PEGylated Liposomal Teriflunomide: A Novel Approach of Targeted Breast Cancer Treatment to Advance Efficacy and Minimize Adverse Effects

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Abstract

Breast cancer (BC) is a life-threatening disease and the most common cancer among females, with 2.3 million cases diagnosed annually worldwide. Current treatment modalities for BC include radiation therapy, hormonal therapy, and surgical interventions, each offering therapeutic benefits but also presenting limitations and adverse effects. As a result, researchers globally are seeking novel, effective, and safer treatment options for BC patients. BC is characterized by the overexpression of human epidermal growth factor receptor 2 (HER2) and the activation of signaling pathways such as mitogen-activated protein kinases (MAPKs). Teriflunomide (TFN), an active metabolite of leflunomide, has demonstrated antiproliferative and anti-inflammatory properties. TFN inhibits de novo pyrimidine synthesis and various protein kinases, including MAPK and phosphoinositide 3-kinase (PI3K), both of which play key roles in BC pathogenesis. By targeting these signaling pathways, TFN has shown potential anticancer effects in BC. PEGylated liposomes represent a novel drug delivery system for BC treatment. This hypothesis proposes the development of teriflunomide-loaded PEGylated liposomes to enhance its therapeutic efficacy against BC. PEGylation may improve TFN's bioavailability, tumor penetration, and anticancer activity. The synergistic interaction between the delivery system, the drug, and targeting ligands is expected to amplify TFN's anticancer effects. This approach offers a promising, innovative solution for BC treatment and warrants further clinical investigation to validate its efficacy and safety.

Keywords: Breast Cancer, Liposome, PEGylation, Teriflunomide, Targeted Treatment

Significance | Developing pegylated liposomal teriflunomide may enhance breast cancer treatment efficacy, reduce side effects, and improve patient outcomes.

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1. Introduction

Breast cancer is the fifth leading cause of mortality and the second leading cause of death among women worldwide (Menon et al., 2024). While developed countries report the highest incidence rates, underdeveloped countries experience higher mortality rates (Ghoncheh et al., 2016; Bellanger et al., 2018; Elmore et al., 2005). Scientific studies indicate that breast cancer is most prevalent in women over the age of 50. Additionally, early onset of menstruation (around 12 years of age) has been linked to an increased risk of lobular breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2012), suggesting that hormonal changes and their downstream signaling pathways play a significant role in breast cancer development.

The development of breast tissue is mainly influenced by the estrogen (Sternlicht et al., 2006). Literature suggests that high circulating levels of estrogen is associated with breast cell

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proliferation (Thomas et al., 1997; Toniolo et al., 1995; Larionov et al., 2002) Estrogens facilitate the progression and development of cancer (Jiang et al., 2013). It also inhibits the granzyme-B and later facilitates the cancer to escape the immune system (Lauricella et al., 2016). Estrogen facilitates the metastasis and recruitment of bone marrow-derived myeloid (BMD) cells (Iyer et al., 2012). Estrogen activates the estrogen receptor (ER) to form ER complexes and the latter has been shown to activate MAPK (mitogen-activated protein kinase) and PI3K (phosphatidylinositide 3-kinase) signaling pathways, implicated in the pathogenesis of breast cancer (Migliaccio et al., 1996). The binding of estrogen to ER, results in the activation of Ras (small guanine nucleotide-binding protein—Ras (GTPase) which then activates Raf (protein kinase). The Raf then phosphorylates the MEK protein to further phosphorylate and activation of MAPK (Zivadinovic and Watson, 2004; Wang et al., 2006; Rocca et al., 2022). Estrogens also stimulate these pathways by stimulating the release of EGF and activation of EGFR, and the latter has been shown to increase the expression of signaling pathways such as MAPK and PI3K signaling pathways implicated in BC (Thomas et al., 2005; Filardo et al., 2002).

Teriflunomide (TFN) (Aubagio®) is FDA approved drug for relapsing multiple sclerosis and an active metabolite of leflunomide (Ali et al., 2013). TFN has been shown to suppress B- and T-lymphocytes which inhibits the enzyme dihydroorotate-dehydrogenase (DHODH) pathways and pyrimidine synthesis (Oh and O'Connor, 2013). TFN has been shown to exhibit antitumor activity (Tallantyre et al., 2008; Wiese et al., 2013; Oh et al., 2013) by inhibiting the proliferation of cancer cells (White et al., 2011; Somnay et al., 2013). TFN has been shown to exert cytotoxic effects by decreasing the expression of anti-apoptotic proteins and receptor tyrosine kinases (RTKs) (Dietrich et al., 2012; Hail et al., 2010; White et al., 2011; Xu et al., 1999). TFN has been shown to inhibit the signaling pathway implicated in the initiation, development, proliferation, and metastasis of breast cancer (Huang et al., 2015; Wu et al., 2022). Besides these anticancer effects, TFN has been shown to exert side effects including nausea, diarrhea, hair thinning, alanine aminotransferase elevation, etc. (Trüeb, 2009). TFN treatment has been shown to cause rare cases of cervical carcinoma, uterine leiomyosarcoma, and lymphoma (O'Connor et al., 2011; Vermersch et al., 2014; Landais et al., 2017; Lebrun and Rocher, 2018).

However, the anticancer activity of TFN is of great interest for the treatment of BC. However, the adverse effects imposed by this may limit its use in patients with breast cancer. Therefore, efforts are required to minimize its adverse effects, to increase its target activity, and to maximize its therapeutic efficacy. Pegylated liposomes are sterically stabilized or 'Stealth' liposomes that have been shown to increase the circulation time and inhibit the uptake by mononuclear phagocytes (Park, 2002, Waziri et al, 2022). Further, pegylated liposomal of various anticancer drugs have been developed to minimize their cardiovascular risk, increase their effectiveness, and minimize their overall adverse effects (Khojasteh Poor et al., 2021). Therefore, it is hypothesized that the development of a Pegylated liposomal formulation of TFN might be the best treatment option for patients with breast cancer.

2. Types of Breast cancer

Breast cancer remains asymptomatic in the initial stages, however when the cancer progresses and the size of the lesion increases, then the patients may feel palpable lump, swelling, redness, ulceration, nipple discharge, edema, and distant metastasis (Baines, 1992; Menta et al., 2018). Therefore, the American college of obstetricians and gynaecologists (ACOG) recommends the routine examinations of breast should in the and symptomatic and women on high-risk (Practice Bulletin Number 179, 2017). Breast cancer may be of different types (Table 1).

3. Breast Cancer Classification

Molecular classification is independent of histological subtypes on the basis of mRNA gene levels and can be classified as 4 molecular subtypes, HER2-enriched, Luminal, Normal Breast-like and Basal-like (Perou et al., 2000).

3.1 Luminal Breast Cancer

Luminal BC are ER-positive tumors with slow growth and low grade. These types of cancers comprise 70% cases in Western part of the world (Howlader et al., 2014) and differentiated into invasive tubular, lobular, mucinous invasive cribriform, and micropapillary carcinomas (Weigelt et al., 2010; Makki, 2015). Luminal BC are characterized by ER mediated activation of genes expression, characteristic of luminal epithelium lining along the ducts of mammary glands (Weigelt et al., 2010; Prat et al., 2013). It also presents a low expression of genes related to cell proliferation (Eroles et al., 2012). Luminal BC can further be divided into Luminal A and B subtypes in which Luminal A tumors are considered to have estrogen-receptor (ER) and/or progesterone-receptor (PR) and absence of HER2 whereas Luminal B tumors have ER positive and may be PR negative and/or HER2 positive with higher grade and worse prognosis (Ades et al., 2014; Cheang et al., 2009; Raj-Kumar et al., 2019)

3.2 HER2-Enriched Breast Cancer

HER2-enriched group are characterized by the high expression of HER2, absence of ER and PR, and expression of proliferation—related genes (e.g., ERBB2/HER2 and GRB7) (Raj-Kumar et al., 2019; Xu et al., 2015; Kaur, 2005). These cancers grow faster than luminal cancers and about 30% of HER2-enriched tumors are clinically HER2-negative (Plasilova et al., 2016). These are responsible for 10–15% cases of breast cancers.

3.3 Basal-Like/Triple-Negative Breast Cancer

Triple-Negative Breast Cancer (TNBC) are characterized as ER-negative, PR-negative, and HER2-negative and are responsible for 20% cases of breast cancers and is more common in the women younger than 40 years (Plasilova et al., 2016, Ahmad et al, 2023). TNBC arises due to the BRCA1 germline mutation, are biologically aggressive and has worse prognosis (Newman et al., 2014). TNBC is responsible for infiltrating ductal carcinoma, but may be present as medullary-like cancers with infiltration of lymphocytes (Pareja et al., 2016; Wetterskog et al., 2012; Badve et al., 2011). TNBCs can be subdivided into various subtypes including basal-like, mesenchymal, mesenchymal stem-like, immunomodulatory, luminal androgen receptor, and unspecified group (Lehmann et al., 2011; Wang et al., 2019).

3.4 Claudin-Low Breast Cancer

Claudin-low (CL) breast cancers mostly ER-negative, PR-negative, and HER2-negative are often genomically stable and has are poor prognosis (Morel et al., 2017; Puisieux et al., 2018). CL subtype have marked immune and stromal cell infiltration (Dias et al., 2017) and are responsible for the 7–14% case of breast cancers (Weigelt et al., 2010).

4. Pathways implicated in the pathogenesis of Breast Cancer

Mitogen-activated protein kinase (MAPK) signaling is involved in the regulation of oncogenesis, tumor progression, and drug resistance (Plotnikov et al., 2015; Chapnick et al., 2011) (Figure 1). Growth factors (GFs) stimulate growth factor receptors (GFRs) and the later activate the transmembrane glycoproteins of receptor tyrosine kinase (RTK) family and stimulates the genes transcription/translation (Cargnello and Roux, 2011; Lemmon and Schlessinger, 2010). These events result in the activation of RAS GTPase (Vo et al., 2016) which then stimulates RAF (e.g., ARAF, BRAF, CRAF), an ultimate downstream effector of RAS (Matallanas et al., 2011; McCain, 2013). RAF then activates MEK (MAP kinse-ERK kinase) and ERK1/2 (Extracellular signal-regulated kinases) to modulate the process of cell survival, proliferation, and differentiation (McCain, 2013; Fanger et al., 1997; Lavoie and Therrien, 2015) (Table 2). p38 MAPK also stimulate the production of cytokines in tumor to promote the survival of cancer cells (Patnaik et al., 2016; Siddique et al., 2025). It has been reported that the RAS acts as an activator for both MAPK and P13k/AKT/mTOR pathways and is a key regulator of the signaling pathway implicated in the pathogenesis of cancer (Burotto et al., 2014).

PI3K/Akt/mTOR pathway also regulates growth, survival, proliferation and metabolism and regulates the critical step involved in the process of oncogenesis (Keegan et al., 2018; Maira et al., 2012). Phosphoinositide 3-kinases (PI3Ks) are lipid kinases that integrate the signals from growth factors, cytokines, and other extracellular stimuli (Thorpe et al., 2015). It has been reported that the PI3K is responsible for the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2), into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) (Yuan and Cantley, 2008) and the late activate enzyme Akt. PTEN (Phosphatase and tensin homolog phosphatase) is the negative regulator of this step, converts PIP3 into PIP2, and is one of the tumour suppressors in different types of cancer (Myers et al., 1998). Akt (RAC-alpha serine/threonine-protein kinase), also known as protein kinase B (PKB), exist in 3 different isoforms of which only Akt1 is mostly associated with cancer (Fresno Vara et al., 2004). Activation of Akt is responsible for the downregulation of p21, p27, and GSK-3β (Manning and Toker, 2017; McCubrey et al., 2014). Akt activate mTORC1 and is responsible for the resistance for endocrine therapies breast cancer patients (Pérez-Tenorio et al., 2002; Tokunaga et al., 2006). mTOR also interacts with MAPK, JAK/STAT and Notch-1 pathways in solid tumors (El-Habr et al., 2014). It has been reported that the JAK2 mutation affected the cross-regulation of MAPK and PI3K pathways in myeloproliferative neoplasms (Wolf et al., 2013).

It has been reported that the activation of PI3K/AKT and p42/44 mitogen-activated protein kinases (MAPK) pathways downregulates the expression of ER and PR (Osborne and Schiff, 2011), reduce the estrogen dependence and contribute to resistance towards endocrine therapies in tumors amplified for HER2 (Lopez-Tarruella and Schiff, 2007; Brinkman and El-Ashry, 2009) (Table 2). Gefitinib, a selective inhibitor of EGFR, restores the effects of tamoxifen in HER2-overexpressing tamoxifen-resistant MCF-7 cells, while trastuzumab, a monoclonal antibody that blocks HER2, can inhibit proliferation of endocrine resistant ZR-75-1 cells (Shou et al., 2004).

5. Teriflunomide

Teriflunomide (TFN) inhibit the de novo pyrimidine synthesis (Bruneau et al., 1998; Cherwinski et al., 1995; Rückemann et al., 1998), in proliferating lymphocytes and block the pyrimidine mediated S phase to exerts a cytostatic effect on proliferating T and B cells (Löffler et al., 2004; Gold and Wolinsky, 2011; Ringshausen et al., 2008). TFN did not affect cell viability (Li et al., 2013) but exerts anti-proliferative effects (Posevitz et al., 2012). TFN also decreases the release of cytokines (such as IL-6, IL-8, etc). (Li et al., 2013) and prevent the oxidative stress-induced mitochondrial dysfunction (Malla et al., 2020; Zorov et al., 2019). TFN also inhibits the multiple signaling pathways MAPK, and the p53 signaling pathway to exert anti-cancer effect (Huang et al., 2015; Hail et al., 2012; Jiang et al., 2018). TFN also affects the survival of cancer cell (Cook et al., 2010; Baumann et al., 2009), promotes mitochondrial disruption (Hail et al., 2010) and exert apoptosis in cancer cells (Dietrich et al., 2012; Hail et al., 2010). TFN has shown anti-tumor efficacy at lower doses (Sykes, 2018) and promote dose- and time-dependent apoptosis in premalignant PWR-1E and malignant DU-

145 human prostate epithelial cells (Hail et al., 2010). TFN also exerted cytostatic effect on SCLC cell proliferation through inhibition of DRP1 phosphorylation at Ser616, mitochondrial fragmentation, and de novo pyrimidine synthesis (Mirzapoiazova et al., 2024). TFN exerts anti-cancer effect in non-small cell lung cancer (NSCLC) H460 cells xenograft model by inhibiting MAPK and p53 pathway (Jiang et al., 2018). TNBC are characterized by higher relapse rate and lower survival compared. TFN has been shown to impose therapeutic benefit in the more aggressive and difficult-to-treat TNBC (Huang et al., 2015). TFN has been shown to improve outcome in basal cell carcinoma (DeWitt et al., 2017). However, some of the studies has shown that the TFN might be associated with rare cases of cervical carcinoma and uterine leiomyosarcoma in clinical trials (O'Connor et al., 2011; Vermersch et al., 2014). One case report has shown the possible association between lymphoma and terifluonomide (Landais et al., 2017; Lebrun and Rocher, 2018). TFN is known to exert the side effects include hair thinning, diarrhea, alanine aminotransferase elevation, nausea, and headache (Trüeb, 2009).

6. Hypothesis and Its Novelty: PEGylation liposomes for the delivery TFN

The new era of novel drug delivery systems provides diffusion of macromolecular agents at a very slow rate through tumor tissue (Park, 2002; Singh et al., 2020). The concept of utilising functional ligands on the surface of nanocarriers is to interact with specific receptors overexpressed in breast cancer cells. Previous studies have shown that the use of nanotechnology provides better treatment, increases the therapeutic index, and lowers the toxicities of various anticancer drugs (Fu et al., 2020, Aslam et al 2022) (Table 3). Therefore, various liposomal formulations of anticancer drugs have been developed and these have lesser toxicity and better efficacy than the conventional formulations of anticancer drugs (Alavi et al., 2019).

PEGylated liposomes are only second-generation liposomal formulations develop to overcome the limitations of the conventional liposomes. Addition of polyethylene glycol to the liposomal surface increases the circulation time, avoid immune response and clearance by macrophages resulting the larger concentrations of liposomes for longer period of time (Klibanov et al., 1990; Senior et al., 1991; Blume and Cevc, 1990; Tenchov et al., 2023). The enhanced circulation half-life promotes the uptake of larger concentrations in cancer tissues, responsible for the enhanced permeation and outcomes in the cancer (Andresen et al., 2005). PEGylation has thus become a gold standard in the development of anticancer drugs formulation to achieve increase circulation time, to improve the efficacy of drugs, and to minimize the adverse effects imposed by the drugs (D'souza and Shegokar, 2016; Torchilin, 1998). Further, various PEGylated liposomes of various anticancer drugs have been developed (Table 4).

TFN has shown promising results in the treatment of various cancers, however, the adverse effects are less as compared to the other anticancer drugs, and therefore to enhance its efficacy and to mitigate these adverse effects, the ligand-targeted liposomal drug delivery system of TFN will be developed. The proposed hypothesis focuses on a novel approach to deliver TFN via a ligand-targeted system to specific targets to reduce its adverse effects. PEGylated liposomes of TFN will provide the synergistic effect of both the delivery system and the drug and therefore improves the specificity of drugs towards cancer cells, increases the therapeutic outcome, increase the compliance, reduces the adverse effects of drug (Figure 2). Further, it circumvents the mechanical and chemical extremities provided by the tumor microenvironment, gastrointestinal tract, and the defence system of the body where the conventional treatment will succumb. Therefore, the emerging concept of TFN-loaded PEGylated liposome surface modified with ligands for the treatment of breast cancer can become the need for present and future.

6.1 Evaluation of hypothesis

The current hypothesis unravels a strong, synergistic approach for the fabrication of TFN loaded ligand targeted PEGylated liposomes which are modified by the process of PEGylation to specifically target breast cancer cells.

6.1.1 Preparation of liposomes

PEG has been widely used in the formulation of liposomes as a polymeric steric stabiliser. PEG coated liposomes help in drug retention, enhanced permeation and improved drug targeting (Sivadasan et al., 2022). Cholesterol anchors PEG in liposomal formulation where PEG attached to the hydroxyl group (3-OH) of the cholesterol. Thus, PEG flexibility and cholesterol's lipophilicity helps in structural compatibility with the phospholipids present in the liposomal membrane (Nag et al., 2013). The presence of PEG represents the hydrophilic part which enhances the circulation time by evading plasma protein adsorption whereas, the hydrophobic part incorporates the anticancer drug (Mahtab et al., 2020). The purported ligand-modified PEGylated liposomes are fabricated using thin film hydration technique and further, characterized and evaluated for several parameters (Torres-Flores et al., 2020, Khan et al, 2022).

Teriflunomide, PEG, phospholipid, cholesterol, and Stearyl amine will be dissolved in a mixture of chloroform and methanol [95:5; v/v] to obtain uniform distribution. The solution will then be added to the rotary evaporator machine at 50 RPM, above 45 °C, for solvent evaporation, leading to the formation of a thin film of lipids. The film will be hydrated using appropriate solvent [e.g., water, phosphate buffer, etc] to form liposomes (Negi et al., 2015). The following steps include ligand coating by mechanism of ionic

Table 1. Various types of breast cancer

Sr. No.	Types	% Cases	Characteristics	References
1	Ductal adenocarcinoma	50% to 75%	Arises in the terminal duct-lobular unit	Watkins, 2019
2	Lobular carcinoma	10% to 15%	Most common, multifocal tumors, exist as discrete mass	McCart Reed et al., 2021
3	Mucinous carcinoma	2% to 5%	Also known as colloid carcinomas, observed in elder individuals, characterized by mucin production	Roux et al., 2019
4	Tubular carcinoma	1% to 2% cases	Infiltrating cells, resulting in the formation of small glands and tubules	Roux et al., 2019
5	Medullary carcinoma	--	Aggressive tumors poorly differentiated More commonly in *BRCA* mutant and younger patients	Cserni, 2020

Table 2. Various MAPK Signaling Modulators in Breast Cancer

Sr. No.	Drug name	Pathway targeted	Dose	Adverse effects	References
1	Dabrafenib	Inhibit BRAF protein kinase, and prevent MEK phosphorylation	150 mg BD	Nasopharyngitis, hair loss, rash, joint pain, muscle aches, redness, chills, swelling, numbness in limbs.	Seo et al., 2020
2	Ulixertinib	ERK1 and ERK2 inhibitor	450–600 mg BD	Dermatitis acneiform, nausea, rash, fatigue, diarrhoea	Ji et al., 2018
4	Vemurafenib	Inhibit B-RAF and C-RAF protein kinase.	960 mg po daily	Hair loss, skin reactions, rashes, fatigue, sun sensitivity, joint pain	Zhang et al., 2016; Sibaud et al., 2013
5	Tipifarnib	H-RAS protein suppressor and target protein farnesyltransferase	200 mg po BD for 2–7 days	Vomiting, dyspepsia thrombocytopenia, nausea problems	Sparano et al., 2009
6	Sorafenib	Inhibit the activated B-RAF and C-RAF protein kinase	400 mg BD	Neutropenia, hand–foot syndrome, thrombocytopenia Rash, fatigue	Zafrakas et al., 2016
7	Simvastatin	Inhibit PI3K/AKT/mTOR signaling pathway, ERK1 and ERK2 inhibitor	20 mg daily	Joint pain, muscle pain, stomach pain, upper respiratory infections, nausea, headache	Wang et al., 2016
8	PLX8394	Inhibit BRAF protein kinase and prevent MEK phosphorylation	150 mg/kg/daily	Skin rash, fatigue, skin inflammation, diarrhoea	Yao et al., 2019

Table 3. Ligands available for breast cancer targeting

Sr. No.	Ligands	Receptors	Advantages	Disadvantages	References
1	Folic acid [FA]	Folate receptors [FRS] fr-α	Opportunity to utilize fr-α as a targeting of tumor selective drug delivery. Surface modulation of various drug carrier for targeted delivery.	Persistent accumulation in the kidneys.	Zhao *et al.,* 2020; Zwicke *et al.,* 2012; Marchetti *et al*., 2014
2	Hyaluronic Acid [HA]	Cluster determinant-44 receptor [CD44]	HA increases cancer cell uptake via CD44-mediated endocytosis. Prolongs the blood circulation and also reduce immunogenicity of nanocarriers.	Accumulation in liver tissues	Zhao *et al.*, 2020; Huang G, Huang *et al*., 2018
3	RGD [argininegly cineaspartic acid] peptide	αvβ3 and αvβ5 integrins	Inhibits the proliferation of cancer cells. High specificity and affinity to a diverse range of targets, and less immunogenicity.	Low biocompatibility, high toxicity, and large size	Zhao *et al.,* 2020; Gierlich *et a*l., 2020
4	Peptide 1	Epidermal Growth factor Receptor [EGFR OR ERBB1]	Higher binding and uptake by TNBC cells Improving the effectiveness of Chemotherapy.	High toxicity, and large in size	Hagimori *et al*., 2023
5	Cell penetrating Peptides [CPPS] IRGD	Co administered With various Poor penetrating Drugs	To promote the intracellular delivery of drug molecules, nucleotides, proteins, and peptides, Overcomes drug resistance.	Immunogenicity	Stiltner *et al*., 2021
6	Aminoclay, Junction opener	Tight junctions [tjs]	Overcomes the drug resistance, Mediate intercellular adhesion and polarity inhibits Tumorigenesis	increased intestinal permeability and could contribute to the type 1 diabetes.	Zhao *et al*., 2020
7	Vascular Endothelial growth factor (VEGF)	Tyrosine kinase inhibitors	Tumor vessel angiogenesis and neovascularization Decrease tumor progression	Enhanced expression of angiogenic cytokines	Gierlich *et a*l., 2020; Zhang *et a*l., 2022
8	Anti-Vcam-1 monoclonal antibodies	Vascular cell Adhesion Molecule-1 [vcam-1]	Cell-to-cell adhesion and potentially extravasation of cancer cells cancer cells, and Metastasis formation	Mechanism is not known completely	Kong *et al*., 2018
9	KCC-[SG]N-lipid derivative	HER2 receptor	Increased association of PEGylated liposomes with HER2 receptors. Efficiently targets itself to HER2 over-expressing breast cancer cells.	Short half-life, Low solubility, Low stability, Expensive, Complex formation	Suga *et al*., 2017
10	Evq-[sg]$_5$/PEGylated Liposomes	MUC16[mucin-16]	Uptake by MUC16-mediated endocytosis in MUC16positive TNBC cells.	Low stability, Expensive, Complex formation	Hagimori *et al*., 2023

Table 4. PEGylated liposomal formulations in the treatment of Breast Cancer

Sr. No.	Study design	Number of Patients	Drugs and Dose	Aim	Results	References
1	Phase Ib study	19 patients with advanced breast	Temsirolimus (10, 15, or 20 mg once weekly) and PLD (30 or 40 mg/m(2) once every 4 weeks). PLD was initiated 2 weeks after start of temsirolimus	Safety and recommended phase two dose (RPTD) of temsirolimus in combination with PLD	RPTD was 15 mg temsirolimus and 40 mg/m(2) PLD. Dose-limiting toxicities include thrombocytopenia, nose bleeding, skin toxicity grade, mucositis, and skin toxicity.	Boers-Sonderen *et al.*, 2014
2	Phase-3 study	78 metastatic breast cancer patients	Six cycles of PLD (45 mg/m(2) every 4 weeks) or eight cycles of capecitabine (1000 mg/m(2) twice daily, day 1-14 every 3 weeks).	Comparison of efficacy and safety of first-line chemotherapy with pegylated liposomal doxorubicin (PLD) versus capecitabine in MBC patients aged ≥65 years in a multicentre, phase III trial.	Median progression-free survival was 5.6 versus 7.7 months (P = 0.11) for PLD and capecitabine, respectively. Median overall survival was 13.8 months for PLD and 16.8 months for capecitabine (P = 0.59) Both PLD and capecitabine demonstrated comparable efficacy and acceptable tolerance as first-line single-agent chemotherapy in elderly patients with MBC, even in vulnerable patients or patients aged ≥75 years.	Smorenburg *et al.*, 2014
3	Phase II study	Fifty patients with stage II-IIIB breast cancer and at least one risk factor for developing cardiotoxicity	PLD 35 mg/m(2) + cyclophosphamide 600 mg/m(2) every 4 weeks for four cycles, followed by 80 mg/m(2) weekly PTX for 12	To assess the efficacy and safety of PCT based on PLD followed by paclitaxel (PTX) in a high risk BC population	PLD followed by PTX was feasible in a fragile population of patients who were not candidates for conventional doxorubicin. Moreover, it achieved a pCR similar to standard therapy and could therefore be an option for elderly patients or cardiotoxicity-prone who present HRBC.	Gil-Gil *et al.*, 2015
4	Open-label, multi-center, non-comparative phase II study	45 patients	PL doxorubicin (40 mg/m(2)), cyclophosphamide (500 mg/m(2)), and 5-fluorouracil (500 mg/m(2)) was administered every 3 weeks.	To evaluate the efficacy and safety of pegylated liposomal doxorubicin (Lipo-Dox®) used as part of a combination salvage therapy for patients with MBC whose tumors progressed during or after taxane-based treatment.	Regimen of combined of pegylated liposomal doxorubicin, cyclophosphamide, and 5-fluorouracil exhibited a promising overall response rate (41.9 %), progression-free survival rate (8.2 months), and overall survival rate (36.6 months). ADE includes neutropenia, leucopenia, and neutropenic fever	Rau *et al.*, 2015
5	Phase II trial	24 patients with HER2-positive MBC progressing under trastuzumab	Lapatinib (1,250 mg) daily until progression plus PLD (40 mg/m(2)) every 4 weeks for maximal 6 cycles	To determine the overall response rate in the patients receiving Lapatinib-plus-pegylated liposomal doxorubicin in advanced HER2-positive breast cancer following trastuzumab	Lapatinib-plus-PLD is active and safe in HER2-positive MBC With overall response rate of 54%, progression-free survival (PFS) of 5.8 months and median over survival (OS) of 23.3 months. One-year PFS rate was 27% and OS rate was 76%.	Pircher *et al.*, 2015
6	Phase-2 study	25 patients with 2 or more prior lines of chemotherapy	PLD (25 mg/m^2) at 2-week intervals for a maximum of 12 courses	To evaluate a biweekly instead of a 4-week schedule of PLD in order to obtain a more flexible and tolerable regimen.	Clinical benefit rate (22.7%), median duration of clinical benefit (12.5 months) and median time to progression (7 weeks), median overall survival was 9.6 months (95% CI, 5.4-13.9). Common ADE include myelosuppression, with no grade 3 or 4 neutropenia or thrombocytopenia, nausea, alopecia, asthenia, and hand-foot syndrome.	Jehn *et al.*, 2016

Table 4. continued.

7	Randomized, phase III, open-label, multicentre trial	210 first-line MBC patients who were ineligible for endocrine or trastuzumab therapy	PLD 50 mg/m^2 every 28 days or capecitabine 1250 mg/m^2 twice daily for 14 days every 21 days	To determine the efficacy and safety of pegylated liposomal doxorubicin (PLD) versus capecitabine as first-line treatment of metastatic breast cancer (MBC).	No significant difference was observed in time to progression as observed Compared to PLD, patients on capecitabine experienced more serious adverse events (P = 0.015)	Harbeck *et al.*, 2017
8	Single-arm open-label phase I/II study	Metastatic breast cancer (n = 6 in phase I and n = 24 in phase II	Escalating doses of PLD were planned (30, 35, and 40 mg/m^2) with cyclophosphamide (60 mg/m^2 orally daily) t	Evaluation of the safety and efficacy of Pegylated liposomal doxorubicin (PLD) with metronomic oral cyclophosphamide.	Max. tolerated dose of PLD from phase I was 30 mg/m^2. Progression-free and overall survival for the entire cohort were 6.4 months and 18.7 months 21 (75%) patients showed clinical benefit and 6 (21%) patients showed partial response Majority ADE was uncomplicated myelosuppression	Chang *et al.*, 2018
9	Open-label, single-group, multicenter, phase 2 trial	Stage II–IIIB HER2-positive breast cancer	Neoadjuvant trastuzumab, pertuzumab, paclitaxel, and a non-pegylated liposomal doxorubicin every three weeks for six cycles.	To optimize activity while minimizing cardiac risk by combining trastuzumab, pertuzumab, and paclitaxel with non-pegylated liposomal doxorubicin in the treatment of HER2-positive early breast cancer.	Combination of dual HER2 blockade with trastuzumab and pertuzumab with paclitaxel and non-pegylated liposomal doxorubicin is associated with a low rate of cardiac events. The HER2-enriched subtype is associated with a high rate of pathological complete response (pCR) rate of 52%.	Gavilá *et al.*, 2019
10	Open-label, multicenter, single-armed clinical trial	125 patients	NAC regimen based on four cycles of PEG-LD 40 mg/m^2 plus cyclophosphamide (CPM) 600 mg/m^2 on day 1 of a 21 day schedule, followed by four cycles of docetaxel (DTX) 85 mg/m^2 on day 1 of a 21 day schedule	To assess the safety and efficacy of the Pegylated liposomal doxorubicin plus cyclophosphamide followed by docetaxel as neoadjuvant chemotherapy in locally advanced breast cancer	The regimen can be utilized as an alternative option for the neoadjuvant treatment of patients with locally advanced breast cancer, especially in those patients with the triple-negative subtype and who cannot tolerate the routine anthracyclines	Li *et al.*, 2019
11	Clinical trial	19 patients	During first four cycles PEG-LD (35, 40, 45, or 50 mg/m2) on day 1, + cyclophosphamide (600 mg/m2). + During the last four cycles, (75 mg/m2) on day 1 of a 21-day scheme.	Assessment of maximum tolerated dose (MTD) and toxicity in patients with locally advanced breast cancer	Combination PEG-LD (40 mg/m2) and cyclophosphamide (600 mg/m2), followed by docetaxel (75 mg/m2) on day 1 of a 21-day scheme, was efficacious and well-tolerated in patients of locally advanced breast cancer. ADE includes neutropenia, anemia, stomatitis, rash, nausea/vomiting, alopecia, transaminase elevation, and cardiotoxicity. Pathological complete response rate was 21.1%.	Cheng *et al.*, 2019
12	Phase II feasibility trial	63 patients	PLD (20 mg/m^2 biweekly for eight courses) intravenously. + Endocrine therapy according to menopausal status. + Trastuzumab was administered in HER2-positive disease.	To evaluate pegylated liposomal doxorubicin (PLD, Caelyx®) as adjuvant chemotherapy.	Primary endpoint (feasibility of this regimen) was found in 84%. 55 of 63 enrolled patients completed treatment (ADEs observed include palmar-plantar erythrodysesthesia (12.2%), fatigue (10.4%), and mucositis (8.5%). None had alopecia.	Dellapasqua *et al.*, 2021

Table 4. continued.

13	Single-arm, phase II study	44 enrolled patients	PLD (Duomeisu®, generic doxorubicin hydrochloride liposome) 40 mg/m^2 every 4 weeks	To evaluate the efficacy and safety of pegylated liposomal doxorubicin (PLD) in patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC)	59.1% patients had ≥ 3 metastatic sites, 86.4% had visceral disease, and 63.6% (28/44) had liver metastases. Median progression-free survival (PFS) was 3.7 months median overall survival was 15.0 months Clinical benefit rate was 36.1%, ADEs were leukopenia (53.7%), fatigue (46.3%), and neutropenia (41.5%), left ventricular ejection fraction decline of 11.4% from baseline after five cycles of PLD therapy. PLD (Duomeisu®) 40 mg/m^2 every 4 weeks was effective and well-tolerated in patients with HER2-negative MBC heavily pretreated with anthracycline and taxanes.	Jiang *et al.*, 2023
14	Standard phase 1, 3 + 3 dose-escalation design	44 patients with recurrent ovarian or triple negative breast cancer were enrolled	50 mg veliparib BID on days 1-14 with PLD 40 mg/mg^2 on day 1 of a 28-day cycle	To determine the recommended phase two dose (RP2D) of veliparib with pegylated liposomal doxorubicin (PLD) in breast cancer.	The RP2D is 200 mg veliparib BID on days 1-14 with 40 mg/m^2 PLD on day 1 of a 28-day cycle. Anti-tumor activity was seen in both strata.	Pothuri *et al.*, 2023

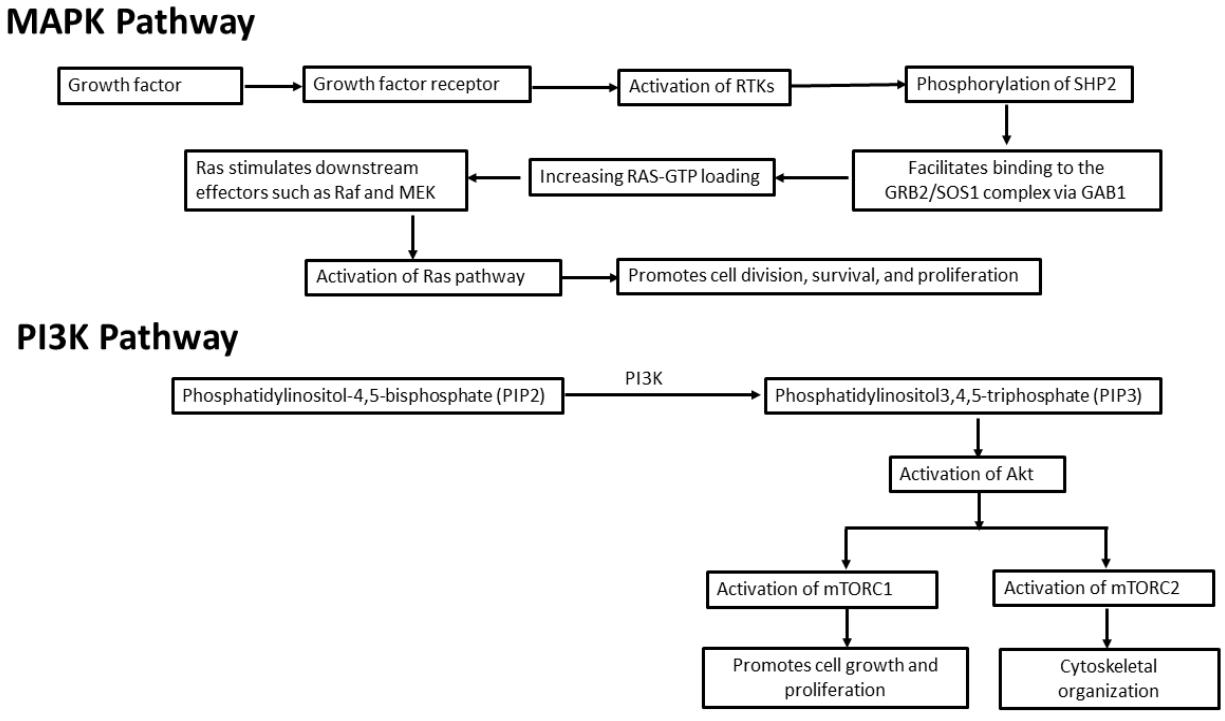

Figure 1. MAPK and PI3K pathways in the pathogenesis of Cancer

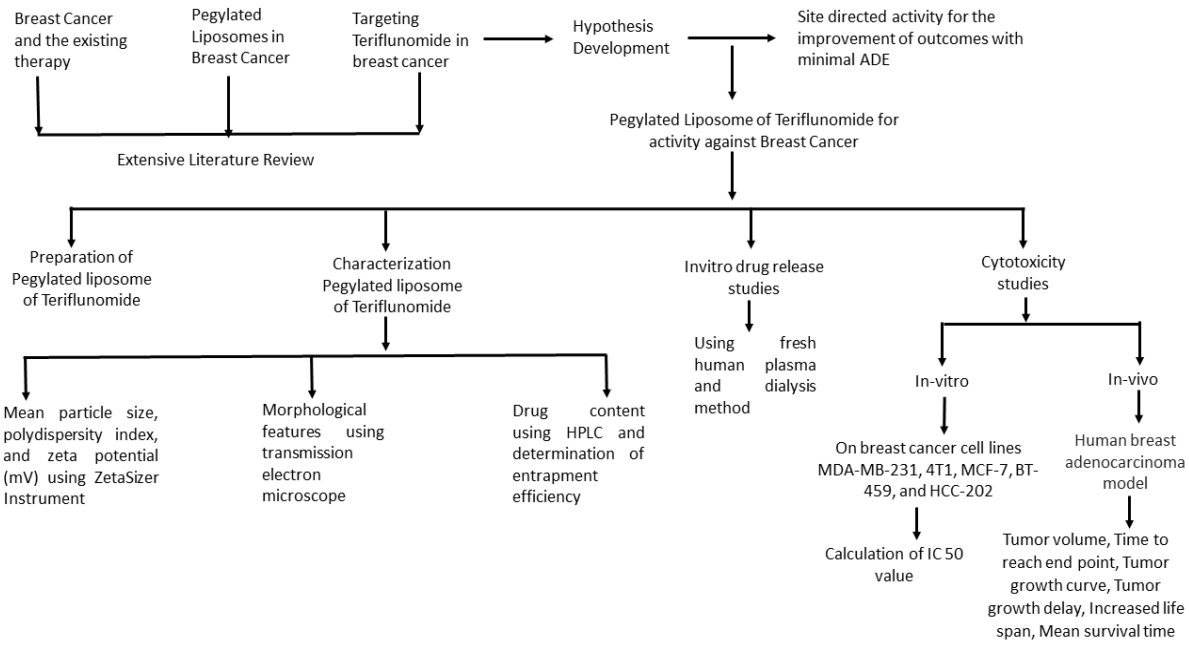

Figure 2. PEGylated liposome of teriflunomide for the treatment of breast cancer

study the amount of TFN released from liposomes (Sivadasan et al, 2022). Stability of conventional and PEGylated liposomes in the gastrointestinal environment of the human body may also be determined by using simulated gastric fluid [SGF, PH 1.2]. An ex-vivo gut permeation study describes drug permeation through the gut wall as it utilizes the non-everted gut sac of female Wistar rats. In vivo, pharmacokinetic studies and acute pharmacological studies can be performed by the reviewed and approved experimental protocol. Histopathological studies offer a method to determine the accumulation and effects of drugs and excipients in different organs (Shavi et al., 2016), such as the spleen, liver, kidney, and heart tissue. A biodistribution study will be performed to observe the localization of the drug-loaded liposomes and ligand-modified drug-loaded liposomes in different organs of the body via gamma-scintigraphic imaging (Turker et al., 2005; Haddad et al., 2018). In conclusion, the optimized TEF-liposomal formulation was stabilized under the guidelines given by ICH Q1A (R2). TEF-liposomal formulation was stored at 4°C with 60% RH and at 25°C with 60% RH for 6 months. At specific time intervals of 1, 3, and 6 months the samples were withdrawn and checked for their physical appearance. Moreover, the particle size, PDI, and EE were also analyzed (Zhang et al., 2021).

7. Conclusion

The present hypothesis focuses on a novel approach regarding the Teriflunomide-EFloaded PEGylated liposomes against breast cancer. The proposed formulation was developed to overcome the present limitations and to achieve the synergistic effects of liposomes with TFN. TFN's PEGylated liposomes have improved the specificity towards cancer cells, therapeutic outcome, compliance, and lesser adverse effects that may improve patient compliance and adherence to achieve the desired anti-cancer effect.

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Competing financial interests

The authors have no conflict of interest.

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