KG-1 leukemia cell line by 80% and 50%, respectively, and may increase antiapoptotic effects by inhibiting ceramide anabolism. The combination of tamoxifen and C6 ceramide treatment of HL-60/VCR cells caused a considerable reduction in cell viability and synergistic apoptotic cell death [89], with further findings indicating that the ceramide pathway plays an important role in tamoxifen metabolism in this cancer type [89], [90].Only about a quarter of patients in chemotherapy-induced remission in acute myeloid leukemia (AML), the most prevalent form of leukemia in adults, will remain cancer free, making it an increasingly relevant field for therapeutic research [89]. AC activity investigations in the human cell lines HL-60 and KG-1 found that as tamoxifen dose was raised, AC activity decreased with no cytotoxic effect. SphK1 was also downregulated, but to a lesser level than AC, suggesting that S1-P's mitogenic action was reduced. Tamoxifen increased apoptosis when combined with the ceramide-generating drug 4-HPR, suggesting that it could be utilized as an adjuvant. In the glucocorticoid-resistant cell line Jurkat for acute lymphoblastic leukemia (ALL), tamoxifen has been demonstrated to inhibit viability and proliferation [91]. In the BGC823 gastric cancer cell line, tamoxifen produces a dose-dependent decrease in cell growth, an increase in apoptosis, and a drop in ER-3687 mRNA expression levels. In the ER-negative SGC7901 cell lines, tamoxifen treatment produced cell cycle G0/G1 phase arrest and increased G2/M phase [92]. The expression of P-gp, p-Akt, and Akt-regulated downstream effectors was reduced, showing that an underlying mechanism was inhibiting the P13K/Akt signaling pathway [93]. Tamoxifen inhibits the proliferation of KATOIII cells (poorly differentiated adenocarcinoma), but not the MKN28 cell line (well differentiated adenocarcinoma) [94].

In bladder cancer cell lines (TCC-Sup, 563 RT4)90, combination therapy with tamoxifen and gemcitabine had the lowest cell viability when compared to either medication alone. The combination of gemcitabine and tamoxifen caused the most DNA fragmentation, PARP cleavage, and thereby increased cytotoxicity after 72 hours [95]. Another in-vitro investigation was conducted to see how tamoxifen affected the effects of doxorubicin, mitomycin-C, and thiotepa [96]. The cytotoxic effects of all three medications were boosted by a concentration of >30 M of tamoxifen, but the dose grew increasingly hazardous as the dose was increased, the effects became more pronounced. Despite extensive research, the mechanism causing off-target consequences remains unexplained.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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