Epidermal Growth Factor Receptor And Double-Imprinted Nanoparticles for Targeted Cancer Drug Delivery – A Review

Lakhan Lal Kashyap [1], Harish Jaiswal [1]

Abstract

The Epidermal Growth Factor Receptor (EGFR) plays a crucial role in maintaining tissue balance, but in conditions like tumors or lung and skin cancer, it acts as a driver for cancer development. Nanoparticles are effective tools for delivering medications to tumor cells while minimizing drug impact on healthy cells. A potent therapeutic approach involves using nanoparticles with tumor-specific ligands for cancer treatment. This review study focuses on double-imprinted nanoparticles, synthesized to target the estrogen alpha cancer cell receptor's linear epitope and loaded with an anti-cancer drug. The challenge in cancer therapy is delivering drugs specifically to cancer cells without causing adverse effects on healthy cells. Advanced high-throughput technologies generate genomic and epigenomic data, and Support Vector Machine (SVM) classification in cancer genomics identifies new indicators, drug targets, and cancer transport genetics. The EGFR-SVM approach is designed to enhance the selectivity and reduce the toxicity of cytotoxic drugs by targeting cancer cells more specifically. Targeted treatment involves interfering with specific proteins that promote tumor growth and spread, and the study demonstrates a molecularly targeted drug delivery method for efficiently and selectively targeting anticancer drugs to tumor cells overexpressing EGFR. This approach has the potential to improve the therapeutic effectiveness of existing anticancer drugs.

Keywords: Support Vector Machine, Epidermal Growth Factor Receptor, Cancer, Drug Delivery.

Significance | A targeted drug delivery approach, using double-imprinted nanoparticles and EGFR-SVM, to enhance anticancer drug effectiveness selectively in tumor cells.

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1. Introduction

Nanoparticles designed for cancer treatment represent a promising breakthrough in drug delivery. Loaded with anti-cancer medication, these minuscule particles address challenges related to stability and controlled drug release. Recent research underscores the potential for these nanoparticles to revolutionize cancer therapy by enabling more precise delivery of chemotherapy drugs to tumors, offering the prospect of improved patient outcomes and reduced side effects.

Nanoparticles, intricately designed to target a specific region of the estrogen alpha cancer cell receptor, are created and loaded with an anti-cancer medication (Qin, Y. T., 2019). Genetic variations in EGFR are associated with various cancers, leading to heightened cell proliferation, growth, and reduced programmed cell death upon EGFR activation (Liu, H., 2021). Manipulating nanoparticle size, surface features, and material allows the development of effective protocols for coating medicinal and diagnostic drugs, incorporating stealth properties. These adaptable nanoparticles can precisely deliver drugs to specific areas, facilitating controlled release treatment (Canfarotta, F., 2018) (Wang, H. Y., 2019).

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However, the widespread use of nanoparticle-based therapeutics is hindered by several limitations, including stability and solubility issues, insufficient transmembrane transport, a brief circulation period, and potential hazards (Singla, P., 2023) (Canfarotta, F., 2018). Employing a Support Vector Machine (SVM) tailored for medical information, this technique proves effective in disease detection, covering conditions such as cancer, hypertension, and diabetes (Feger, G., 2020).

Tiny drug nanoparticles can navigate from the lungs through the bloodstream and reach the brain via skin endothelial cell connections, thanks to their compact size and extensive surface coverage (Liu, H., 2021). However, in nanoparticle-assisted drug delivery, opsonization within the reticuloendothelial system poses a significant challenge, emphasizing that the mass of nanoparticles affects overall access and diffusion (Cherkasov, V. R., 2020). Targeting chemotherapy drugs directly to cancer tumors is identified as a strategy to enhance patient outcomes and minimize harmful side effects (Shevchenko, K. G., 2022).

The utilization of nanomaterials in crafting a drug-delivery system emerges as a key approach to improve the water solubility and efficacy of promising anticancer medicines (Huang, C. H., 2020) (Wang, H. Y., 2019). In the context of cancer, the epidermal growth factor receptor (EGFR) stands out as one of the most overexpressed, amplified, and mutated genes. Targeting EGFR through suppression blocks signal transduction pathways, effectively regulating tumor cell growth, proliferation, and death (Kassem, S., 2022). The intricate processes of cell proliferation, survival, migration, and differentiation are primarily orchestrated by growth factors and their transmembrane receptor tyrosine kinases (Sabbah, D. A., 2020) (Qin, Y. T., 2020). EGFR, functioning as a cell-surface receptor within the tyrosine kinase family, plays a pivotal role in regulating cell proliferation, survival, and development (Harrison, P. T., 2020).

Customizing chemotherapy for breast cancer cells can greatly improve patient outcomes and reduce severe side effects. In experiments with breast epithelial cells, certain relatives of EGFR-SVM show significant effects, leading to increased scattering and invasion. This behavior is linked to the loss of cell polarization and various traits related to epithelial differentiation. The progress in targeted drug delivery systems is crucial, as they can extend, localize, target, and carefully manage medication interactions with diseased tissue. Unlike traditional drug delivery methods relying on absorption through a biological membrane and controlled release, targeted drug delivery systems provide a more precise and effective approach to treating breast cancer.

2. Literature Review

In a study by Meenakshi D. U. et al. (2022), the significance of the Artificial Neural Networks (ANN) technique in evaluating and predicting a drug's affinity for specific targets is emphasized. The focus is on developing a site-specific drug delivery system aimed at enhancing treatment efficacy while minimizing medication-related toxicity, ensuring a protected interaction with diseased tissue. The integration of computational techniques with a site-specific drug delivery system is highlighted as a strategy to improve treatment outcomes. The use of ANN is particularly stressed to alleviate the financial burden on pharmaceutical companies, addressing the need to overcome expensive failures and generate target-specific new drug candidates for effective treatment regimens that positively impact human life.

Xin-Yi Yuan and colleagues (2022) showed optimizing drug delivery to tumor locations during transarterial chemoembolization treatment. Their research introduced an advanced model based on Deep Convolutional Neural Networks (DCNN) with reduced effects, allowing precise and real-time predictions of drug trajectories and concentration fields (Yuan, X. Y., 2022). By inputting data on injection locations and blood vessel geometry, the network model produces detailed maps of drug concentrations and trajectories. The notable strengths of the DCNN model, including strong performance, accuracy, and speed, suggest its potential to assist clinicians in dynamically directing chemoembolization medications to tumor-bearing segments. This innovation holds promise for enhancing the real-time effectiveness of the procedure in clinical settings.

Nan Zheng and colleagues (2023) addressed the ongoing challenge of diagnosing breast cancer swiftly, emphasizing the critical need for timely detection to mitigate the worst consequences of the condition (Zheng, N., 2023). Their approach involves employing an Adaptive Neuro-Fuzzy Inference System (ANFIS) to analyze data from various sources and facilitate early breast cancer diagnosis. The precision of this mechanism is particularly sensitive to the selected radius value, and the ANFIS classifier effectively identifies breast cancer using nine factors describing cancer signs as inputs. Fuzzy functions are applied to these parameters, and the resulting dataset is used to train the algorithm, demonstrating a promising methodology for early breast cancer detection.

On another front, the utilization of double-imprinted nanoparticles with epidermal growth factor receptors in cancer drug delivery faces contemporary challenges. In the context of cancer, the activation of epidermal growth is primarily attributed to mutations, amplifications at the gene level, and paracrine pathways leading to excessive transcription or ligand synthesis (Meenakshi, D. U., 2022). To address the limitations observed in studies by Yuan (Yuan, X. Y., 2022) and Zheng (Zheng, N., 2023), the proposed EGFR-SVM method is introduced and compared, aiming to offer an alternative and potentially more effective solution.

3. EGFR-SVM and double-imprinted nanoparticles for cancer drug delivery

In this review, we have discussed the stability, safety, and ability of liposomes in drug discovery technology. Lieposomes are very impotant nanocarrier for both hydrophilic and lipophilic substances. Liposomes are explored as effective carriers for chemotherapy and potential safer options for chemotherapeutic formulations. The section concludes with mathematical models and equations related to feature selection in radiomics and the use of hyper-osmotic mannitol to open endothelial tight crossings for nanoparticle delivery to the

The controlled release of drugs depends on their diffusion across the polymeric membrane, particularly when the nanoparticle is coated with a polymer. The speed of medication release is influenced by the drug's solubility and its capacity to diffuse within the polymer barrier associated with the membrane. Enhancing the delivery of chemotherapeutic agents is a primary goal of EGFR-SVM, specialized nanoparticles designed to bind to angiogenic endothelial cell surface receptors. Another objective is to boost drug accumulation in the tumor endothelium, ultimately inhibiting the growth of blood vessels that supply the tumor, rather than directly inhibiting tumor cells.

Figure 1 illustrates that activating mutations in EGFR-SVM serve as a predictive factor for the efficacy of tyrosine kinase inhibitors in treating non-small-cell lung cancer (Zaidi, S. A., 2020). This study aims to develop a predictive model capable of determining whether a patient with brain metastases harbors a mutation in EGFR-SVM. While targeted therapy for EGFR-SVM mutations has become standard in non-small cell lung cancer, there is currently no effective genetic screening for these patients. The objective of this research is to create a prediction model that incorporates clinical parameters, offering a more precise genetic testing strategy for identifying EGFR mutation status. This model holds the potential to be a valuable resource for identifying EGFR mutations and planning appropriate therapy. Although sequencing is a straightforward genetic testing method, its time-consuming nature and inherent insensitivity make it impractical for large-scale clinical samples (Zaidi, S. A., 2020). For relatively common mutations, molecular biology methods prove to be more sensitive and specific than sequencing. However, genetic testing with biopsy specimens is influenced by various factors beyond the assay itself, such as sample quality, content, pathology format, and degree of differentiation. Thus, there is an urgent need for a quick, easy, cost-effective, and accurate mutation detection strategy (Piletsky, S., 2020). Various methods, including polymerase chain reaction amplification gene direct sequencing, high-resolution lysis analysis, and fragmentation analysis, have been developed to detect EGFR mutations. However, these methods involve invasive, pathological biopsies that are not only costly and time-consuming to replicate but also carry the risk of generating false-negative results (Yuksel, N., 2022). The researchers in this study focused on a novel, non-invasive genetic detection method by correlating radiomic characteristics with routine genetic testing of EGFR status in malignancy (Liu, R., 2021).

Figure 2 illustrates the potential of cancer medication delivery targeting and other nanostructures as pivotal tools in the future of cancer therapy. In various research trials, predominantly in animal models, targeted cancer medication delivery has demonstrated its capability to selectively administer significant quantities. The impact of targeted delivery in cancer medication delivery extends across multiple facets of cancer research and care, encompassing prevention, early detection, diagnosis, imaging, and treatment. The advantages of targeted cancer medication delivery are manifold. It enables the precise localization and imaging of tumors, facilitates the detection of pathological changes in tumor cells, allows the release of therapeutic genes or drugs based on tumor properties, employs external triggers for agent release, certifies the tumor's response, and identifies any residual tumor cells. Importantly, these delivery systems must possess the ability to discriminate between normal and malignant tissues by exploiting subtle changes in cell structure. Current research is heavily focused on nanoparticles with the capacity to evade the immune system and selectively target cancer cells. These nanoparticles can be actively directed towards tumors by attaching specific ligands to their surfaces. The distinguishing feature of these ligands lies in their ability to identify and bind to specific surface receptors and chemicals on tumor cells, enhancing the precision and effectiveness of cancer treatment.

Figure 3 highlights the extensive history and prevalent use of liposomes in medication distribution, particularly in various clinical trials. Liposomes, which are bilayer vesicles formed from amphiphilic lipid molecules, play a crucial role in enhancing the stability and rigidity of liposomal membranes. They contribute to the improved efficiency of medication, protein, or oligonucleotide delivery, as well as pharmacokinetics. Constructed primarily from cholesterol, phosphatidylcholine, and ethanolamine phosphates, liposomes offer several advantages. They are not only safe but also versatile, capable of carrying both hydrophilic and lipophilic substances. The formulation of liposomes to enhance the unloading of nanovesicle contents relies on factors such as lipid variety, heat, and light. For instance, the development of thermosensitive nanoparticles loaded with DOX has been shown to increase cytotoxicity against Lewis lung cancer cells in vitro by a significant factor. Liposomes prove to be valuable for transporting drugs to cancer cells, allowing them to exert their therapeutic effects. In the realm of cancer treatment, pegylated liposomal chemotherapy has demonstrated effectiveness as a second line of treatment for epithelial ovarian cancer. Combinations such as

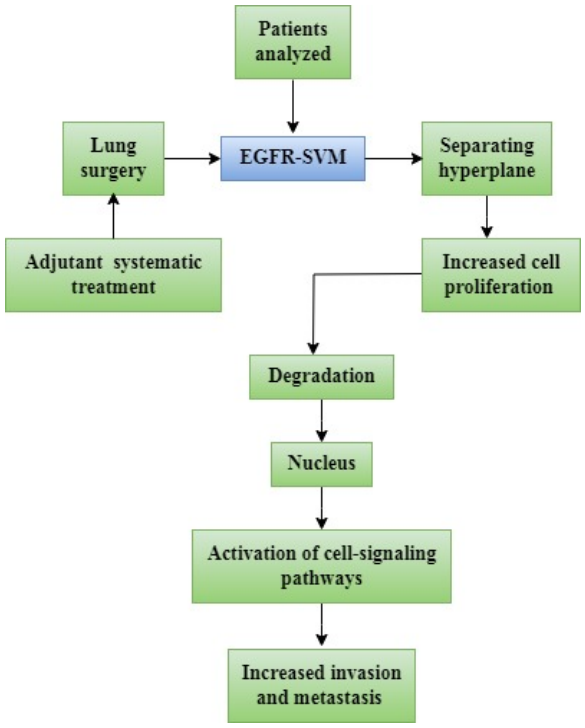

Figure 1. Overview of EGFR-SVM

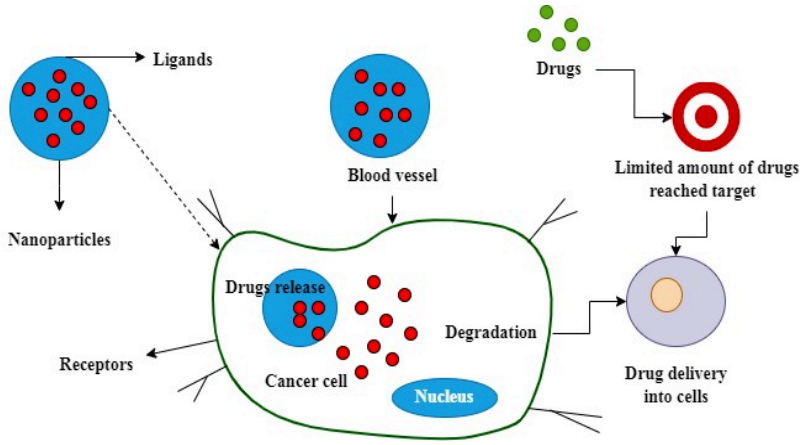

Figure 2. Architecture of targeted cancer drug delivery

Table 1. EGFR Mutations as Prognostic and Predictive Markers in Non-Small-Cell Lung Cancer

Aspect	Description
EGFR Mutations in Non-Small-Cell Lung Cancer	Employed as both prognostic and predictive markers according to the study.
EGFR Protein Role	EGFR (Epidermal Growth Factor Receptor) is a cell protein promoting cell proliferation.
Consequences of EGFR Gene Mutation	Mutation in the EGFR gene may lead to overproduction of cells, contributing to cancer development.
Application of SVM in Breast Cancer	SVM (Support Vector Machine) method is utilized for analysis in breast cancer research.
Dose-Response Curve Strategy	Common strategy in lung and prostate cancer involves deriving a single-value summary statistic from the dose-response curve, summarizing the response for a cell-drug combination.
Continuous Response Values in Supervised Regression Models	Numerous techniques used for calculating continuous response values serve as the prediction objective in supervised regression models.
Probabilistic Database Integration	A probabilistic database integrates cancer medication response prediction with pharmacogenomics analysis.

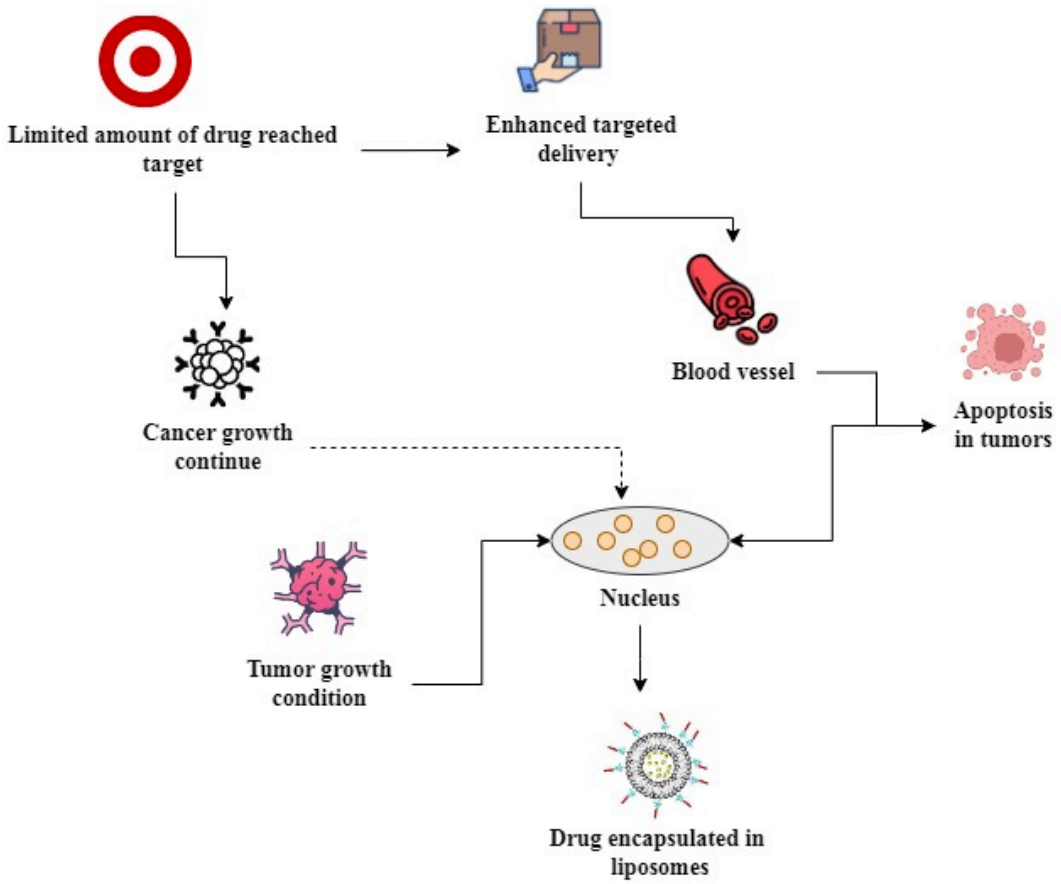

Figure 3. Nanoparticle-based targeted drug delivery upgraded and sustained drug release

daunorubicin and liposomal encapsulation have shown superior efficacy compared to individual treatments. To mitigate toxicity, patients were administered non-pegylated liposomal chemotherapy alongside cyclophosphamide. The results suggest that non-pegylated liposomal chemotherapy could serve as a safer option in chemotherapeutic formulations for first-line treatment of metastatic breast cancer. Furthermore, findings support the notion that peptide-modified liposomes containing amino acids like arginine, glycine, and aspartic acid hold promise in preventing tumor formation or binding to integrin receptors on tumor cells.

$$\emptyset_i^x = \frac{1}{N}\sum\{i\}\ \left(\frac{N-1}{S}\right)\ (v_X\ (S \cup \{i\} - v_x\ (S))$$

(1)

where N is the total number of features, S represents a feature subset of i and represents an essential parameter transferred from the subset. The effect of v_x in the combination model outperformed that of the single radionics features model or clinical features, and the combined features subset's prediction effect was greater.

$$W = \frac{x}{y} \times \frac{\vartheta - h_t}{w_{Cxt}}$$

(2)

Where W Hyper-osmotic mannitol opens endothelium tight crossings, $\frac{x}{y}$ allowing nanoparticles to pass the blood-brain barrier and $\frac{\vartheta - h_t}{w_{Cxt}}$ deliver therapeutic medicines for brain tumors. Smaller particles offer a h_t higher surface area-to-volume ratio; thereby, most of their medicine is near the particle surface, ϑ releasing the drug quicker. Larger particles may encapsulate more medicine and release that slowly due to their huge cores.

4. Discussion

Nanoparticles as Theragnostic Agents Carriers

Nanoscale Advantages:

Nanoparticles emerge as ideal carriers for theragnostic agents, leveraging their remarkable physicochemical properties. These properties include nanoscale sizes, functional versatility, active or passive tumor targeting capabilities, specific cellular uptake mechanisms, and outstanding optical properties. These attributes align seamlessly with the requirements of phototherapy.

Enhancing Drug Delivery:

Nanoparticles enable cell-targeted delivery of cytotoxic drugs, presenting a potential avenue to reduce overall toxicity while simultaneously enhancing effectiveness and selectivity. This targeted approach involves the modification of drug containers with functional groups that specifically target cell receptors.

Essence of Targeted Delivery:

The crux of targeted delivery lies in the surface properties of drug containers. Modified drugs or molecules attached to nanoparticles carry functional groups that precisely target cell receptors. This strategy aims to improve the precision of drug delivery, ensuring that therapeutic agents reach the intended cells with greater accuracy.

Autocrine/Paracrine Pathways in EGFR Activation:

While targeted delivery holds promise, challenges arise from autocrine/paracrine pathways, contributing to transcriptional upregulation and ligand overproduction. These pathways are documented and are implicated in the inappropriate activation of the Epidermal Growth Factor Receptor (EGFR) in malignancies. Understanding and addressing these pathways are crucial for developing effective and safe nanoparticle-based theragnostic approaches.

Nanoparticles in Cancer Treatment:

The dataset explores the versatile application of nanoparticles in cancer diagnostics and medication delivery. Gold nanoparticles serve as a multipurpose platform targeting receptors, enabling multimodality imaging, and delivering various medicinal molecules for enhanced cancer treatment.

Enhancing Chemotherapy with Nanotechnology:

Figure 4 highlights the integration of nanotechnology in cancer treatment to improve chemotherapy pharmacokinetics, reduce systemic toxicity, and selectively target and deliver therapeutic drugs to tumor tissues. Nanosized structures facilitate efficient drug absorption, transport, and activity within the intended site.

Polyamidation Nanoparticles in Drug Delivery:

Polyamidation nanoparticles act as nanocarriers for localized delivery of anti-malarial medicines. The combination of doxorubicin with polymers improves drug solubility, blood half-life, toxicity, and targeting.

Double Imprinted Polymers for Enhanced Characteristics:

Figure 5 introduces double imprinted polymers, showcasing their chemical and biological inertness, physical strength, and resistance to high temperatures and pressures. Challenges include clearance by the reticuloendothelial system and potential toxicity due to high surface area-to-volume ratios.

Nanoparticle-Assisted Drug Administration Challenges:

Toxic compounds may attach to nanoparticles, posing risks upon absorption. The dataset emphasizes the difficulty in evaluating risks associated with nanoparticulate materials, given their widespread use. Development focuses on regulating particle size, surface properties, and drug dispersion for site-specific activity.

Medication Delivery Assessment and Optimization:

Figure 6 outlines routine assessment tests for medication delivery, including factors like hardness, friability, drug content, and in vitro drug release. The mode of medication distribution

significantly impacts effectiveness. EGFR-SVM inhibitors are explored as medications binding to specific regions of EGFR, with high affinity for sensitizing and resistance mutations.

Optimizing Nanocarrier Systems:

Figure 7 introduces mean squared error and deviation as measures of estimation accuracy. Optimizing particle stability, drug loading, release characteristics, and cell-targeting capability aims to create an ideal EGFR-SVM targeted nanocarrier system for cancer-specific delivery. Nanoparticles hold promise for targeted drug delivery, enhancing bioavailability, biodistribution, and therapeutic accumulation in diseased areas.

The table 1 summarizes key aspects related to the use of EGFR mutations in non-small-cell lung cancer, the role of EGFR protein, application of SVM in breast cancer, strategies in lung and prostate cancer research, and the integration of cancer medication response prediction with pharmacogenomics analysis.

Nanoparticles, with their tailored properties, offer a versatile platform for advancing targeted drug delivery in cancer therapy. The integration of nanotechnology with insights into autocrine/paracrine pathways contributes to the development of sophisticated theragnostic strategies, aiming for enhanced efficacy, reduced toxicity, and improved precision in cancer treatment.

5. Conclusion:

Nanoparticles represent innovative approaches to drug delivery, minimizing drug leakage into healthy cells. Incorporating cancer-specific tumor indicator ligands into nanoparticles proves highly effective for treating cancer. Various types of nanoparticles, such as metal nanoparticles, liposomes, nanocrystals, and polymeric nanoparticles, are commonly used. Their diminutive size and expansive surface area enhance solubility, resulting in increased bioavailability. Additionally, these nanoparticles demonstrate the potential to traverse the blood-brain barrier, access the pulmonary system, and be absorbed through the robust connections of skin endothelial cells.

The EGFR-SVM plays a pivotal role in regulating the growth and maintenance of epithelial tissues. In pathological conditions, particularly in glioblastoma, breast, and lung cancer, EGFR acts as a driver of carcinogenesis. Leveraging nanoparticles for drug delivery offers advantages like transporting insoluble pharmaceuticals via stable colloidal systems and controlling drug release in a regulated manner.

The landscape of cancer treatment has transformed with advancements in targeted medications. Despite this progress, treatment resistance and mortality due to cancer progression persist. Targeted drug delivery using nanoparticle therapeutic systems presents a promising solution, circumventing the adverse reactions associated with conventional therapies. The adaptability of nanoparticles allows for a multitude of material, modification, and carrier combinations, offering hope for further advancements in the field.

Author Contributions

L.L.K. and H.J. conceptualized, wrote and reviewed the study.

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Competing financial interests

The authors have no conflict of interest.

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