SIMVASTATIN-LOADED LIPID-BASED NANOCARRIERS FOR BREAST CANCER THERAPY: FROM MECHANISTIC RATIONALE TO FORMULATION STRATEGIES

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Abstract

The primary clinical problem is metastatic and therapy-resistant breast cancer, which continues to be the most often diagnosed cancer in women globally and a major cause of cancer-related mortality. Dose-limiting toxicities, inadequate tumor selectivity, and multidrug resistance limit conventional systemic chemotherapy and targeted therapies, prompting the hunt for safer and more efficient therapeutic approaches. Because they target the mevalonate system and have pleiotropic anti-tumor actions, such as inducing apoptosis, cell cycle arrest, and inhibiting pro-survival signaling, statins-especially the lipophilic agent simvastatin-have become intriguing drug-repurposing candidates in cancer. The pharmacokinetic and pharmacodynamic drawbacks of free simvastatin, such as poor aqueous solubility, quick first-pass metabolism, and off-target toxicity, can be addressed by lipid-based nanocarriers, such as liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanoemulsions. Preclinical research shows that lipidic systems loaded with simvastatin, either by themselves or in conjunction with chemotherapeutics or natural bioactives, greatly increase cytotoxicity against breast cancer cells, improve tumor growth inhibition, and decrease systemic toxicity when compared to the free drug. The translational justification for simvastatin-based nanomedicine is further supported by meta-analytic clinical data that indicate statin exposure both before and after breast cancer diagnosis is linked to decreased recurrence and enhanced overall and breast cancer-specific survival.

Keywords: *Breast cancer, simvastatin, lipid nanocarrier, nanomedicine.*

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1. INTRODUCTION

1.1 Global burden and clinical challenges of breast cancer

Despite improvements in screening and treatment, breast cancer continues to be the most frequent cancer among women worldwide and a leading cause of cancer-related mortality (Trapani et al., 2022; Li et al., 2019). Its clinical burden is increased by its high incidence, late-stage appearance in several areas, and tendency to spread to the brain, liver, lung, bone, and lymph nodes. Tumor heterogeneity, innate and acquired resistance to chemotherapy and targeted therapies, and dose-limiting toxicities that impair quality of life are among the therapeutic obstacles (Benson & Jatoi, 2012; Xu et al., 2021).

1.2 Limitations of current chemotherapy and targeted therapies

Surgery, radiation, endocrine therapy, and HER2-targeted therapy are examples of conventional therapeutic techniques that have increased survival but are frequently insufficient in cases of advanced, triple negative, or metastatic cancer (Curigliano & Criscitiello, 2014; Joo et al., 2013). Dose escalation is limited by the short therapeutic windows, non-selective biodistribution, and cumulative cardiotoxicity or neurotoxicity of small-molecule chemotherapeutics like paclitaxel and doxorubicin (Casali, 2014; Yap et al., 2009; Saijo, 2012). Furthermore, changes in drug targets, activation of survival pathways, and multidrug resistance mediated by efflux pumps diminish the long-term effectiveness of conventional regimens.

1.3 Drug repurposing in oncology: rationale for statins

By utilizing the established pharmacokinetics and safety profiles of current medications for novel indications, drug repurposing provides an economical and time-efficient approach (Regulska et al., 2019; Abdullah et al., 2018). In epidemiologic and mechanistic investigations, statins-which are often prescribed HMG-CoA reductase inhibitors for hypercholesterolemia-have been linked to decreased cancer incidence, postponed progression, and enhanced survival in a variety of tumor forms (Tripathi et al., 2024; Tran & Prasad, 2020). Their promise as supplemental anti-cancer drugs, especially in breast cancer, is supported by their capacity to suppress the mevalonate pathway, deplete isoprenoid intermediates, and alter oncogenic signaling networks (Turabi et al., 2022; Wang et al., 2022; Benjamin et al., 2024).

1.4 Overview of lipid-based nanocarriers

Among the most clinically sophisticated nanocarrier systems are lipid-based nanoparticles, which include liposomes, SLNs, NLCs, and lipid nanoemulsions (Patidar et al., 2010; Pardeshi et al., 2012). Several of these formulations have already received approval for use in

cancer treatment. By encasing hydrophobic medications in lipid bilayers or cores, these carriers can improve solubility, shield medications from deterioration, and alter pharmacokinetics and biodistribution (Plaza-Oliver et al., 2021; Talluri et al., 2016). They are especially well suited for repurposed drugs like simvastatin because of their biocompatible lipid content and adjustable surface characteristics, which allow for both passive and aggressive tumor targeting (Zhao et al., 2022; Musacchio & Torchilin, 2011). This review focuses on lipid-based nanocarriers as shown in figure 1 as allowing platforms to fully utilize simvastatin's anti-tumor potential and simvastatin as a model statin for therapeutic repurposing in breast cancer. In order to provide a thorough framework for the logical design of simvastatin-loaded lipid nanomedicines against breast cancer, it combines molecular evidence on simvastatin's anti-cancer activities with formulation science, preclinical efficacy, and translational concerns.

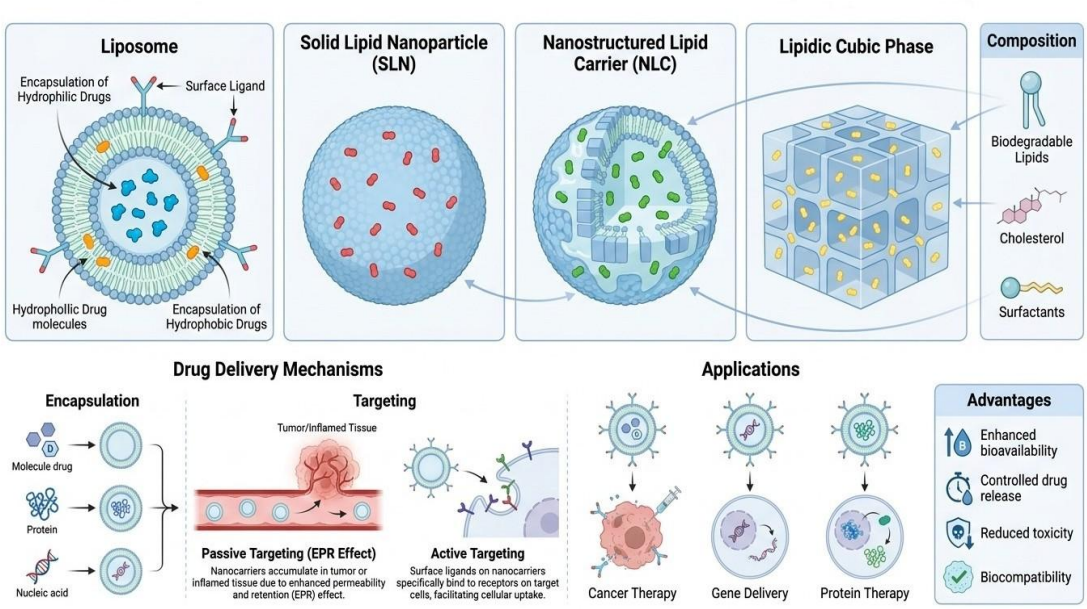

Figure 1 Lipid-based nanocarriers systems such as liposomes, SLNs, NLCs, and LCPs; labelled with structural characteristics and drug encapsulation techniques; compositions include phospholipids and glycerides; mechanisms: passive (EPR) and active targeting; applications: gene/protein delivery, cancer therapy; benefits: biocompatibility, high encapsulation, controlled release.

2. Simvastatin in Cancer Therapy: Mechanistic Insights

2.1 Pharmacological profile and physicochemical properties of simvastatin

The mevalonate pathway's rate-limiting enzyme, HMG-CoA reductase, is competitively inhibited by simvastatin, a lipophilic lactone prodrug that hydrolyzes in vivo to its active β-hydroxy acid form (Althanoon et al., 2020; Todd & Goa, 1990). Its restricted oral

bioavailability and extensive first-pass metabolism are caused by its high lipophilicity and poor water solubility, which make it difficult to achieve therapeutic systemic concentrations in cancer applications. However, these characteristics also make simvastatin especially suitable for encapsulation in lipidic matrices and bilayers, where solubility and controlled release are enhanced by partitioning into hydrophobic domains (Schachter, 2005; Catapano, 2012; Saoji et al., 2016).

2.2 Mevalonate pathway inhibition and anti-cancer activity

The mevalonate system produces cholesterol and non-sterol isoprenoids like geranylgeranyl pyrophosphate and farnesyl pyrophosphate, which are necessary for the post-translational prenylation of small GTPases (including Ras, Rho, and Rac) that control migration, survival, and proliferation (Iannelli et al., 2018; Wang et al., 2015). Simvastatin depletes these intermediates by blocking HMG-CoA reductase, which hinders oncogenic signaling and encourages tumor cell death. Simvastatin-induced apoptosis and deactivation of the PI3K/Akt/mTOR and MAPK/ERK pathways in breast cancer cells are reversed in add-back tests using mevalonate, FPP, or GGPP, demonstrating the critical involvement of mevalonate pathway inhibition in its anti-tumor activities (Fritz, 2009; Swanson & Hohl, 2006).

2.3 Induction of apoptosis and cell cycle arrest

Through caspase activation and Bcl 2 family protein modification, simvastatin causes apoptosis in ER-positive (MCF 7, T47D) and ER-negative (MDA MB 231, BT 549) breast cancer cells in a dose-dependent manner (Relja et al., 2010; Tu et al., 2011). According to mechanistic research, simvastatin activates the JNK/CHOP/DR5 axis, upregulating CHOP and death receptor-5. Statin-induced apoptosis is significantly reduced when DR5, CHOP, or JNK are knocked down by siRNA. Additionally, simvastatin inhibits proliferation in monolayer and spheroid models by promoting G0/G1 cell cycle arrest and decreasing cyclin and CDK expression (Saito et al., 2008; Chan et al., 2008; Jin et al., 2002).

2.4 Anti-metastatic and anti-angiogenic effects

By interfering with cytoskeletal structure and focal adhesion signaling, processes reliant on prenylated Rho and Rac GTPases, statins prevent cancer cells from invading and spreading (Maurya et al., 2025; Jones et al., 2017). By altering epithelial–mesenchymal transition markers, hindering spheroid formation, and preventing migration and invasion both in vitro and in vivo, simvastatin has been shown to lower the metastatic potential of triple negative breast cancer cells. Statins also have anti-angiogenic properties that further limit tumor growth by inhibiting endothelial migration and proliferation and lowering the production of angiogenic factors (Fritz, 2005).

2.5 Modulation of tumor microenvironment and immune response

Simvastatin can alter the tumor microenvironment by influencing stromal cells, endothelial cells, and immunological infiltrates in addition to its effects on cancer cells. Statins affect T-cell receptor signaling and may improve anti-tumor immune responses via changing the lipid raft composition in immune cells (Zhu et al., 2021). Preclinical evidence supports the use of statins in combination regimens by indicating that they may enhance tumor radiosensitivity and sensitize tumors to other treatments, in part through microenvironmental modulation (Yu et al., 2022; Lee et al., 2024).

2.6 Limitations of free simvastatin in oncology

Pharmacokinetic limitations, such as poor water solubility, low oral bioavailability, and significant hepatic absorption, make it difficult to translate simvastatin into an effective systemic anti-cancer medication despite strong molecular and epidemiologic data (Duarte et al., 2021; Shimoyama, 2011). Doses that raise the risk of myopathy, hepatotoxicity, and other dose-dependent side effects may be necessary to achieve anti-tumor concentrations, especially when coupled with chemotherapeutics. These drawbacks emphasize the need for delivery methods that can improve tumor-selective accumulation and lower off-target exposure, such as lipid-based nanocarriers (Alarfi et al., 2020; Chou et al., 2025).

3. Lipid-Based Nanocarriers: Platforms and Design Considerations

3.1 Classification of lipid carriers

Lipid-based nanocarriers used in oncology can be broadly classified into liposomes, SLNs, NLCs, and lipid nanoemulsions, each with distinct structural and functional features.

3.1.1 Liposomes

Liposomes are spherical vesicles that can contain both hydrophilic and hydrophobic medications. They are made up of one or more phospholipid bilayers encircling an aqueous core. As demonstrated by clinically authorized liposomal doxorubicin formulations for breast cancer, they can be modified with surface PEGylation and targeting ligands to extend circulation and enhance tumor homing (Alavi et al., 2017; Yadav, 2017).

3.1.2 Solid lipid nanoparticles (SLNs)

SLNs have a stiff core that can solubilize hydrophobic medications and shield them from deterioration since they are made of a solid lipid matrix stabilized by surfactants. Although there are still issues with restricted drug loading and the possibility of drug expulsion during crystallization, their benefits include biocompatibility, controlled release, and comparatively simple large-scale manufacture (Manjunath et al., 2005; Yoon et al., 2013).

3.1.3 Nanostructured lipid carriers (NLCs)

NLCs are second-generation SLNs that combine liquid and solid lipids to create a more flawed, less ordered matrix that improves drug loading and reduces expulsion during storage. When compared to traditional systems, NLCs have been employed to create topical and systemic formulations for simvastatin that have better encapsulation efficiency, stability, and prolonged release (Fang et al., 2013; Elmowafy & Al-Sanea, 2021).

3.1.4 Lipid nanoemulsions

Lipid nanoemulsions, which are usually between 20 and 200 nm in size, are kinetically stable dispersions of oil droplets in water (or vice versa) stabilized by surfactants. They can be prepared for parenteral or oral delivery and offer a high solubilization capacity for hydrophobic medications. Depending on the lipid content, they may also target the lymphatic system.

3.2 Advantages of lipid-based systems in cancer therapy

Lipid-based nanocarriers make poorly water-soluble medications more soluble and bioavailable, allowing for reduced dosages and better therapeutic indices. Through the increased permeability and retention effect, their nanoscale size and surface characteristics promote passive tumor accumulation, while surface modification enables active targeting to receptors that are overexpressed on tumor or stromal cells. Lipid carriers can also co-encapsulate many drugs for combination therapy and offer stimuli-responsive or regulated release to align drug exposure with cues from the tumor microenvironment (Arias et al., 2011; García-Pinel et al., 2019).

3.3 Key formulation parameters

The choice of solid and liquid lipids, surfactants and stabilizers, and drug loading techniques are crucial formulation factors for simvastatin-loaded lipid carriers because they affect physicochemical characteristics and biological performance. Triglycerides, fatty acids, and phospholipids are examples of lipid composition that affects entrapment efficiency and release kinetics by determining matrix structure, melting behavior, and compatibility with simvastatin. Particle size, interfacial stability, and potential toxicity are determined by the kind and concentration of surfactant, therefore careful optimization is required for safe systemic usage. Drug distribution inside the carrier and total loading capacity are impacted by drug loading strategies, such as inclusion in the lipid melt, solvent-based methods, or post-loading.

3.4 Physicochemical characterization

In order to ensure quality, repeatability, and in vivo performance, simvastatin-loaded lipid nanocarriers must be thoroughly characterized. Particle size, polydispersity index (PDI), and

zeta potential are important characteristics that affect colloidal stability, biodistribution, and cellular uptake (García-Pinel et al., 2019). These parameters are commonly assessed by dynamic light scattering and electrophoretic mobility. Chromatographic techniques are used to measure drug loading and encapsulation efficiency, which helps with dosage and formulation optimization. Shelf-life, release mechanisms, and suitability for controlled delivery are all revealed by stability studies and in vitro release profiling, frequently conducted in sink settings or in biorelevant environments.

4. Formulation Strategies for Simvastatin-Loaded Lipid Carriers

4.1 Preparation techniques

Simvastatin-loaded lipid nanocarriers have been made using a variety of preparation strategies, with the method used influencing the scalability and particle properties. Because it is solvent-free and scalable, high-pressure homogenization is a popular method for producing SLN and NLC by using mechanical shear to convert coarse emulsions into nanoscale dispersions. Simvastatin and lipids are dissolved in a volatile organic solvent, emulsified into an aqueous phase, and the solvent is removed via the solvent emulsification–evaporation process, which produces fine nanoparticles but necessitates careful management of residual solvents (Kumbhar et al., 2023; Ćetković et al., 2019). Microemulsion-based techniques take advantage of thermodynamically stable microemulsions that produce nanoparticles with comparatively narrow size distributions when diluted or cooled. Rapid mixing of organic and aqueous phases to create liposomes or lipid nanoparticles is made possible by solvent injection (ethanol or acetone injection), which provides gentle processing conditions suitable for delicate payloads (Ullah et al., 2022).

4.2 Optimization approaches (DoE, BBD, QbD)

In line with quality by design (QbD) principles, response surface approaches like Box-Behnken design (BBD) and design of experiments (DoE) are being used more and more to systematically optimize lipid nanocarrier formulations for desired quality attributes. BBD has been used to assess the effects of lipid ratio, surfactant concentration, and sonication time on particle size, entrapment efficiency, and drug release for simvastatin NLC gels, allowing for the selection of ideal conditions with few experimental runs. The development of gefitinib/simvastatin co-loaded NLCs has been guided by similar DoE frameworks, which have identified formulation parameters that optimize cytotoxicity and stability (Vakhariya et al., 2017).

4.3 Surface modification and targeting strategies

Simvastatin-loaded lipid carriers can be surface engineered to increase circulation time, decrease opsonization, and provide active targeting to endothelium or tumor receptors. By reducing protein adsorption and phagocytic clearance, PEGylation-the covalent bonding of polyethylene glycol chains-creates a hydrophilic steric barrier that prolongs systemic exposure and promotes tumor formation through the EPR effect. Ligand-mediated targeting increases cellular uptake and selectivity by using compounds like folic acid, antibodies, peptides, or RGD motifs to identify overexpressed receptors (such integrins, HER2, and folate receptors) on breast cancer cells. Dual-targeting ligands and stimuli-responsive surface moieties that trigger binding or charge reversal in the tumor microenvironment are examples of emerging tactics (Abd-Elghany et al., 2024; Li et al., 2017).

4.4 Co-delivery systems (simvastatin with chemotherapeutics)

When chemotherapeutics and simvastatin are combined in a single lipid nanocarrier, complimentary pathways can be simultaneously modulated, potentially bypassing resistance and producing synergistic cytotoxicity. For metastatic and drug-resistant breast cancer, gefitinib/simvastatin-loaded NLCs have been created as a hybrid therapy. Optimized formulations exhibit particle sizes between 200 and 400 nm, negative zeta potentials, and increased MCF 7 cell death when compared to free medicines. In MCF 7 and MDA MB 231 cells, NLCs co-loaded with simvastatin and thymoquinone showed enhanced intracellular accumulation, prolonged release, and synergistic apoptotic induction, with much lower IC50 values than single-agent formulations (Duarte et al., 2023). These results validate the use of simvastatin in combination nanomedicine procedures as a metabolic modulator and chemosensitizer.

5. Mechanisms of Tumor Targeting and Drug Delivery

5.1 Enhanced permeability and retention (EPR) effect

The EPR effect, which allows for the preferential accumulation of macromolecules and nanoparticles within tumor tissue due to leaky tumor vasculature and reduced lymphatic drainage, can be exploited by lipid-based nanoparticles in the 50–200 nm range. By decreasing exposure to healthy organs and increasing local medication concentration at the tumor site, this passive targeting mechanism improves therapeutic indices for encapsulated drugs like simvastatin (Leporatti, 2022).

5.2 Active targeting mechanisms

By adorning the surfaces of nanocarriers with ligands that bind selectively to receptors on cancer cells or related stromal components, active targeting is accomplished. When compared to non-targeted carriers or free medication, RGD peptides that target integrins or other

ligands that recognize overexpressed receptors can significantly boost tumor absorption and anti-tumor activity for statin-loaded nanoparticles. In heterogeneous breast cancers, where receptor expression patterns may direct the development of customized nanomedicines, this approach is particularly promising (Alavi & Hamidi, 2019).

5.3 Cellular uptake and intracellular trafficking

Depending on their size, surface charge, and ligand decorating, lipid nanoparticles are mostly internalized through endocytic pathways such clathrin-mediated, caveolae-mediated, or macropinocytosis. After uptake, they go through endosomal–lysosomal compartments, where environmental factors (pH decrease, enzymatic activity) might encourage drug release; formulations intended for cytosolic or lysosomal release exhibit increased intracellular accumulation and statin-loaded systems' cytotoxicity. For instance, in MDA MB 231 cells, simvastatin-loaded albumin nanoparticles and cubosomes show better internalization, G0/G1 arrest, and induction of apoptosis and ferroptosis than free simvastatin (Yu et al., 2014).

5.4 Controlled and stimuli-responsive drug release

Long-term maintenance of therapeutically relevant drug levels in the tumor microenvironment is possible with controlled release from lipid carriers, which also reduces peak–trough swings. In cancers, which frequently have acidic pH, elevated ROS, and high enzymatic activity, stimuli-responsive designs that take advantage of pH, redox status, enzymatic activity, or external triggers (such as heat, ultrasound) allow for on-demand release selectively. Simvastatin NLCs and cubosomes have been shown to exhibit pH-responsive activity and sustained release over a 24-hour period, which may contribute to increased cytotoxicity and decreased systemic exposure (Kong et al., 2013). As shown in Figure 2, the different mechanisms of tumor targeting are illustrated.

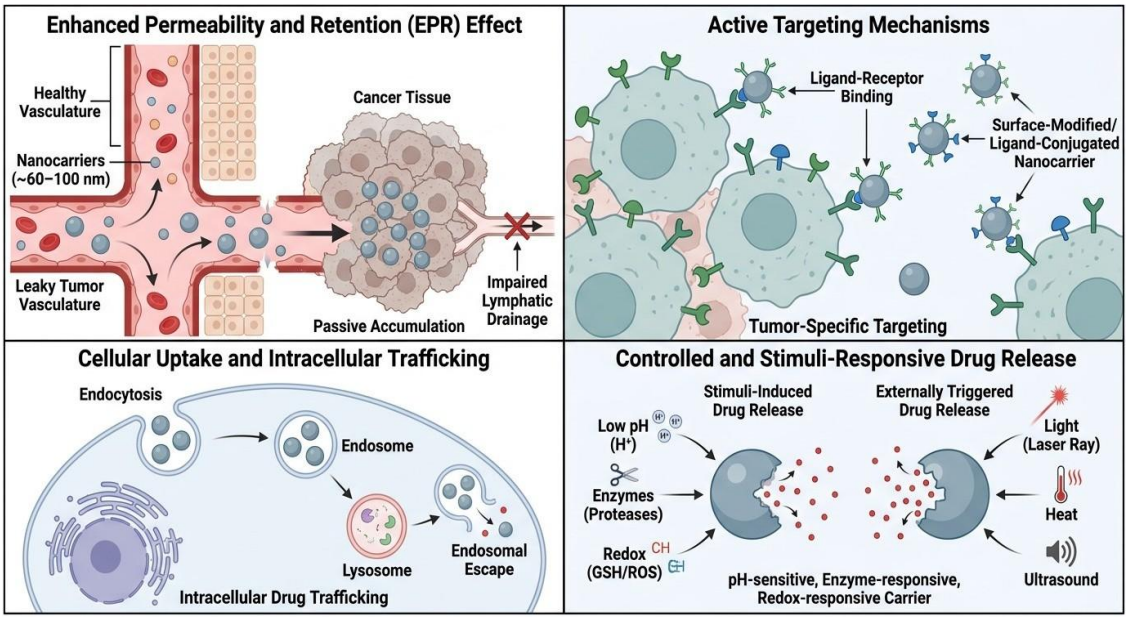

Figure 2 Illustration of mechanisms of tumor targeting and drug delivery, including the **a)** enhanced permeability and retention (EPR) effect where nanocarriers accumulate in tumor tissue due to leaky vasculature, **b)** active targeting through ligand-receptor interactions on tumor cells, **c)** the process of cellular uptake and intracellular trafficking involving endocytosis and endosomal escape, and **d)** controlled or stimuli-responsive drug release activated by internal or external signals.

6. Challenges and Limitations

6.1 Stability and storage issues

Since lipid polymorphism, aggregation, and drug expulsion might impair efficacy, the physical and chemical stability of simvastatin-loaded lipid nanoparticles during storage is crucial. Optimizing lipid composition, surfactants, and lyophilization or cryoprotectant techniques is necessary to maintain proper particle size, PDI, and drug content throughout shelf life. Because simvastatin is prone to hydrolysis and oxidation, protective formulation and appropriate packing conditions are required (Ball et al., 2017).

6.2 Reproducibility and scalability

It is difficult to scale laboratory-size simvastatin nanocarrier formulations to industrial production while preserving constant quality characteristics. Microfluidization and high-pressure homogenization are scalable methods, but they require careful control over process parameters, batch-to-batch variability, and regulatory restrictions on solvents and excipients. Reproducible production of clinical-grade simvastatin nanomedicines requires strong in-process controls and QbD-guided process design (Roces et al., 2020).

6.3 Biological barriers and off-target effects

Endothelial barriers, opsonization, absorption by the mononuclear phagocyte system, and diverse tumor vasculature are only a few of the intricate biological obstacles that systemically delivered lipid nanoparticles must overcome. Even if PEGylation and ligand targeting reduce some obstacles, there is still a significant amount of off-target accumulation in the liver and spleen, which could result in cumulative toxicity, especially when paired with statins' natural hepatic tropism. Moreover, individual differences in the EPR effect and receptor expression can lead to uneven tumor targeting (Hu et al., 2024).

6.4 Cost-effectiveness and commercialization hurdles

Compared to generic oral statins, the creation of complicated nanomedicines like simvastatin-loaded lipid carriers includes greater production costs and regulatory hurdles, raising concerns regarding cost-effectiveness. Few statin-based nanocarriers have advanced past preclinical review, despite the fact that commercialization requires demonstrating a demonstrable therapeutic benefit over current medications in well planned trials. The appeal of investment and commercial translation is also influenced by intellectual property issues pertaining to repurposed medications and formulation technology (Rotolo et al., 2020).

7. Emerging Trends and Future Perspectives

7.1 Personalized nanomedicine approaches

The goal of personalized nanomedicine is to customize treatment plans and nanocarrier design to each tumor's unique biology, including molecular subtype, receptor expression, and microenvironmental characteristics. Patient stratification based on statin sensitivity, mevalonate pathway reliance, and targeting receptor expression (e.g., integrins, folate receptor) could maximize benefit for simvastatin-based systems. Theranostic systems for real-time drug delivery and response monitoring may be made possible by the incorporation of imaging tracers and companion diagnostics into lipid nanocarriers (Lammers et al., 2012).

7.2 Combination therapy and multi-drug delivery

In order to target several cancer hallmarks at once, future simvastatin nanomedicines are anticipated to take advantage of sensible combinations with chemotherapeutics, targeted therapies, or natural products. By coordinating the administration of simvastatin with drugs like gefitinib, doxorubicin, paclitaxel, or thymoquinone, co-loaded NLCs and liposomes can improve apoptosis, overcome resistance, and lower systemic toxicity. Statins may also increase the efficacy of regular regimens at the clinical level, according to meta-analytic data, which justifies the creation of combination nanomedicine trials (Gadde, 2015).

7.3 Stimuli-responsive and smart lipid carriers

To improve the spatial and temporal control of drug release, smart lipid nanocarriers with stimuli-responsive lipids, polymers, or linkers are being created. Simvastatin can be released preferentially within tumors or metastatic habitats by designs that are sensitive to pH, enzymes, redox conditions, or external stimuli. This maximizes on-target activity. An emerging area of autonomous cancer nanotherapy is the integration of biosensing capabilities and feedback-controlled release (Majumder & Minko, 2021).

7.4 Integration with immunotherapy

The treatment of many tumors has been revolutionized by immunotherapy, and preliminary data points to a possible synergy between statins and immune checkpoint inhibitors or other immunomodulators. By altering T-cell activity, myeloid cell morphologies, and tumor antigen presentation, statins can increase the immunoreactive microenvironment. Co-delivering simvastatin with immunotherapeutic drugs or adjuvants via lipid-based nanocarriers may increase anti-tumor immunity while reducing systemic immune-related side effects, which calls for methodical investigation in breast cancer models (Zhang et al., 2023).

7.5 AI and computational modeling in formulation design

By predicting structure-property-performance correlations and optimizing formulations, artificial intelligence and computer modeling are being used more and more to speed up the development of nanomedicine. Machine learning models trained on formulation factors, physicochemical descriptors, and biological readouts could direct the selection of lipid mixes, surfactants, and processing conditions for simvastatin-loaded lipid carriers in order to satisfy predetermined target product profiles (Hamilton & Kingston, 2024; Bhujel et al., 2025). Personalized dosing and carrier design may be further informed by in silico simulations of tumor penetration, biodistribution, and nanoparticle transport.

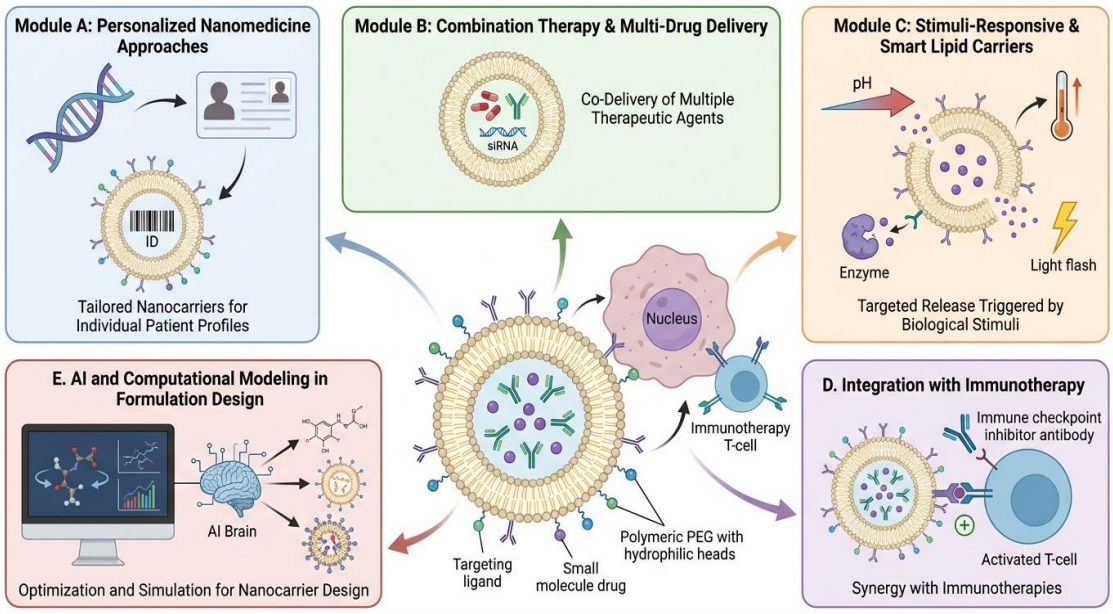

Figure 3 Schematic representation of a lipid-based nanocarrier in proximity to a breast cancer cell and an immune cell, highlighting key advancements including personalized nanomedicine, combination and multi-drug delivery, stimuli-responsive lipid carriers, integration with immunotherapy, and AI-assisted formulation design. Color-coded modules and directional arrows illustrate the distinct roles of each strategy in enhancing therapeutic efficacy.

8. Conclusion

With strong molecular evidence for anti-proliferative, pro-apoptotic, anti-metastatic, and microenvironment-modulating actions in breast cancer models, simvastatin is an excellent example of a drug-repurposing option in oncology. Although causality has not yet been established in prospective randomized studies, clinical and epidemiologic evidence suggest that statin use around the time of breast cancer diagnosis is linked to decreased recurrence and increased survival. Lipid-based nanocarriers offer a flexible and clinically useful platform to improve tumor targeting, enable sensible combination therapy, and get beyond the pharmacokinetic restrictions of free simvastatin. Simvastatin-loaded NLCs, albumin nanoparticles, and cubosomes exhibit better cytotoxicity, apoptosis induction, and tumor growth inhibition than free drug, especially when co-delivered with other anti-cancer drugs, according to preclinical research. However, in order to implement these systems in clinical practice, major issues pertaining to stability, scalability, biological heterogeneity, and regulatory and economic constraints must be resolved. To fully utilize simvastatin-based lipid nanocarriers as a potential therapeutic option for breast cancer, future research combining

customized nanomedicine, smart and stimuli-responsive carriers, immunotherapy, and AI-driven formulation optimization offers promise.

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10. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

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