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REVIEW

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Harnessing nanotechnology for enhanced delivery of erlotinib: a dynamic duo in cancer treatment

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Abstract

Erlotinib is a reversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that acts by inhibiting signaling pathways, resulting in the disruption of cancerous cell proliferation. Erlotinib is a promising anticancer agent mainly utilized in the mitigation of non-small cell lung cancer cells (NSCLC) and pancreatic tumor. Apart from NSCLC and pancreatic tumor, erlotinib has also been employed in different malignancies, including metastatic colorectal cancer, malignant glioma, breast cancer, gastrointestinal cancers, etc. Despite erlotinib's distinctive qualities as a targeted drug, its applications are still limited by poor solubility, variable oral bioavailability, a high daily dose requirement, large protein binding, and primitive or acquired therapeutic resistance. Nanotechnology is a favorable approach to increase therapeutic effectiveness of erlotinib. It is one of the newest scientific field directed toward the diagnosis and targeted treatment of cancer. This technology aids in the distinction between normal and malignant cells, which overlays the strategy for targeted delivery. This manuscript discussed the advances of erlotinib nanoformulations in the management of different cancers. Moreover, the manuscript also comprises various research outcomes of erlotinib nanoformulations with other therapeutic agents as combinational therapy. Erlotinib can be delivered to a precise target in the body utilizing different polymers, lipids, and metals.

Keywords Nanotechnology, Erlotinib, Anticancer, EGFR, Drug delivery

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1 Background

Cancer is the leading cause of death globally [1]. In the previous few decades, considerable advancements have been made to diagnose and treat cancers [2]. Erlotinib (Fig. 1) is a US Food and Drug Administration-approved first-generation epidermal growth factor receptor (EGFR) tyrosine kinase reversible inhibitor [3]. The upregulation of EGFR has been implicated in various aspects of tumor development and advancement, such as cellular proliferation, suppression of programmed cell death, metastasis, and the formation of new blood vessels [4]. Initially it was approved for the treatment of pancreatic cancer and NSCLC [5, 6]. Later, it was found that it could also treat several other malignant tumors, such as metastatic breast cancer [7], metastatic colorectal tumor [8], gastrointestinal carcinomas (hepatocellular, biliary, and

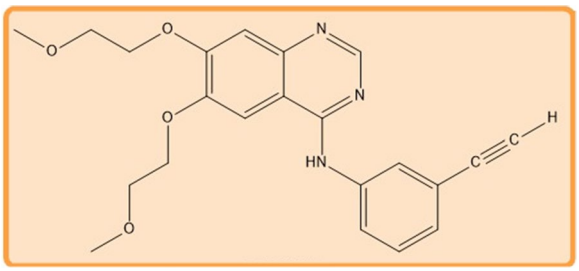

Fig. 1 Chemical structure of erlotinib

gastroesophageal junction) [9, 10], squamous cells of the head and neck cancers [11], and relapsed malignant glioma [12]. Several clinical trials of erlotinib in combination or individually in the management of cancer have either been completed or are now ongoing [13]. Despite its widespread use in cancer therapy, erlotinib has been linked to several serious side effects, including acute renal failure and renal insufficiency, cardiac arrhythmias when combined with hepatotoxicity, gemcitabine, and hepatorenal syndrome, INR elevations when combined with warfarin, exfoliative skin disorders, and gastrointestinal perforations that result in death [14].

TGF-α and EGF are examples of extracellular ligands that engage with the EGFR receptor, converting inactive monomers into active homo- or heterodimers by conformational modifications and phosphorylation of tyrosine residues. These residues trigger a series of signaling pathways that lead to the development and proliferation of tumor cells. Erlotinib is a competitive, reversible EGFR inhibitor that binds to the cytoplasmic tyrosine kinase domain (ATP binding site) and stops signal transmission by stopping autophosphorylation [4]. This leads to an enhanced tumor cell apoptosis, decreased tumor cell growth, and differentiation (Fig. 2) [15–23].

Modifying high-affinity ligands or aptamers allows nanodrug delivery systems to actively target tumor cells and deliver chemotherapeutics [24]. Different biological ligands, their advantages, and limitations in nanocarriers are shown in Table 1. Through receptor-mediated endocytosis, ligands can facilitate the delivery and accumulation of nanocarriers into the tumor site by attaching themselves to the receptors expressed on cancer cells with ease. The drug can then be delivered to the target site; the structure and composition of nanocarriers directly affect their ability to carry drugs [25]. Table 2 presents various ligand-based active tumor-targeted nanocarriers.

This review covered numerous nanocarrier approaches for delivering erlotinib to increase its anticancer activity. Erlotinib's water solubility, dissolution, and bioavailability can be increased by polymer, lipid, inorganic, and hybrid systems. This publication also covered erlotinib's mechanism of action and pharmacokinetics aspects. The manuscript comprises various research outcomes of erlotinib nanoformulations with other therapeutic agents such as combinational therapy.

2 Main text

2.1 Therapeutic applications of erlotinib

In addition to NSCLC, metastatic breast tumors, colorectal malignancy, and gastrointestinal tumors, erlotinib offers a wide range of therapeutic potential in other types of cancer. Different therapeutic applications and benefits of erlotinib are illustrated in Fig. 3.

NSCLC, one of the most often diagnosed malignancies and a heterogeneous class of tumors, is the main reason for cancer-related mortality globally. Tobacco use is the risk factor for developing this disease, although other risk factors, including exposure to radon gas and air pollution and the decay of isotopes that emit alpha particles, also play a role in disease progression [27, 28]. Erlotinib is one of the EGFR inhibitors that helps in the treatment of NSCLC [29]. Pérez-Soler et al. evaluated the survival response and tumor response of erlotinib in fifty-seven NSCLC patients who received a 150 mg daily dose of erlotinib orally. The objective response rate, median survival time, and one-year survival rate were 12.3%, 8.4 months, and 40%, respectively. Cutaneous rash (75%) and diarrhea (56%) were the most common drug-related toxicities. However, patients who experienced a rash had a significantly longer survival time. Results showed that erlotinib increased the overall survival response and improved symptoms with its well-tolerance ability. However, fifty-four patients reported symptoms at baseline, including cough, dyspnea, and fatigue. Five patients had a partial response, and two patients achieved a complete response, as determined by both the World Health Organization and the Response Evaluation Criteria in Solid Tumor criteria. Out of fifty-seven patients enrolled, thirty-five had adenocarcinoma, of which four responded to therapy (three partial and one complete response). Out of the remaining twenty-two patients (two not specified, nine with squamous cell carcinoma, and eleven with large-cell carcinoma), three responded to therapy (two with large-cell carcinoma and one with squamous cell carcinoma) [30]. Giaccone et al. conducted a phase II study of erlotinib on fifty-three patients with advanced NSCLC. The study reported about 22% of the tumor response rate, with one complete response, eleven partial responses, and sixteen cases of stable disease. Two progressing patients exhibited EGFR point mutations (one with the T790M mutation). Ten non-responders exhibited K-ras mutations. Phase II study findings showed considerable antitumor activity in first-line management

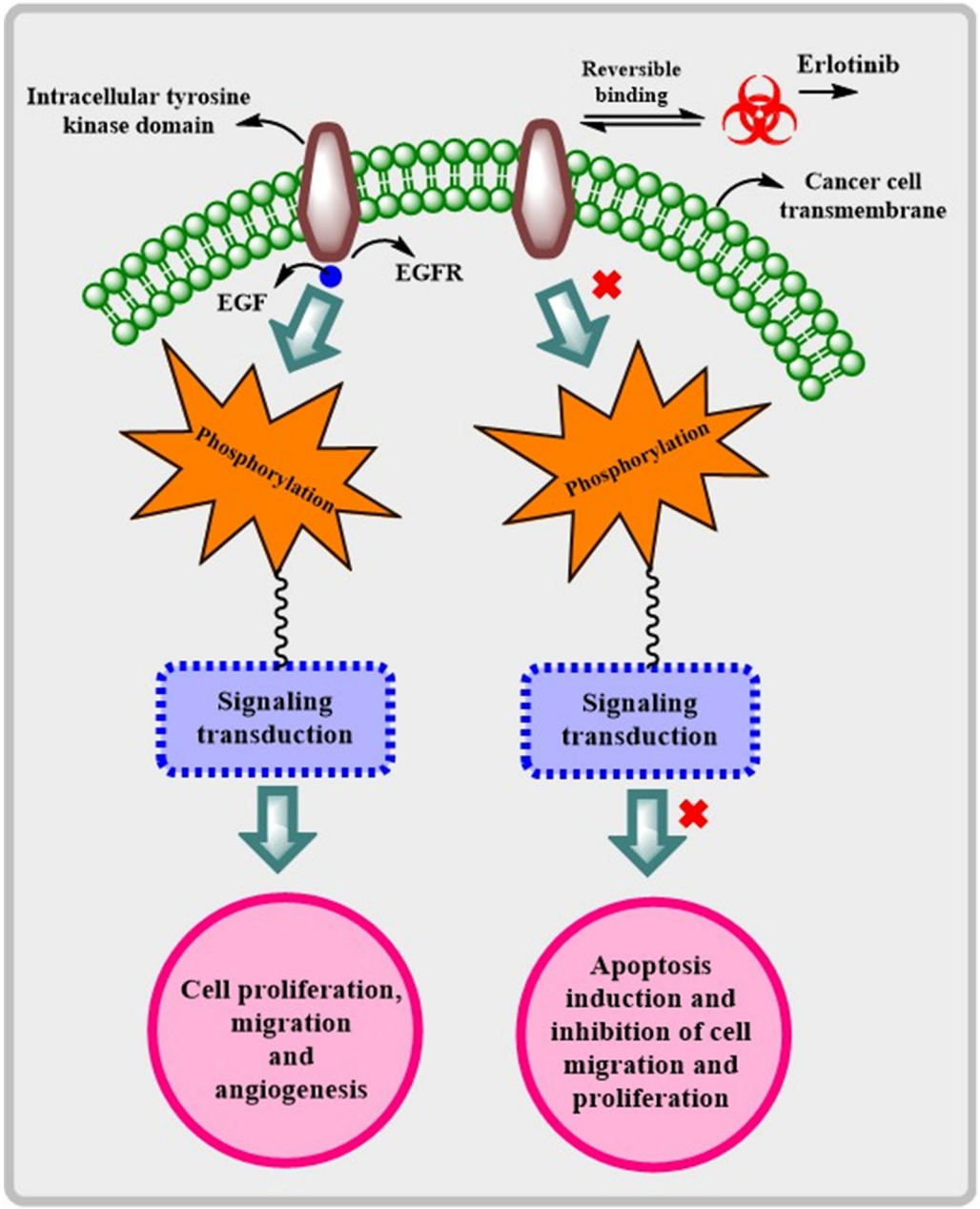

Fig. 2 Mechanism of action of erlotinib

Table 1 Ligands for active targeting of nanodrug delivery systems [26]

Ligands	Advantages	Disadvantages
Transferrin, antibodies	High specificity	Large size, low stability
Hyaluronic acid	Can be used in nanoparticles production	Overexpressed receptors in liver tissue
IL4RPep-1, RGD	Small size, easy fabrication	Cleavable by peptidase
GBI-10, AS-1411	High specificity, small size	Cleavable by nuclease, high cost
Anisamide phenylboronic acid folate	Low cost, small size	Normal tissues also express targets

Table 2 Ligand-based active tumor-targeted nanocarriers [25]

Nanosystem	Ligand	Conjugation strategy	Cancer type
Polymeric nanoparticles (NPs)	Folic acid	Amide bond	Cervical adenocarcinoma
Polymeric NPs	Folic acid	Amide bond	Lung carcinoma, cervical carcinoma
Micelles	Biotin	Ester bond	Lung carcinoma
Liposomes	Folic acid	Covalent bond	Cervical carcinoma
Liposomes	Folic acid	Covalent bond	Breast cancer
Solid lipid nanoparticles (SLNs)	Apolipoprotein E	Electrostatic interaction	Glioblastoma multiforme
Liposomes	Hyaluronic acid	Hyaluronic acid-phospholipid conjugate inserted in liposome	Pancreatic cancer

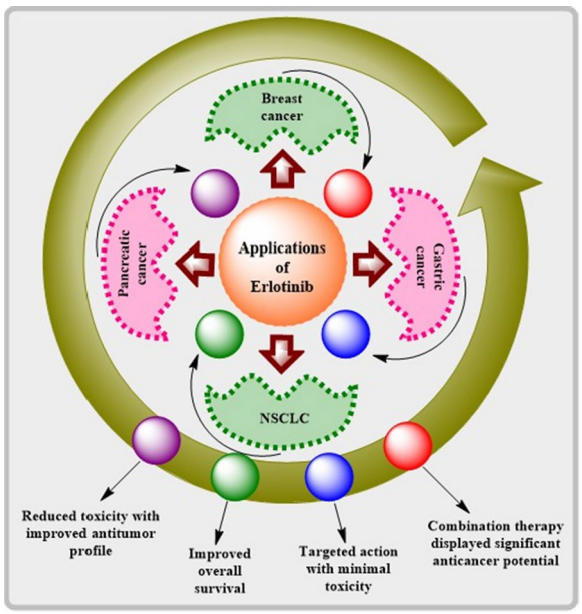

Fig. 3 Therapeutic applications and benefits of erlotinib in treating breast cancer, gastric cancer, NSCLC, and pancreatic cancer

of advanced non-small lung cancer cells. For NSCLC, it could be used as an alternative to chemotherapy [31]. The subsequent subsections provide a discussion on the therapeutic applications of erlotinib.

2.2 Pancreatic cancer

Pancreatic cancer, a devastating form of gastrointestinal cancer, is characterized by delayed diagnosis and poor treatment outcomes [32]. Cigarette smoking, alcohol use, diabetes, pancreatitis, and obesity are the major risk factors that induce pancreatic cancer [33]. Erlotinib is used in the management of pancreatic tumors in association with gemcitabine. Han et al. enrolled thirty-seven patients (median age 61.5 years) to conduct a phase-II study of erlotinib in combination with gemcitabine in pancreatic cancer treatment. Results from this study demonstrated 12.5% overall response rate and 71.9% disease control rate. The overall survival and median progression-free survival were 6.7 months and 3.7 months, respectively. This combination provided an acceptable toxicity profile [34]. Further, Lu et al. evaluated antitumor efficacy of erlotinib in the BxPC-3 pancreatic cell line, triggered G1 arrest, and induced cell apoptosis and suppressed capillary formation of endothelium. Results demonstrated that erlotinib suppressed growth of the BxPC-3 pancreatic cell line in a dose-dependent manner. At a concentration of 50 μmol/L, no significant change in cell growth was observed between 24 and 48 h, 72 and 96 h. Immunohistochemical staining revealed decreased EGFR expression, while reverse transcription-polymerase chain reaction revealed lower vascular endothelial cell growth factor expression in treated animals. It could be used as an adjunct in place of chemotherapy in the management of pancreatic cancer [35].

2.3 Squamous carcinoma of head and neck

Head and neck squamous cell carcinomas, which originate from the mucosal epithelium of the mouth, throat, and larynx, are the most common types of cancer in these regions [36]. Soulieres et al. conducted a phase-II study to evaluate the effectiveness and security profile of erlotinib in patients with intermittent and metastatic squamous cell carcinoma of the head and neck. Results of one hundred and fifteen patients showed significant improvements in overall survival and disease stabilization with good tolerability. Disease stabilization was observed in 44 patients for 16.1. The median progression-free survival and the median overall survival were 9.6 weeks and 6.0 months, respectively. However, rash and diarrhea were reported in 79% and 37% patients, respectively, as the most common drug-related toxicities [37]. In an additional study, Tsien et al. evaluated the inhibitory effect of erlotinib on twelve head and neck cancer patients. Erlotinib inhibited pEGFR and reduced total EGFR protein in tumors. However, there was heterogeneity in EGFR inhibition in the normal mucosa [38].

2.4 Malignant gliomas

Among primary malignant brain tumors, malignant gliomas are the most prevalent. Several genetic changes that occur sequentially and cumulatively because of internal and external causes lead to the development of malignant gliomas [39]. Prados et al. conducted phase I/II studies of erlotinib in combination with sorafenib in malignant gliomas. Observations demonstrated that the combination of both drugs is moderately well tolerated. Sorafenib affected pharmacokinetic (metabolism or clearance) of erlotinib suggesting drug–drug interaction [40]. In another study, Prados et al. conducted a phase-I study of temozolomide in combination with erlotinib in patients with stable or recurrent malignant gliomas. On a 28-day treatment regimen, erlotinib was initiated at 100 mg orally once daily; the dose was increased by 50 mg/day until it reached 500 mg/day. A total of 83 patients underwent examination. Fatigue, rash, and diarrhea were the most frequently reported adverse effects, which exhibited a mild to moderate intensity. Six of the 57 patients, including four with partial responses, had a progression-free survival of more than six months. Results displayed significant antitumor action with acceptable toxicities and demonstrated a well-tolerated combination in this disease [41].

2.5 Metastatic colorectal cancer

EGFR is a crucial target in the therapy of colorectal cancer because it controls the main signaling pathways that cancer cells use for survival, migration, adhesion, proliferation, and angiogenesis [42]. Townsley et al. [43] conducted a phase-II study of erlotinib on 38 patients with metastatic colorectal cancer at 150 mg of the daily oral dose. Results showed that erlotinib was well tolerated and had common side effects (diarrhea in 23 patients and rash in 34 patients). Also, a correlative study following one-week treatment showed that the levels of phosphorylated EGFR ($p=0.008$) and phospho-extracellular signal-regulated kinase ($p=0.008$) dropped significantly. One-third of patients had stable disease for a minimum of 8 weeks. Xu et al. [44] analyzed safety and survival profile of erlotinib plus bevacizumab as maintenance therapy in patients with colorectal tumors that have spread to other parts of the body. In patients with metastatic colorectal cancer, the addition of erlotinib to bevacizumab as maintenance therapy significantly improved progression-free survival (hazard ratio 0.79; 95% confidence interval 0.68–0.92; $p=0.002$) and overall survival (hazard ratio 0.78; 95% confidence interval 0.66–0.93; $p=0.006$). Mild side effects were observed, which are controllable and reversible.

2.6 Metastatic breast cancer

Breast cancer is a malignancy that develops when cells in the breast grow out of control. It is characterized by the formation of lumps in the breast or nearby areas, alterations in the skin of the breast, or nipple discharge. Overexpression of EGER is associated with breast cancer [45]. Therefore, erlotinib, as an EGFR inhibitor, plays a crucial role in the management of breast tumors, either alone or in combination [46]. Dickler et al. [47] conducted a phase-II study on sixty-nine locally advanced or metastatic breast cancer patients. The patients were divided into cohort 1 (progression after anthracyclines, taxanes, and capecitabine, n = 47) and cohort 2 (progression after > 1 chemotherapy for advanced-stage disease, n = 22). Observation showed erlotinib (150 mg orally daily) as a monotherapy agent was well tolerated but had minimal activity in previously treated patients. Eight patients had stable disease and two patients had partial response. The median time to progression was 43 days for cohort 1 and 43 days for cohort 2. Dry skin, diarrhea, asthenia, nausea, rash, and anorexia were the common adverse events because of the anti-EGFR/human epidermal growth factor receptor 1 (HER1) activity in normal EGFR/HER1-expressing tissue. Britten et al. [48] conducted a phase I/II trial of erlotinib in combination with trastuzumab against metastatic breast cancer. In phase I trials, the patients enrolled were those who had previously received chemotherapy and/or trastuzumab for the treatment of metastatic disease. Patients who participated in phase II had never received chemotherapy for metastatic illness and were unfamiliar with trastuzumab. The observation revealed that erlotinib has minimal anticancer activity in individual patients. The combination was well tolerated, and no pharmacokinetic interaction occurred. However, anorexia, alopecia, diarrhea, dry skin, fatigue, nausea, pruritus, stomatitis, and rash were the most common toxicities. The study does not adequately address the efficacy of dual- or pan-ErbB therapy. However, this approach alone is unlikely to be sufficient in the treatment of metastatic disease.

2.7 Other gastrointestinal carcinomas

Gastrointestinal tract carcinomas involve the stomach, colon, and rectum. A variety of environmental and genetic factors contribute to the development of gastrointestinal cancer [49]. Rohrberg et al. [50] conducted a phase II trial of erlotinib and bevacizumab on 102 patients (66 male and 36 female) with an upper gastrointestinal tumor. Although the combination was well tolerated, there was no improvement in overall survival or progression survival rates. Diarrhea, skin reactions, and fatigue were the most common toxicities. Overall response rate, median progression-free survival, and

overall survival were 6%, 2.2 months, and 4.3 months, respectively. Plasma placental growth factor concentration increased in most of the patients who received treatment. However, the interaction between urokinase plasminogen activator receptor domain I and soluble vascular endothelial growth factor receptor 2 and their potential predictive value warrant further preclinical and clinical evaluation. Philip et al. [51] conducted a phase II study of erlotinib on 42 patients with advanced biliary cancer. In this study, over half of the enrolled patients had previously received treatment for their advanced biliary cancer. In 29 patients, tumor cell immunohistochemistry revealed HER1/EGFR expression. Two patients responding to erlotinib were HER1/EGFR positive. Erlotinib inhibited EGFR in biliary cancer, which improved the therapeutic effect. After six months of treatment, seven patients were progression free. Three patients had toxicity-related dose reductions of erlotinib due to grade 2/3 skin rash. The study concluded that erlotinib may offer a better treatment option for patients experiencing treatment failure after cytotoxic therapy. These results reveal that erlotinib has a wide range of therapeutic uses, treating a variety of carcinomas.

3 Tarceva®—a commercially available erlotinib formulation

The US Food and Drug Administration has approved erlotinib for the treatment of NSCLC and pancreatic cancer. Tarceva® is Genentech's (a division of Roche Pharmaceutical) commercially available product containing erlotinib for first-line and maintenance treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations. Tarceva® is not prescribed for use in combination with platinum-based chemotherapy. Patients with locally advanced, unresectable, or metastatic pancreatic cancer can receive Tarceva® in combination with gemcitabine as their first-line treatment. This product is available as a film-coated tablet for oral use. Diarrhea, dehydration, electrolyte imbalance, and renal failure are common side effects reported for this product. Reports have documented rare cases of hepatic failure. Patients receiving Tarceva® are at increased risk of developing gastrointestinal perforation. There have been reports of bullous, blistering, and exfoliative skin conditions. While it has shown efficacy in many patients, it does have limitations, such as limited absorption and bioavailability caused by poor water solubility, off-target effects, and the development of erlotinib resistance over time, leading to treatment failure [6, 15, 46]. Generic version of Tarceva is manufactured by Alembic Pharmaceuticals, India; Apotex Inc., Canada; MSN Pharmaceuticals Inc., USA; Natco Pharma Ltd., India; Rising Pharma Holdings Inc., New Jersey; Shilpa Pharma Life Sciences, India; Sun Pharmaceutical Industries Ltd., India; Teva Pharmaceutical Industries Ltd., Israel; and Zydus Pharmaceuticals, India. Exploring erlotinib nanoformulations could improve its therapeutic effectiveness and patient outcomes in the treatment of different types of cancer by addressing these issues.

4 Nanoformulations for anticancer potential of erlotinib

Poor solubility and low oral bioavailability of erlotinib can often result in its suboptimal pharmacokinetic and pharmacodynamic profile. This implies that addressing issues related to solubility and bioavailability is crucial for optimizing the pharmacokinetic and pharmacodynamic profile of erlotinib. Antacids or proton-pump inhibitors increase gastrointestinal pH reduces solubility and absorption of erlotinib. The apparent volume of distribution of erlotinib is around 232 L. About 93% of erlotinib is bound to alpha-1 acid glycoprotein and albumin [4]. In the gastrointestinal environment, it displays poor solubility, permeability, and instability (high first-pass metabolism with rapid clearance). Additionally, it causes hematological adverse effects like anemia, thrombocytopenia, and neutropenia and shows dose-dependent severe side effects like rash, diarrhea, appetite loss, and frontal alopecia [52–54]. These challenges require the advancement of an effective drug delivery strategy that not only increases treatment efficacy but also minimizes harmful effects. Nanoparticles can alleviate these problems. Effective EGFR-TKIs nanoscale delivery technologies not only help to address fundamental challenges such as poor solubility and quick degradation but also help to decrease adverse effects by the selective accumulation at tumor tissues. With its controlled release mechanism, nano-DDS can assist in extending the drug's half-life. Nanoformulations have significant advantages, such as extended blood circulation, high drug loading, lower cytotoxicity, and inadequate immunogenicity [55–57]. With the aid of nanotechnology, it is possible to simultaneously measure several targets with excellent selectivity and sensitivity [58]. Successful fabrication of several multifunctional agents at the nanoscale has been made possible by the swift advancement of nanotechnology, and these agents have enormous potential as nanomedicines for the detection, prevention, and management of disease [59].

Numerous nanoformulations, such as nanoparticles, nanoemulsions, nanosuspensions, and nanocarriers, are available for enhancing the pharmacokinetic profile, tumor targeting, stability, and biocompatibility of different anticancer drugs, as well as to circumvent their limited bioavailability and solubility. As shown in Fig. 4, erlotinib nanoformulations are classified into four groups: polymer-based nanoparticles, inorganic

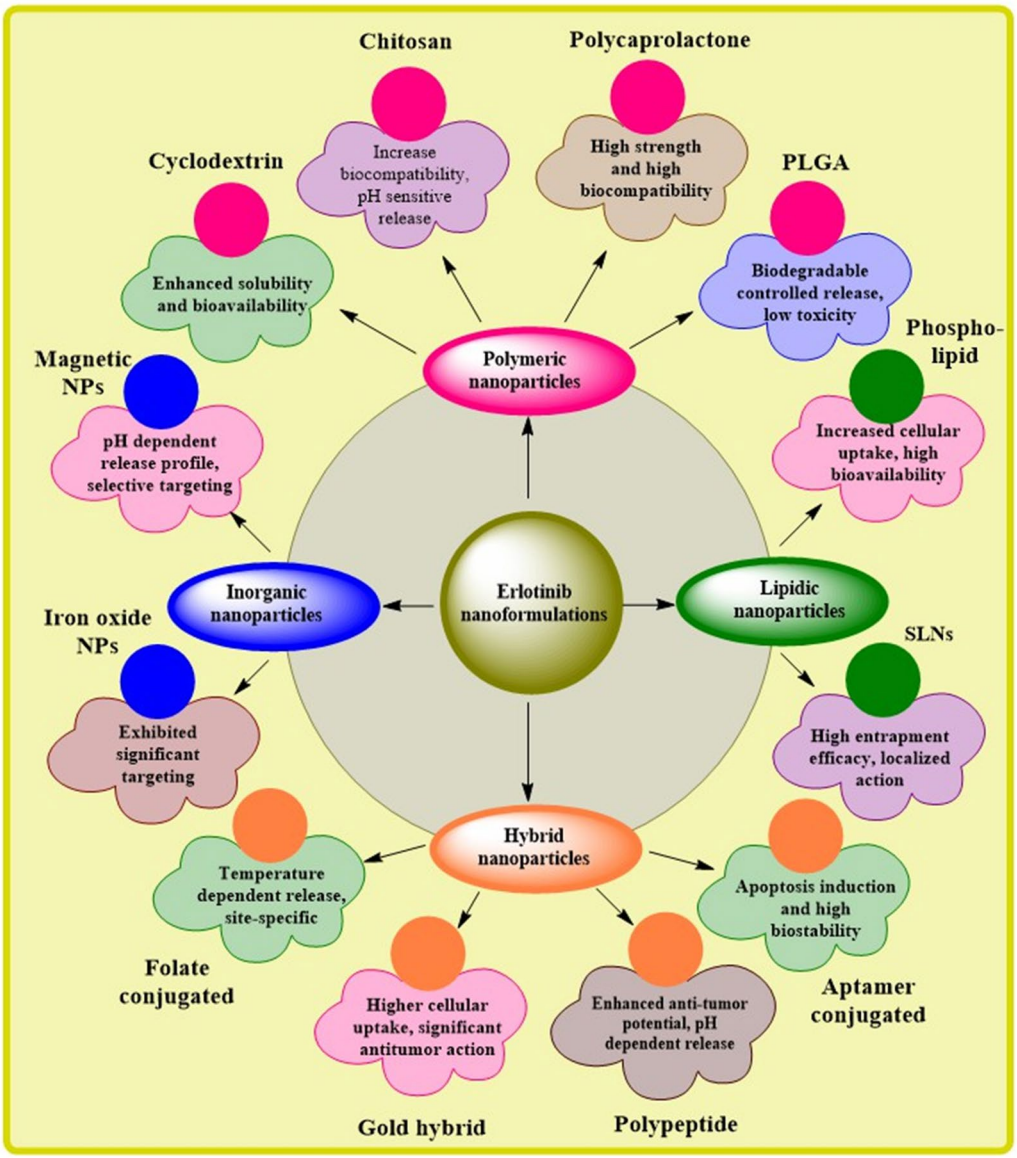

Fig. 4 A comprehensive overview and multifaceted attributes of polymeric, lipidic, inorganic, and hybrid nanoparticles, which are instrumental in addressing a wide range of challenges and advancing numerous drug delivery applications

nanoparticles, lipid-based nanoparticles, and hybrid system-based nanoparticles.

4.1 Polymeric nanoparticles

Polymeric NPs (PNPs) are colloidal macromolecules with submicron sizes between 10 and 1000 nm. PNPs act as a drug carrier, enabling their sustained release to the intended malignant areas [60]. Additionally, the use of PNPs increases stability, improves drug loading ability, and reduces undesirable toxicities [61]. Non-biodegradable polymers like polyacrylamide, polymethyl methacrylate (PMMA), polystyrene, and polyacrylates show toxicity. Therefore, to overcome these constraints, biodegradable polymers have been developed that help in optimizing drug release kinetics, minimizing toxicity, and boosting biocompatibility [62, 63]. Nowadays, tumor-specific delivery in diseases such as cancer is no longer a nightmare because of the development of polymeric nanotechnology, which provides site-specific release and easy penetration into cancerous cells, etc. [64]. Considerable stability, excellent structural design, variable and tunable solubility, lower immunogenicity, and strong cellular biocompatibility of nanoparticles make them appealing for medical applications. Furthermore, the

antigenicity, three-dimensional geometric structure, and precise tissue/cell targeting capabilities of nanoparticles are also widely used in medical applications [65, 66].

Poly-(ε-caprolactone) (PCL) can regulate drug release. It is biodegradability, and biocompatibility, resulting in a general reduction in toxicity and an improvement in the potency of the encapsulated therapeutics. These nanocarriers can increase both in vitro and in vivo anticancer effectiveness. Therefore, Bruinsmaan et al. formulated erlotinib-loaded nanocapsules using PCL. Resulting nanocapsules displayed significant antitumor activity against cancerous cells. In addition, nanocapsules caused 2.5 times more cell death and stopped the growth of A549 cells compared to the erlotinib solution [67]. In an additional study, Marslin et al. [68] synthesized poly-(D, L-lactic-co-glycolic acid) (PLGA) nanoparticles of erlotinib using sonication-solvent evaporation technique to evaluate subacute toxicity in rats. The histopathological examination displayed that the internal body organs were considerably injured with the free drug, while less damage to internal organs was obtained with erlotinib-loaded PLGA nanoparticles. Moreover, the resultant nanoparticles showed fewer adverse effects as compared to the free drug. Similarly, to investigate the in vitro anticancer potential of erlotinib, Barghi et al. [69] formulated erlotinib-loaded polycaprolactone-polyethyleneglycol-polycaprolactone (PCEC) nanoparticles by using solvent displacement method. The resulting nanoparticles showed a sustained release profile of erlotinib, but its release rate decreased when carbolactone/polyethyleneglycol molar ratio increased. Cell growth inhibition by erlotinib was time and dose dependent. Resulting nanoparticles showed excellent antiproliferative activity in comparison to free erlotinib.

Cyclodextrin creates a hydrophobic cavity that is nanometrically large and can easily fit non-polar visitors that are the right size. As a result, cyclodextrin has been widely used to increase the bioavailability of several poorly soluble therapeutic agents. Varan et al. [70] created cyclodextrin nanoparticles of erlotinib to improve its bioavailability, solubility, and breakdown in the digestive tract. The developed nanoparticles showed a significant improvement in anticancer potential against lung and liver cancer cells and induced apoptosis by extracting cholesterol from cancerous cells (Fig. 5). Dora et al. [71] developed an erlotinib-loaded cyclodextrin nanosponge using the freeze-drying method. The resulting nanoformulations showed a twofold increase in dissolution rate

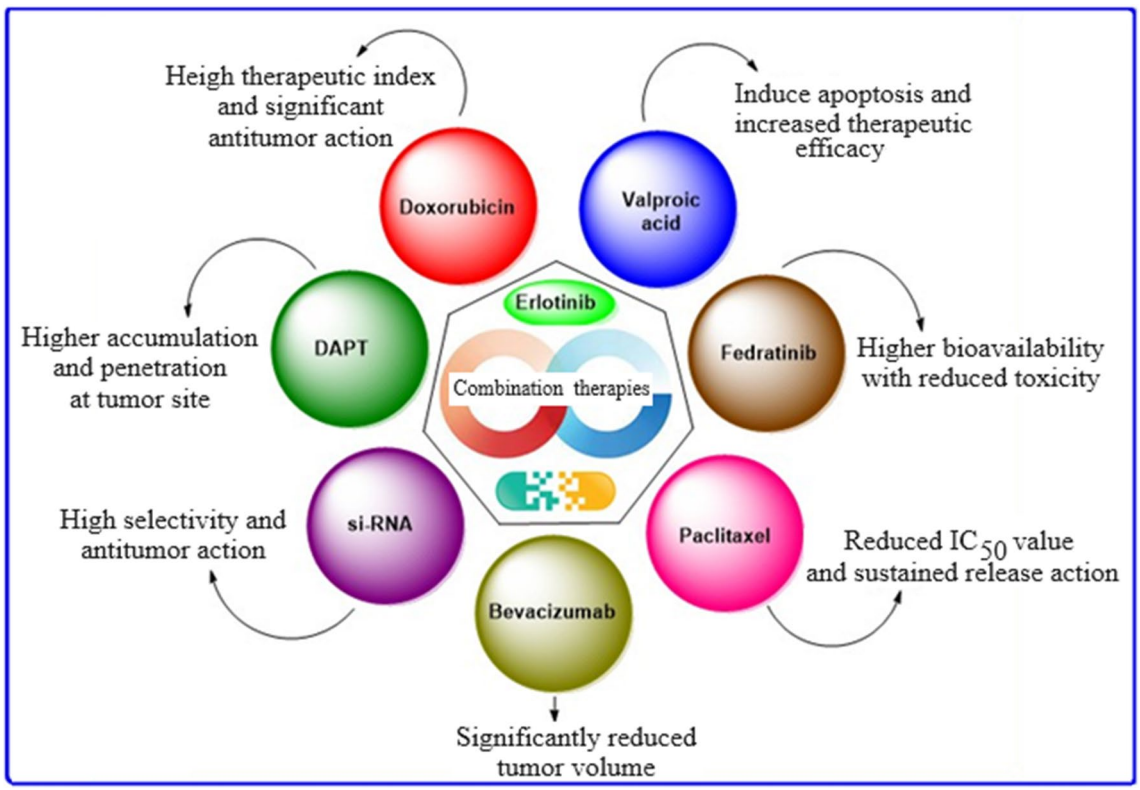

Fig. 5 Therapeutic benefits of erlotinib combination therapy with doxorubicin, valproic acid, fedratinib, paclitaxel, bevacizumab, si-RNA, and DAPT (a gamma secretase inhibitor)

and improved bioavailability. Moreover, the nanosponges also displayed higher uptake efficiency in comparison to the plain drug.

Vaidya et al. [72] synthesized cyclodextrin-modified erlotinib-loaded PLGA nanoparticles using solvent evaporation method. The resulting nanoparticles showed improved therapeutic efficacy against NSCLC with enhanced apoptosis and autophagy inhibition. Cyclodextrin-modified PLGA nanoparticles showed superior anticancer potential in comparison to plain erlotinib. Chitosan was chosen as a polymer due to its biocompatibility, biodegradability, safety, and bioadhesive properties. Its mucoadhesive properties extend the residual period at the site of absorption, and its cationic nature enables ionic cross-linking with multivalent anions.

Pandey et al. [73] developed chitosan nanoparticles of erlotinib-loaded by ionic gelation following probe sonication technique. The developed nanoparticles showed a significant improvement in the circulation time of the drug, which provides efficient delivery of therapeutic agents at the targeted site. Nanoformulations exhibited considerable cytotoxic effects and a slow-release rate in comparison to marketed formulations. Similarly, to investigate the anticancer potential of erlotinib, Pandey et al. [74] synthesized chitosan nanoparticles of erlotinib. The resulting nanoformulations showed noteworthy anticancer potential and stability for up to six months without any transformation. Erlotinib is released slowly from chitosan nanoparticles in comparison to the marketed formulation, which also improves therapeutic efficacy and reduces adverse effects of erlotinib. To increase targeted therapy against NSCLC, Saravanakumar et al. [75] synthesized aptamer AS1411-decorated erlotinib chitosan nanoparticles. Aptamers stick to nucleolin, which is only found in cancer cells and not in healthy cells. This lets erlotinib get inside cancer cells deeply and release itself in a way that depends on the pH. A more precise payload targeting of cancer cells is possible with active targeted drug delivery. Such an active targeted drug delivery system is typically achieved by covalently attaching a monoclonal antibody (mAb) to the surface of a nanoparticle, which can detect and bind to a specific receptor expressed in cancer cells. In this context, Srinivasan et al. [76] developed antibody-functionalized chitosan nanoparticles of erlotinib. Nanoformulations showed that antibody-functionalized chitosan nanoparticles slowly released erlotinib as compared to non-functionalized chitosan nanoparticles. Momin et al. [77] formulated erlotinib glutathione nanosponge using a one-step reaction between β-cyclodextrin and pyromellitic dianhydride. The resulting erlotinib-loaded glutathione nanosponge showed considerable cytotoxicity and excellent cancer inhibition in comparison to free erlotinib. Nanosponge containing erlotinib showed significant antiproliferative activity with higher cellular drug uptake. Glutathione-responsive nanosponges showed site-specific delivery of drugs and bypassed exposure to non-target tissues.

To improve poor bioavailability of erlotinib Yang et al. [78] developed erlotinib-loaded nanoparticles by employing nanoparticulation utilizing fat and supercritical fluid. The resulting formulation displayed considerable inhibition of EGFR signaling and suppressed the proliferation of A549 cancerous cells. Owing to the improved solubility and bioavailability of erlotinib, nanoparticles containing erlotinib overcome side effects and fed-fasted bioavailability variances. Li et al. [79] developed silk fibroin nanoparticles of erlotinib. Erlotinib-loaded nanoparticles displayed better bioavailability than the free drug. Apoptosis of cancerous cells leads to better anticancer effects of nanoparticles. Furthermore, nanoparticles showed considerable apoptosis and improved therapeutic efficacy in comparison to free drugs. These studies showed that significant scientific efforts have been made globally to improve the targeted action and controlled release of therapeutic agents by using different polymers like cyclodextrin and chitosan. Table 3 presents various study outcomes based on PNPs.

4.2 Inorganic nanoparticles

Owing to their greater physicochemical characteristics (such as magnetic, thermal, optical, and catalytic performance) and outstanding functionalities like imaging, targeted drug administration, and controlled drug release, inorganic nanoparticles have been extensively utilized in the detection and treatment of malignancies. Inorganic nanomaterials utilized in cancer treatment include magnetic nanoparticles, silica nanoparticles, and iron oxide nanoparticles. These are effective in the treatment of tumors due to their prolonged systemic circulation, higher accumulation in tumors due to their improved permeability, enhanced drug stability, and regulated drug release in tumor cells [82, 83].

In MRI, superparamagnetic iron oxide (SPIO) is used to monitor the distribution of NPs in vivo. SPIO can also be used to track, target, and assess the effectiveness of therapeutic interventions when it is combined with certain small-molecule drugs. Hsu et al. [84] formulated erlotinib-loaded superparamagnetic nanoparticles using quantitative resonance imaging and the Nuclear Factor Kappa-B Reporter Gene System (NF-κB). The resulting nanoformulations showed significant inhibition of tumor growth and activated intrinsic and extrinsic apoptotic pathways by inhibiting NF-κB. Similarly, to boost the targeting of EGFR-overexpressing pancreatic cancerous cells, Nebu et al. [85] synthesized erlotinib-loaded gold nanoclusters

Table 3 Polymeric nanoparticles-based research findings

Type of nanoformulation	Method of preparation	Particle size (nm)	Zeta potential	Entrapment efficiency	Drug release	Cell line	Outcomes	Refs
Albumin nanoparticles	Desolvation method	10.3 to 14.0	–	44%	–	PANC-1, ASPC-1	Reduced drug dose regimen, good cytotoxicity activity	[80]
Albumin nanoparticles	Precipitation method	112.5 ± 2.8	− 21.2 ± 3.2 mV	81.2%	5% at 1 h	A549	Significant tumor growth inhibition, superior bioavailability	[81]
Cyclodextrin nanoparticles	Nanoprecipitation	88 ± 9 to 152 ± 8	+ 62.1 ± 5 to + 74.9 ± 7 mV	–	Rapidly in the first 30 min	HepG2, A549	Enhanced antitumor efficacy	[70]
PLGA nanoparticles	Solvent evaporation method	210 ± 8	–	61.5 ± 3.2%	At pH 7.4 32 ± 4% after 5 days	A549, H157, H460, H4006	Enhanced therapeutic efficacy	[72]
Cyclodextrin nanosponge complex	Freeze drying	372 ± 31	− 32.07 ± 4.58 mV	–	71.26 ± 0.54% in 60 min	MIA PaCa-2 and PANC-1	Improved dissolution, oral bioavailability, and solubility	[71]
Chitosan nanoparticles	–	195.46 ± 1.85 to 199.13 ± 2.72	9.55 ± 0.28 to − 57.46 ± 1.36 mV	70.94 ± 1.83 to 4.28 ± 1.78%	–	A549, NIH3T3	Improved cellular uptake	[75]
Chitosan nanoparticles	Ionic gelation method and probe sonication	138.5	26.9 to 25.4 mV	49.02 ± 0.24%	91.57% in 0.1 N HCl after 24 h	A549	Enhanced cytotoxic effect on A549 cancerous cell line	[73]
Chitosan nanoparticles	Ionic gelation and spray drying	170.2	–	43 ± 0.57%	89.46% in 0.1 N HCl after 24 h	A549	Highest cytotoxic effect on A549 cancerous cell line	[74]
Chitosan nanoparticles	–	237.5 ± 1.8	27.26 ± 1.88 mV	–	–	–	pH influenced drug release	[76]
PLGA nanoparticles	Sonication-solvent evaporation technique	217	–	22.86%	60% after 12 days	–	Decreased drug-induced toxicity	[68]
PCEC nanoparticles	Solvent displacement method	–	− 24.4 to − 26 mV	58.7 to 44.4%	A549	–	Increased antitumor effect	[69]
Glutathione nanosponge	–	212 ± 2.45	− 30.21 ± 0.47 mV	92.34 ± 5.31%	76.89 ± 0.1% release at 168 h	A549	Increased cellular uptake and extensive drug release	[77]
Nanoparticles	–	250	–	–	–	A549	Reduced side effects and decreased fed fasted bioavailability variances	[78]
Lipid nanocapsules	Interfacial deposition	171	− 8 mV	99%	–	A549	Higher cytotoxicity, overcome tumor recurrence	[67]
Silk fibroin nanoparticles	–	219 ± 5.7	–	7.7%	100% after 7 days	4T1	Enhance drug bioavailability	[79]

enveloped with magnetic iron oxide nanoparticles. Resulted nanoparticles show a significant ability to kill EGFR overexpressing pancreatic tumor cells and show signs of pH-triggered release. Erlotinib-loaded nanoparticles displayed selective targeting of pancreatic cells in comparison to free drugs. The core–shell nanocomposites enhanced the uptake and cytotoxicity of erlotinib in pancreatic cancer cells. In an additional study, Mohammadzadeh-Asl et al. [86] developed erlotinib-loaded magnetic nanoparticles. Erlotinib-loaded magnetic nanoparticles displayed three times the signal enhancement as compared to erlotinib. The signal enhancement method could be used for tumor cell detection via interacting with overexpressed cancerous cells. Ali et al. [87] formulated erlotinib-loaded iron oxide nanoparticles using the alkaline co-precipitation method. Resulted nanoparticles displayed that cellular uptake and intracellular accumulation were higher in comparison to non-erlotinib conjugated nanoparticles. Erlotinib-loaded nanoparticles showed excellent antitumor effects with targeting properties against cancerous cells. Owing to the ultra-small size of the erlotinib-loaded nanoparticles, it is a tremendous candidate for magnetic resonance imaging in metastatic brain cancer.

Numerous alterations in the context of magnetic and iron oxide nanoformulations enhanced the overall diagnosis and treatment process with higher efficacy. Moreover, this concept also improved the accumulation of drugs at the target site. Table 4 presents various study outcomes based on inorganic nanoparticles.

Zhou et al. [88] synthesized erlotinib-loaded injectable flowing solution of mesoporous silica NPs (MSNs) using thermosensitive poly(d,l-lactide)-poly(ethylene glycol)-poly(d,l-lactide) hydrogel. The MSNs showed prolonged peritumoral and intratumoral drug retention. He et al. [89] designed a novel erlotinib and doxorubicin loaded pH-sensitive charge conversion nanocarrier using a synthetic zwitterionic oligopeptide lipid (1,5-dioctadecyl-l-glutamyl2-histidyl-hexahydrobenzoic acid) for lung cancer therapy. The amino-functionalized MSNs were obtained by coating them with oligopeptide lipid. The faster release of erlotinib than doxorubicin during cellular transport was due to its presence in the exterior lipid bilayer. Lipid-coated nanocarriers became more positive at tumor intracellular pH and enhanced Coulombic repulsion with amine-functionalized MSNs, leading to increased sequential staggered release of payloads. In vivo study demonstrated that pH-sensitive charge conversion co-delivery nanoparticles suppressed tumor growth in Lewis lung carcinoma tumor bearing mice with no systemic toxicity. Erlotinib-loaded magnetic MSNs of Fe_3O_4 core coated with mesoporous silica and poly-(ethyleneimine)-conjugated folic acid released 63% payload and had negligible hemolytic activity. The synthesized drug-loaded magnetic MSNs inhibited the proliferation of HeLa cell lines. Folic acid-conjugated nanoparticles showed higher cytotoxicity in HeLa cells [90].

Cellular uptake study demonstrated internalization of desmethyl erlotinib-loaded quantum dots. In A549 cell lines resistant to erlotinib, quantum dots conjugated with desmethyl erlotinib demonstrated an IC_{60} of 2.5 μM [91]. Rahmanian et al. [92] reported a graphite rod electrode-based electrochemical sensor for determining erlotinib that was modified by a ternary nanohybrid comprising copper nanoparticles, nitrogen-doped graphene quantum dots and polyaniline, graphene oxide. This sensor system showed the electrocatalytic activity toward erlotinib between 1 nM and 35 μM, a sensitivity of 1.3604 μA/μM, and a detection limit of 0.712 nM. The developed system successfully monitored erlotinib in the drug-injected aqueous solution, urine, and serum samples. The study concluded that the developed electrochemical sensor system has the sensor capability for erlotinib monitoring in biological samples. The surface functionalization of nitrogen-doped carbon nanodots by erlotinib has been explored as a fluorescent contrast agent for live pancreatic cancer cell imaging. This enables *in vitro*

Table 4 Inorganic nanoparticles-based research findings

Type of nanoformulations	Particle size (nm)	Drug release	Cancer cells used	Outcomes	Refs.
Superparamagnetic nanoparticles	–	–	CL1-5-F4	Enhanced therapeutic efficacy against lung cancer, inhibited apoptotic mechanisms	[84]
Magnetic iron oxide nanoparticles	41.8 ± 2.4	78.3% at pH 5	L-929, PANC-1	pH-dependent release, selective targeting of EGFR overexpressing pancreatic cells	[85]
Magnetic nanoparticles	110.8	–	A549	Enhanced surface Plasmon resonance signal	[86]
Iron oxide nanoparticle	6.06 ± 0.9 to 4.28 ± 1.1	70% at pH 5 after 2 h	CL1-5-F4	Exhibited significant therapeutic and targeting properties	[87]

targeting of human pancreatic cancer cell lines that are overexpressed to the EGFR. The confocal fluorescence microscopic images show uniform fluorescence staining on human pancreatic cancer cell lines and localized fluorescence staining on the central region of normal L929 mouse fibroblast cells, confirming its potential in cellular imaging [93].

4.3 Hybrid system-based nanoparticles

Hybrid nanoparticles combine the properties of different nanoparticles, which makes them more unique [94]. Some of the benefits of hybrid systems over non-hybrid platforms are lower rates of encapsulation and structural disintegration, higher stability, premature release, and unspecific release kinetics [95].

Nanoparticles have evolved from having a simple core–shell structure to one that is more complex. This strategy made it possible to incorporate several features into a single drug delivery platform. To make lipid hybrid nanoparticles of erlotinib, Mandal et al. [96] used a single-step sonication method and polycaprolactone as a polymer. The resulting erlotinib nanoparticles showed a biphasic release pattern and a considerable decline in cell viability as compared to the free drug. Erlotinib nanoparticles displayed good storage stability. The resulting formulation enhanced cellular uptake in comparison to the plain drug. Fathi et al. [97] synthesized thermosensitive, folate-conjugated o-maleoyl-modified chitosan micellar nanoparticles for site-specific delivery of erlotinib. Folate-conjugated micelles were delivered rapidly and successfully to the targeted cancerous cells. Folate-conjugated micelle chitosan nanoparticles of erlotinib showed an improved cytotoxic effect as compared to plain erlotinib nanoparticles and displayed temperature-dependent release. Avedian et al. [90] synthesized erlotinib-loaded folic acid labeled pH-sensitive mesoporous magnetic nanoparticles. The resulting formulation showed a higher cytotoxic effect and inhibition of HeLa cancer cell line proliferation.

To overcome the resistance to erlotinib, Li et al. [98] formulated aptamer-loaded chitosan-anchored liposomal complexes of erlotinib. The resulting formulation displayed superior biostability and binding properties for EGFR-mutated cancerous cells. Aptamer-loaded chitosan-anchored liposomal complexes of erlotinib exhibit excellent stability by preventing drug leakage and nanoparticle aggregation. Fathi et al. [99] reported erlotinib-loaded thermosensitive gold hybrid nanoparticles using chitosan as a copolymer in an additive-free reducing-based reaction. Nanoparticles displayed temperature-dependent release with a higher cytotoxic effect and cellular uptake.

Kim et al. [100] synthesized nanocapsules of PEGylated polypeptide lipid to improve the antitumor potential of erlotinib. Erlotinib-loaded nanocapsules displayed dose-dependent cytotoxicity in lung cancerous cells. Furthermore, it exhibited significant therapeutic efficacy with greater tumor inhibition. Erlotinib-loaded lipid nanocapsules showed a pH-dependent release profile and a considerable antitumor effect. To improve the stability and anticancer potential of erlotinib in the management of lung cancer, Tan et al. [101] developed pH-sensitive and redox-responsive lipid nanoparticles. Erlotinib-loaded lipid nanoparticles were prepared by emulsification and solvent evaporation method using poly-(acrylic acid)-cystamine-oleic acid. In vitro cytotoxicity and in vivo tumor growth inhibition of erlotinib-loaded lipid nanoparticles were superior in comparison to the erlotinib solution. Furthermore, nanoparticles revealed a sustained drug release profile after 72 h. These outcomes revealed that hybrid nanoformulation overcomes the pitfalls of single agents and improves the pharmacokinetic behavior of therapeutic agents. Table 5 reports various hybrid nanoparticle-based therapeutics.

4.4 Lipid-based nanoparticles

A potential colloidal transporter for bioactive organic substances is lipid-based nanoparticle systems. Large thermal and temporal stability, high loading, and ease of preparation are some of the benefits of lipid-based nanoparticles. Moreover, delivery of chemotherapeutics using lipid nanocarriers reduces drug dose and its toxicity, reduces resistance, and maintain drug levels in tumor while protecting healthy tissues [102, 103].

SLNs are solid lipid-based nanoscale drug delivery systems. As phase emulsifiers, surfactants (such as phospholipids) are typically needed in these systems to combine the internal lipid phase with the external water phase of SLN dispersions. Naseri et al. [104] formulated SLNs using self-nanoemulsification method. The resulting nanoparticles showed inhibition of cell growth depending upon dose and time, with high entrapment efficacy. Erlotinib-loaded SLNs were spray-dried into microparticles with better flowability and showed good potential for lung cancer via the pulmonary route. Nanoparticles also displayed great cytotoxicity in comparison to the free drug. Similarly, Bakhtiary et al. [105] synthesized SLNs of erlotinib by hot homogenization to treat NSCLC. Erlotinib-loaded nanoparticles improved the cytotoxic effect on A549 cancerous cells in NSCLC. Nanoparticles displayed enormous potential for localized delivery of erlotinib in the lung. Furthermore, nanoparticles of erlotinib showed excellent anticancer potential on the A549 cancerous cell line as compared to the free drug. The resulting nanoparticles showed a sustained drug release pattern and could be a promising management modality for NSCLC. To further improve the therapeutic potential

Table 5 Studies reported on hybrid nanoparticles-based therapeutics

Type of nanoformulations	Methods of preparation	Particle size (nm)	Entrapment efficacy	Zeta potential	Drug release	Cancer cells used	Outcomes	Refs.
Lipid hybrid NPs	Single step sonication	170	66%	−15 to −30 mV	50% after 3 h	A549	Enhanced uptake efficiency Reduction in cell viability	[96]
Folate-conjugated chitosan micellar NPs	–	100	–	−10.6 mV	At 25 ^{0}C and 37 ^{0}C, 77%, 90% after 48 h, respectively	OVCAR-3, A549	Temperature-dependent release, site-specific delivery	[97]
Thermosensitive gold hybrid NPs	Additive-free reducing-based reaction	83–105	–	+0.6 mV	–	A549	High stability at different pH, excellent antitumor effect	[98]
Aptamer-conjugated chitosan anchored liposomal complexes	–	179.4 ± 1.16	–	35.70 ± 0.43 mV	60% at pH 5.5	PC-9, H1975	Suppression of cell growth, apoptosis overcome resistance	[90]
PEGylated polypeptide lipid nanocapsule	–	~200	95%	−20 mV	–	NCI-H358 and HCC-827	Improved antitumor effect, pH-dependent release	[100]
Poly(acrylic acid)-cystamine-oleic acid-based lipid NPs	Emulsification and solvent evaporation method	170	85%	-32 mV	–	A549, NCI-H460, HUVEC	Improved stability and anticancer potential, higher tumor inhibition efficacy	[101]
Mesoporous magnetic NPs	–	213	–	-27.3 mV to 39.4	63% at lower pH	HeLa	Superior antiproliferative effect	[90]

of erlotinib, Vrignaud et al. [106] developed an erlotinib-loaded lipid nanocarrier using reverse micellar incorporation. The resulting formulation demonstrated nearly 40% pancreatic cancerous cell lysis in comparison to the free erlotinib formulation. The nanocarrier of erlotinib showed improved antiproliferative activity.

To enhance the oral bioavailability and water solubility of erlotinib, Truong et al. [107] developed an erlotinib-loaded solid self-emulsifying drug delivery system (SEDDS). A dissolution study demonstrated that formulation had higher in vitro drug release in comparison to pure drug powder. Furthermore, it also showed enhanced solubility and bioavailability of erlotinib-loaded SEDDS as compared to erlotinib powder. In an additional study, Dora et al. [108] formulated a phospholipid complex of erlotinib using the solvent evaporation method. In vitro drug release studies of the resulted formulation displayed improved release of erlotinib from the erlotinib phospholipid complex. Erlotinib-loaded phospholipid displayed a twofold increased cellular uptake in comparison to the free drug. Resulted phospholipid complex showed 1.7-fold increased bioavailability, improved therapeutic efficacy and solubility, and reduced toxicity in comparison to the free drug. The above studies suggest that lipid nanoparticles are biocompatible and enhance therapeutic efficacy with lesser side effects. Table 6 reports various lipid nanoparticle-based therapeutics.

5 Combination therapy

Combination therapy, which combines two or more anticancer drugs or multiple therapeutic modalities, can increase treatment effectiveness, lower tumor drug resistance, and lessen adverse effects [109]. Salient benefits of combination therapy are described in Fig. 5. When erlotinib is used alone for a long time, it can cause resistance. Combining it with other anticancer drugs may have some benefits, such as better antitumor effects, a better pharmacokinetic profile, and lessened resistance problems that come with using a single drug. In addition to therapeutic applications, this approach is also cost-effective [110]. When different anticancer drugs are mixed together in nanoformulations, the therapeutic dose is lowered. This may also make it possible to target more than one target at the same time, which greatly reduces drug resistance [111]. Combining erlotinib with paclitaxel, cisplatin, doxorubicin, and other drugs has been

Table 6 Research findings based on lipid nanoparticles

Type of nanoformulation	Methods of preparation	Particle size (nm)	Zeta potential (mV)	Entrapment efficacy (%)	Drug release	Cancer cells used	Outcomes	Refs
SLNs	Self-nanoemulsifying method	300 to 800	−18 to −32	80–85	–	–	Higher cytotoxicity	[104]
Lipid nanocarrier	Phase inversion temperature	85 ± 1.4	−17.5	53 ± 1.4	–	BxPC-3	Improved antiproliferative activity	[105]
SLNs	Hot homogenization	> 100	–	78.21	12% at 8 h	A549	Improved anticancer ability	[106]
PEGylation liposomes	Thin film hydration	102.4 ± 3.1	–	85.3% ± 1.8	62% at 12 h	–	Enhanced bioavailability	[107]
Phospholipid complex	Solvent evaporation	183.37 ± 28.61	−19.52 ± 6.94	–	60.4% in 8 h	Caco-2	Improved bioavailability, therapeutic efficacy, solubility	[108]

Table 7 Recent research findings on erlotinib combination therapy in different cancers

Drugs/active moieties	Nanoformulations	Diseases	Cell lines	In vitro cytotoxicity	Apoptosis analysis	Refs
Paclitaxel and erlotinib	Solid lipid core nanocapsules	NSCLC	NCI-H23	threefold decrease than free drugs	Significant increase in apoptosis rate than free drugs	[111]
Erlotinib and doxorubicin	PNPs	Triple-negative breast cancer	MDA-MB-468	Increased cytotoxic effect	–	[110]
Doxorubicin/erlotinib	pH-sensitive charge conversion nanocarrier	Lung carcinoma	A549	IC_{50} (5.81 µg/mL)	Increased cell apoptosis	[89]
Doxorubicin/erlotinib	Double emulsion nanoparticles	Cancer	SCC7	Exhibit significant cytotoxic effect	–	[112]
Erlotinib and DAPT (a gamma secretase inhibitor)	Peptide functionalized nanoparticles	Triple-negative breast cancer	MDA-MB-231	Improved cytotoxicity	–	[113]
Erlotinib and fedratinib	Biodegradable nanoparticles	NSCLC	NSCLC, H1650	Increased cytotoxicity against NSCLC cells	–	[114]
Erlotinib and bevacizumab	pH-sensitive lipid polymer hybrid nanoparticles	NSCLC	NSCLC, A549, H1975	Increased cytotoxicity than free drugs	–	[115]
Paclitaxel and erlotinib	PLGA nanoparticles	Breast cancer	–	–	–	[116]
Doxorubicin and erlotinib	Liposomal nanoparticles	Glioblastoma	–	–	Higher apoptotic effect	[117]
Erlotinib and valproic acid	Liquisolid formulation	Lung cancer	HCC827	2 to fivefold increased cytotoxicity	Combination improved apoptotic effect (around 60%)	[118]
Co-delivery of erlotinib and oxygen	Liposomal complexes	Lung carcinoma	A549, H1975, and PC-9	Concentration-dependent cytotoxic effect	Induced apoptosis	[119]
Erlotinib/ssurvivin shRNA co-delivery	Aptamer modified nanocomplexes	NSCLC	PC-9 and H1975	Enhanced cytotoxicity	Stronger apoptotic effect	[120]
Erlotinib	Chitosan-based self-assembles theranostics	Lung cancer	PC-9 and A549, H1975	–	–	[121]
Erlotinib and doxorubicin	Gold nanocages	–	A431, MCF-7	–	Significant apoptosis effect	[122]

shown to improve anticancer efficacy. Recent research findings on erlotinib nanoformulations in combination with other drugs are summarized in Table 7. Results from the above findings suggest that combination therapy can be an effective tool against lethal diseases like cancer as it aids in mitigating the resistance problem.

6 Future perspectives

Erlotinib, an EGFR-targeted drug, is effective against pancreatic cancer, NSCLC, and colorectal cancer. Despite its potential use in cancer treatment, it has low solubility, low bioavailability, and various side effects that can be mitigated by nanotechnology. There could be a lot of benefits to using erlotinib nanoformulations, such as better tumor targeting, fewer side effects, and better compliance. Despite the aforementioned benefits, erlotinib nanoformulations are still required to be examined in numerous areas, like large-scale production in a cost-effective manner. Patents and clinical trial sections still needed to be studied, and optimizing erlotinib resistance could increase cancer patients' survival. More research needs to focus on better understanding of mechanism of action of nanoformulations, their long-term effects, and drug clearance mechanisms. The heterogeneity of tumor cells, their intricate tumorigenic pathways, and a high dose of cytotoxic chemotherapeutic drugs can cause side effects. Designing targeted nanoscale delivery systems with increased antitumor activity and decreased drug toxicity is therefore crucial. Cancer detection and therapeutic management have been profoundly impacted by nanotechnology, which can significantly impact tissue distribution and cellular uptake. Polymers and moieties used as delivery vehicles in erlotinib nanoformulations may produce hazardous byproducts, resulting in systemic adverse effects. Regulating the polymer concentration can be a potential strategy to achieve the desired therapeutic action against different cancers. Moreover, different chemically modified polymers can also be a sturdy approach toward targeted action. Nanoformulations have demonstrated potential in improving bioavailability and tumor-targeting capabilities of chemotherapeutic agents, including erlotinib. Therefore, it is reasonable to expect that erlotinib nanoformulation may provide better therapeutic results in comparison to conventional therapies. The translation of erlotinib nanoformulations from preclinical investigations to clinical applications will greatly contribute to the progress of cancer treatment. Most of the scholarly literature has been focused on preclinical in vitro cell-based assays or in vivo animal models. The progression of human clinical trials is crucial for assessing the real-world efficacy and safety of these innovative formulations. Biomarker-driven selection of patient cohorts based on tumor characteristics, genetic profiles, and treatment response parameters can optimize treatment outcomes and minimize the risk of adverse events.

7 Conclusion

This communication addressed several nanocarriers explored for delivering erlotinib to enhance its anticancer activity. Lipid-based, polymer-based, inorganic, and hybrid systems have been reported to improve erlotinib's characteristics, such as its dissolution, and bioavailability. Combinations of erlotinib and other therapeutic agents that have been explored to prevent tumor resistance and augment the erlotinib potential are discussed. The present manuscript also highlights the importance of the mechanism of action and pharmacokinetic aspects of erlotinib. This article illustrates several pivotal studies, including preparation methods, physicochemical characteristics, delivery effectiveness, and potential benefits of the erlotinib nanoscale delivery system that results in improved tumor microenvironment responsiveness and targetability. Moreover, nanosystem-based combination therapy of erlotinib with other medicaments to demonstrate synergistic anticancer potential is also discussed. The influence of siRNA and polymeric derivatives in cancer treatment has also been clearly illustrated. Different scientific studies have shown that a significant therapeutic response can be successfully achieved with a potential tool like nanotechnology. Numerous outcomes from different studies have been cautiously illustrated and summarized systematically in the current manuscript.

Abbreviations

EGFR	Epidermal growth factor receptor
NSCLC	Non-small cell lung cancer cells
INR	International normalized ratio
ATP	Adenosine triphosphate
NPs	Nanoparticles
SLNs	Solid lipid nanoparticles
PMMA	Polymethyl methacrylate
PCL	Poly-(ε-caprolactone)
PLGA	Poly-(D, L-lactic-co-glycolic acid)
PCEC	Polycaprolactone-polyethyleneglycol-polycaprolactone
SPIO	Superparamagnetic iron oxide
NF-κB	Nuclear factor Kappa-B reporter gene system
MSNs	Mesoporous silica nanoparticles
SEDDS	Solid self-emulsifying drug delivery system
DAPT	A gamma secretase inhibitor
si-RNA	Small interfering ribonucleic acid

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