VITAMIN D3-ASSOCIATED LYOTROPIC LIQUID CRYSTALLINE NANOPARTICLES FOR GEMCITABINE AND THYMOQUINONE DELIVERY FOR TREATMENT OF LUMINAL BREAST CANCER WITH RESISTANT CHARACTERISTICS

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Faculty : Science

Breast cancer is a leading cause of cancer death in women worldwide. About 70 – 80% of breast cancers are estrogen receptor-alpha (ERα) positive, dependent on estrogen for growth. Primary or acquired resistance towards endocrine therapy has remained a therapeutic barrier for patients in this subgroup, hence, there is an increasing interest in the development of novel targeted anticancer treatment strategies, including cancer nanomedicines that potentially translate to enhanced efficacy and reduced toxicity. Lyotropic liquid crystalline nanoparticles (LLCNs) are formed via self-assembly of amphiphilic molecules in a mixture composed of a lipid-based fraction, stabilizer and/or surfactant, and aqueous media/dispersant. The unique tunable modality of LLCNs presents the development of versatile nanostructures for a range of biomedical application. In this study, multifunctional LLCNs were investigated for gemcitabine-thymoquinone (Gem-TQ) co-delivery and targeting to hormone receptor-positive (HR+) breast cancer cells with potential resistance against tamoxifen (i.e., TamR cells) by surface modification with vitamin D_3-polyethylene glycol (VD-PEG). LLCNs were prepared using soy phosphatidylcholine (SPC), phytantriol (PHYT), or glycerol monostearate (MYVR), in optimized ratios containing citrem or Poloxamer 407 (F127). The series of nanoformulation exhibited hydrodynamic particle sizes ranging between 96 – 365 nm, lattice parameters between 4.8 – 8.0, negative zeta potential between -4 to -79 mV, hexagonal, cubic, or micellar phases, and high entrapment efficiency. Low cytotoxicity of SPC/citrem LLCNs was demonstrated in non-malignant breast epithelial MCF10A cells consistent with modulation of hemocompatibility. Therefore, SPC/citrem was selected for co-encapsulation, whereby entrapment efficiency of 99.5 ± 0.1% (TQ) and 98.3 ± 0.1% (Gem) was demonstrated by SPC/citrem/Gem-TQ LLCNs comprising an optimized composition of 2.5:2.5 wt% of SPC:citrem, and 2:9 μM ratio of Gem and TQ. Meanwhile, the formulation with the addition of VD-PEG was designated

as VD/SPC/citrem/Gem-TQ and the entrapment efficiency was 99.0 ± 0.1% (TQ) and 97.7 ± 0.1% (Gem) at the compositional ratio of 2.5:2.5:0.1 wt% of SPC: citrem:VD-PEG. Notably, the inhibitory concentrations (IC_{50s}) following 24 h treatment with drug-loaded SPC/citrem/Gem-TQ were 14.5 ± 3.0 μM and 19.6 ± 2.3 μM, while IC_{50s} of VD/SPC/citrem/Gem-TQ nanodispersion were 33.4 ± 8.0 μM and 9.7 ± 1.1 μM against MCF7 and T-47D-TamR breast cancer cells, respectively. Synergistic interaction between Gem and TQ shown in MCF7 cells was retained by SPC/citrem/Gem-TQ (i.e., treatment time of 24 h and fractional inhibition of 0.5), and by VD/SPC/citrem/Gem-TQ (i.e., treatment time of 24 h and fractional inhibition of 0.95), against T-47D-TamR cells. In addition, VD/ SPC/citrem/Gem-TQ LLCNs upregulated the expression of caspase-3, Akt-1 (serine/threonine-protein kinase) and vitamin D_3-receptor (VDR) in T-47D-TamR cells, and cell cycle arrest at G2 phase (15.25% of total cell population) was evident following the treatment with VD/SPC/citrem/Gem-TQ LLCNs. Herein, multifunctional biocompatible LLCNs were described as a potential therapeutic co-delivery system for luminal breast cancer treatment.

Keywords: Lyotropic liquid crystalline nanoparticles; Hexosomes; Citrem: Soy phosphatidylcholine; Surface functionalization; Co-delivery; Breast cancer

SDG: 3 (Good Health and Well-being)

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

NANOPARTIKEL KRISTAL CECAIR LIOTROPIK BERKAITAN VITAMIN D3 UNTUK PENYAMPAIAN GEMSITABIN DAN TIMOKUINON DALAM PERAWATAN KANSER PAYUDARA LUMINAL DENGAN CIRI-CIRI TAHAN

Oleh

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Kanser payudara merupakan punca utama kematian akibat kanser di kalangan wanita, di seluruh dunia. Kira-kira 70 – 80% daripada kanser payudara adalah estrogen reseptor-alfa (ER-α) positif, di mana pertumbuhan sel-sel kanser bergantung kepada estrogen. Rintangan (yang sedia-ada atau yang diperolehi) terhadap terapi endokrin masih tetap menjadi penghalang terapeutik bagi pesakit-pesakit dalam subkumpulan ini, oleh itu, terdapat minat yang semakin meningkat berkenaaan penggunaan strategi rawatan antikanser termasuk nanoperubatan yang berpotensi untuk meningkatkan keberkesanan dan mengurangi ketoksikan. Nanozarah kristal cecair liotropik (LLCNs) adalah terbentuk melalui pemasangan sendiri molekul ampifilik dalam campuran yang terdiri daripada lipid, bahan penstabil dan/atau surfaktan, dan media akueus/dispersan. Modaliti unik LLCN ini menunjukkan nanostruktur yang boleh disesuaikan dalam pelbagai aplikasi bioperubatan. Dalam kajian ini, LLCN pelbagai-fungsi telah dinilai untuk penyampaian kombinasi gemsitabin-timokuinon (Gem-TQ) dan penyasaran ke sel-sel kanser payudara reseptor positif (HR+) dengan potensi rintangan terhadap tamoxifen (iaitu, sel TamR), melalui pengubahsuaian permukaan nanozarah dengan vitamin D_3-polietilena glikol (VD-PEG). LLCN disediakan menggunakan fosfatidilkolin soya (SPC), fitontriol (PHYT), atau gliserol monostearat (MYVR), dalam nisbah optima yang mengandungi citrem atau Poloxamer 407. Siri nanoformulasi ini mempamerkan ciri-ciri saiz zarah hidrodinamik antara 96 – 365 nm, parameter kekisi antara 4.8 – 8.0, cas permukaan negatif antara -4 hingga -79 mV, fasa heksagonal, kubik, atau misel, dan kecekapan pemerangkapan yang tinggi. Aktiviti sitotoksik rendah SPC/citrem LLCNs yang ditunjukkan dalam sel MCF10A epitelium payudara bukan kanser adalah selaras dengan modulasi hemokompatibiliti (darah). Oleh

itu, formulasi tersebut dipilih untuk pengkapsulan kombinasi, di mana kecekapan pemerangkapan 99.5 ± 0.1% (TQ) dan 98.3 ± 0.1% (Gem) telah ditunjukkan oleh SPC/citrem/Gem-TQ LLCN yang terdiri daripada komposisi optima 2.5:2.5 wt% SPC:citrem dan nisbah 2:9 μM antara Gem dan TQ. Sementara itu, formulasi dengan penambahan VD-PEG ditetapkan sebagai VD/SPC/citrem/Gem-TQ, dan kecekapan pemerangkapan formulasi ini ialah 99.0 ± 0.1% (TQ) dan 97.7 ± 0.1% (Gem) pada nisbah komposisi 2.5:2.5:0.1 wt% SPC:citrem:VD-PEG. Khususnya, dos/konsentrasi perencatan (IC_{50}) seiring dengan rawatan 24 jam menggunakan SPC/citrem/Gem-TQ (dimuatkan 2:9 μM Gem dan TQ), ialah 14.5 ± 3.0 μM and 19.6 ± 2.3 μM, manakala IC_{50} formulasi VD/SPC/citrem/Gem-TQ ialah 33.4 ± 8.0 μM and 9.7 ± 1.1 μM dalam sel kanser MCF7 dan T-47D-TamR masing-masing. Interaksi sinergistik antara Gem dan TQ yang ditentukan pada sel MCF7 dikekalkan oleh SPC/citrem/Gem-TQ (iaitu, perawatan selama 24 jam, pada perencatan fraksional 0.5), dan terhadap sel T-47D-TamR dengan menggunakan VD/SPC/citrem/Gem-TQ (iaitu, perawatan selama 24 jam, pada perencatan fraksional 0.95). Di samping itu, VD/SPC/citrem/Gem-TQ telah meningkatkan ekspresi kaspase-3, Akt-1 (serin/treonin-protin kinase) dan reseptor vitamin D_3 (VDR) dalam sel T-47D-TamR, dan penghentian kitaran sel pada fasa G2 (15.25% daripada jumlah sel populasi) terbukti berikutan perawatan dengan VD/SPC/citrem/Gem-TQ. Dalam kajian ini, LLCN biokompatibel pelbagai-fungsi ditelitikan sebagai sistem pengkapsulan kombinasi yang berpotensi untuk perawatan kanser payudara luminal.

Kata kunci: Nanopartikel kristal cecair lyotropik; Heksosom; Citrem: Fosfatidilkolin soya; Kefungsian permukaan; Penyampaian kombinasi; Kanser payudara

SDG: 3 (Kesihatan Baik dan Kesejahteraan)

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LIST OF ABBREVIATIONS

AI	Aromatase inhibitor
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
ATCC	American Type Culture Collection
CDK4/6	Cyclin-dependent kinase 4 and 6
CDK4/6i	Cyclin-dependent kinase 4 and 6 inhibitor
CI	Combination index
CPP	Critical packing parameter
Cryo-TEM	Cryogenic transmission electron microscopy
ctDNA	Circulating tumor DNA
Cy5	Cyanine 5
DAPI	4',6-Diamidino-2-phenylindole, dihydrochloride
DOX	Doxorubicin
DSC	Differential scanning calorimetry
EDS	Energy-dispersive X-ray spectroscopy
EDTA	Ethylenediaminetetraacetic acid
EE	Entrapment efficiency
EME	Emulsified micelles
ER	Estrogen receptor
ER−	Estrogen receptor-negative
ER+	Estrogen receptor-positive
ESR1	Estrogen receptor 1 gene
F127	Pluronic F127/Poloxamer 407
FACS	Fluorescence-activated cell sorting
FBS	Fetal bovine serum

FDA	Food and Drug Administration
FTIR	Fourier-transformed infrared
Gem	Gemcitabine
GDO	Glycerol dioleate
GMO	Glycerol monooleate/monoolein
GRAS	Generally recognized as safe
H_1/H_I	Normal hexagonal phase
H_2/H_{II}	Inverse hexagonal phase
HR+	Hormone receptor-positive
HER2	Human epidermal growth factor receptor 2
HER2−	Human epidermal growth factor receptor 2-negative
HER2+	Human epidermal growth factor receptor 2-positive
IC_{50}	Inhibitory concentration 50
ISAsomes	Internally self-assembled-somes
λ	Wavelength
Λ_{max}	Wavelength at maximum peak
L_2	Inverse micellar solution
L_α	Lamellar phase
LD_{50}	Lethal dose 50
LLCNs	Lyotropic liquid crystalline nanoassemblies
mTOR	Mammalian target of rapamycin
MB	Methylene blue
MCF7	Michigan Cancer Foundation-7
MCF10A	Michigan Cancer Foundation-10A
mPEG	Methoxy(polyethylene glycol)
MPS	Mononuclear phagocyte system

MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MYVR	Myverol 18-04K
nm	Nanometres
NLCs	Nanostructured lipid carriers
NPs	Nanoparticles
PARP	Poly(ADP-ribose) polymerase
PBS	Phosphate buffered saline
PEG	Polyethylene glycol
PEO	Polyethylene oxide
PFS	Progression-free survival
PHYT	Phytantriol
PI	Propidium iodide
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PFA	Paraformaldehyde
PPG	Polypropylene glycol
PR	Progesterone receptor
PTX	Paclitaxel
Q_1/Q_I	Normal bicontinuous cubic phase
Q_2/Q_{II}	Inverse bicontinuous cubic phase
Q_{II}^D	Schwarz diamond inverse bicontinuous cubic phase
Q_{II}^G	Schoen gyroid inverse bicontinuous cubic phase
Q_{II}^P	Primitive inverse bicontinuous cubic phase
RNAse A	Ribonuclease A
ROS	Reactive oxygen species

RPMI-1640	Roswell Park Memorial Institute-1640
SAXS	Small angle X-ray scattering
SERDs	Selective estrogen receptor downregulators
SERMs	Selective estrogen receptor modulators
SLNs	Solid lipid nanoparticles
SPC	Soy L-α-phosphatidylcholine
Tam	Tamoxifen
TamR	Tamoxifen-resistant
TEAA	Triethylammonium acetate
TEM	Transmission electron microscopy
TNBC	Triple-negative breast cancer
TPGS	D-α-tocopheryl-polyethylene glycol (2000) succinate
TQ	Thymoquinone
VD-PEG	Vitamin D_3-methoxypolyethylene glycol (2000)
VDR	Vitamin D_3 receptor
WAXS	Wide angle X-ray scattering
WB	Whole blood
XPS	X-ray photoelectron spectroscopy

CHAPTER 1

INTRODUCTION

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1.1.1 Background of the Study

Cancer arises from aberrant cellular division leading to malignant tumors, i.e., mass of cancerous tissue, capable of abrogating natural apoptosis and/or necrosis. The perpetual hallmarks of cancer involve complex mechanisms, coupled to inter- and intra-individual heterogeneous factors to either cause cancer progression or remission. According to the World Health Organization (WHO)'s cancer agency, the International Agency for Research on Cancer (IARC) Global Cancer Observatory, worldwide cancer incidence and cancer-related deaths in 2022 had accounted to as much as 20 million and 9.7 million, respectively. In addition, WHO stated that more than 60% of the world's total new annual cases occur in Africa, Asia, and Central and South America, for which 70% of the world's cancer-associated deaths has been reported. Cancer incidence per year would be expected to increase to 24.6 million by 2030 (Global Cancer Observatory, IARC, 2023), and low- and middle-income countries (LMICs) could be largely impacted given the current social and economic burden of cancer in these regions. This corresponds to the observed 5-year net survival trends for most cancers throughout the period of 2000 – 2014 (CONCORD-3) that were reportedly highest in the U.S., Canada, Australia, New Zealand, Finland, Iceland, Norway, and Sweden (Allemani et al. 2018).

Breast cancer is the second most commonly diagnosed type of cancer worldwide, as of the latest estimates (2022) available from IARC Global Cancer Observatory. In the United States alone, an annual incidence surmounting to 297,790 (31%) breast cancer cases and 43,170 (15%) estimated deaths were estimated for year 2023 (Siegel et al. 2023), whereas 2.3 million new cases of female breast cancer and 670,000 deaths were estimated worldwide in 2022 (Global Cancer Observatory, IARC, 2024). Breast cancer has remained a pressing concern of widespread prevalence as evident by global surveillance data. In Asia, the overall 5-year survival rates in female breast cancer patients have gradually improved across three intervals, (i) 2000 – 2004, (ii) 2005 – 2009, and (iii) 2010 – 2014. However, lower survival rates following breast cancer diagnosis were, still, observed in LMICs compared to high-income nations (Ley et al. 2016, Rauniyar et al. 2023). Among cancers diagnosed in Malaysian women, breast cancer accounted for the highest percentage of newly diagnosed cancer, followed by colorectal, cervical-uteri, ovarian, and lung cancer (Global Cancer Observatory, IARC, 2018). Mortality rate associated with breast cancer in Malaysia is second to highest, and predisposition is underpinned by various risk factors including germline (inherited) genetic mutations, aging, obesity and diabetes (leptin signaling in breast cancer development; VanSaun 2013, Schmidt et al. 2015), smoking, and heavy alcohol consumption.

Luminal estrogen receptor (ER)-positive breast cancer constitutes approximately 70–75% of all breast cancers diagnosed, whereas human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients represent about 15–20% and are primarily recommended for anti-HER2 therapies (Tang et al. 2016). Molecular pathogenesis of breast cancer subtypes is associated with a range of cellular pathways that normally control cell cycle progression (Harbeck et al. 2019, Nolan et al. 2023). In estrogen receptor-positive (ER+) breast cancer, the binding of the hormone, estrogen, to receptors results in their translocation to the nucleus, where they act as nuclear transcription factors leading to the modulation of gene expressions. The ER-dependent carcinogenic action of estrogen, therefore, results from ER-mediated aberrant regulation of estrogen-responsive genes, leading to increased cell proliferation and accumulation of deoxyribonucleic acid (DNA) damage (Saha et al. 2019).

Currently, first-line hormonal therapy or endocrine therapy is the standard-of-care in both early-stage and metastatic HR+ breast cancer treatment. Commercially available endocrine therapy includes three main types: the aromatase inhibitors (AIs), anastrozole, exemestane, and letrozole, the selective estrogen receptor modulators (SERMs), tamoxifen, raloxifene, and toremifene, and the selective estrogen receptor downregulators (SERDs), fulvestrant and elacestrant. On the other hand, HER+ breast cancer is treated with a different class of medication, i.e., HER2-targeted therapy (trastuzumab and pertuzumab) that may be administered in the neoadjuvant or adjuvant (before or after surgery) setting (Harbeck 2022). The treatment of HER+ breast cancer, depending on the stage or spread of lesions, may also involve antibody drug conjugates [e.g., trastuzumab emtansine (T-DM1)], tyrosine kinase inhibitor (TKI) drugs (e.g., lapatinib and neratinib), or chemotherapy. First-line treatment of triple-negative breast cancer (TNBC) may, generally, comprise a chemo-therapeutic regimen (e.g., capecitabine), pembrolizumab [antibody which selectively inhibits the programmed death-1 (PD-1) receptor], olaparib, or talazoparib [poly ADP ribose polymerase (PARP)-inhibitors], or antibody-drug conjugates [e.g., sacituzumab govitecan, a trophoblast cell-surface Ag-2 (Trop-2)-directed antibody and topoisomerase inhibitor (SN-38) drug conjugate] (Adams et al. 2021).

The growing burden of breast cancer is attributed to its complex etiology, tumor heterogeneity, and cancer recurrence despite promising outcomes for HR+ breast cancer during early disease compared to the more aggressive triple-negative or basal subtypes. In about 40% of patients with luminal breast cancer pre-treated with tamoxifen, endocrine resistance has been reported; acquired endocrine resistance is defined by cancer recurrence while receiving, or were within 1 year of completing adjuvant endocrine treatment (Robinson et al. 2013, Ballinger et al. 2018, Horibata et al. 2018, Hultsch et al. 2018). A study has also shown that even among patients with small, node-negative (T1N0), low-grade breast tumors, who ceased treatment following 5 years of adjuvant endocrine therapy, the risk of distant relapse is approximately 10% between 5 – 20 years (Pan et al. 2017). FDA-approved trastuzumab (recombinant monoclonal anti-body against HER2), everolimus (mTOR inhibitor), and cyclin-dependent kinase (CDK) 4/6 inhibitors, palbociclib, ribociclib, and abemaciclib, are examples of treatments to overcome endocrine resistance. They are, however, costly

treatment options and may be administered in combinations with second-line endocrine-modulating agents (Matutino et al. 2018, Mistry et al. 2018, Zhang et al. 2019, Loke et al. 2020, Yang et al. 2020a, Zhu et al. 2022). Moreover, uncertainties remain about the selection of biomarkers to predict patient response following treatments with CDK4/6 inhibitors, and guidelines are required to determine whether a given CDK4/6 inhibitor (CDK4/6i) should be continued/switched following disease progression, whether CDK4/6 inhibitors may be combined with therapies other than endocrine-based therapies, and whether the use of these agents can be extended to HR+/HER2− early-stage and HR+/HER2+ breast cancers (Shah et al. 2018, Portman et al. 2019, O'Brien et al. 2020). As of March 2023, Verzenio® is the only CDK4/6 inhibitor approved by the U. S. Food and Drug Administration (FDA) for adjuvant treatment of HR+/HER2- high risk early breast cancer. Therefore, as researchers continue to unravel the molecular mechanisms contributing to endocrine resistance in breast cancer, there is an increasing urgency in the need to develop novel and targeted anticancer treatment strategies which can potentially translate to enhanced efficacy and reduced toxicity.

Major discoveries in the nanotechnology field, such as carbon nanotubes (CNTs), were recognized throughout the 1990s. By the early 2000s, nanomaterials were being used in consumer products (National Geographic Society, 2023). Among nanomedicine strategies comprising nanoparticles (NPs) ranging between 1–1000 nanometers (nm) in size, lipid and amphiphilic polymer-based systems constitute the majority as they concur with endogenous lipids in components of cell membranes, glycolipids, lipoproteins, and cholesterol. Nonlamellar lyotropic liquid crystalline nanoparticles (LLCNs) are lipid-based internally self-assembled (ISA)-somes that occur in an intermediate state of matter between the liquid and solid (crystalline) phase (van't Hag et al. 2016). LLCNs are self-assembled to form versatile colloidal nanocarriers with ordered internal nanostructures. LLCNs present a unique feature in that their phase transition (e.g., lamellar-to-cubic, or cubic-to-hexagonal) can be modulated according to the curvature energy of the lipid monolayers (Fong et al. 2012). Cubic and hexagonal LLCNs have been widely studied for drug delivery applications through various routes (transdermal, oral, intravenous, intranasal, etc.) (Azmi et al. 2015a). Importantly, nanoparticle strategies may be designed to enhance biodistribution, control drug release, prolong systemic circulation of the encapsulated therapeutic agent, and/or multiple functions may be engineered into one treatment platform that may include theranostics. In formulations with polyethylene glycol (PEG), NPs are equipped with properties to evade macrophage clearance, promote stability and longer blood circulation time, and improve cellular uptake. In recent years, a wide range of phyto-chemical-loaded NPs has been investigated (Majolo et al. 2019, Kashyap et al. 2021). Nanoencapsulation of natural products comprise the approaches to overcome hurdles associated with low bioavailability and poor absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, and to enable protection from rapid natural product degradation.

1.2 Problem Statement

The combination between gemcitabine (Gem) and thymoquinone (TQ), resulted in a synergistic anticancer effect against MCF7 breast cancer cells (Bashmail et al. 2018). Gem is an FDA-approved chemotherapeutic agent (nucleoside analogue), while TQ is a naturally-derived monoterpene found in *Nigella sativa* (Linn.) and *Carum carvi* seed oil. Respectively, Gem and TQ are associated with pharmacokinetic caveats, including, (i) rapid metabolism of Gem into inactive 2′,2′-difluoro-2′-deoxyuridine (dFdU) that is, in turn, rapidly eliminated from the body (Ciccolini et al. 2016), and (ii) low plasma concentration following oral administration of TQ (Kalam et al. 2017). The combination between Gem and TQ also supports the role of phytochemicals to potentiate the efficacy and/or protect from adverse side-effects of chemotherapy. In addition, there is a current need to investigate the potential of LLCNs as multifunctional nanocarriers for therapeutic delivery and targeting to hormone receptor-positive luminal breast cancer, particularly since the development of primary or secondary (acquired) resistance in this breast cancer subtype has been a major impediment to standard endocrine therapies.

1.3 Significance of the Study

LLCNs remain to be fully explored for the systemic treatment of breast cancer, employing multifunctionality in their therapeutic actions. To the best of our knowledge, the incorporation of vitamin D_3 in combination therapy for the simultaneous anticancer action of biocompatible soy L-α-phosphatidylcholine (SPC)-based LLCNs is a novel approach which has not been reported. As experimental studies have identified key roles of vitamin D_3 and its derivatives in the inhibition of breast cancer cell growth, this study, therefore, contributes new insights into the surface functionalization of lipid-based liquid crystalline nano-assemblies modified with vitamin D_3-polyethylene glycol (PEGylation). The surface-functionalized nanoparticles were further evaluated for their anticancer activity against breast cancer cells, including a potentially tamoxifen-resistant breast ductal carcinoma cell line.

1.4 Research Hypotheses

Co-loading and incorporation of Gem-TQ in LLCNs is hypothesized to demonstrate high encapsulation efficiency, sustained release, and maintain hemocompatibility assessed in human blood, and biocompatibility examined in zebrafish embryos. Secondly, the vitamin D_3 surface-functionalized LLCNs (VD/SPC/citrem/Gem-TQ) are hypothesized to demonstrate anticancer activity against hormone receptor-positive breast cancer cells corresponding to VDR expression. Synergistic anticancer effect is, therefore, postulated for the VD/SPC/citrem/Gem-TQ LLCNs.

1.5 Research Objectives

The general objective of the current study is to investigate multifunctional and biocompatible LLCNs for co-delivery of gemcitabine (Gem) and thymoquinone (TQ), followed by evaluation of their anticancer activity in hormone receptor-positive breast cancer cells. At the same time, the LLCNs were developed for biocompatibility and *in vitro* targeting to tamoxifen-resistant breast cancer cells. The specific research objectives comprise the following:

1. To develop and characterize gemcitabine-thymoquinone (Gem-TQ) co-encapsulated lyotropic liquid crystalline nanoparticles (LLCNs), followed by surface modification of optimized LLCNs with vitamin D_3-polyethylene glycol (VD-PEG) and characterization of targeted nanoparticles (VD/SPC/citrem/Gem-TQ LLCNs) **(Chapter 3)**.

2. To investigate hemocompatibility, biocompatibility, and stability of LLCNs, including VD/SPC/citrem/Gem-TQ LLCNs, in contact with isolated human blood and zebrafish (*Danio rerio*) embryos **(Chapter 4)**.

3. To evaluate the *in vitro* anticancer activity and cellular uptake of LLCNs, including VD/SPC/citrem/Gem-TQ LLCNs, in MCF10A, MCF7, T-47D, and T-47D-TamR breast cancer cells bearing resistant characteristics towards tamoxifen (Tam) **(Chapter 5)**.

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