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Nano drug delivery systems as promising tools for cancer therapy

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Abstract

Despite the remarkable medical advances, cancer is still a lethal threat to humans, causing tremendous social and economic problems. The emerging and following developments of nanomedicine for cancer therapy during past recent years brought outstanding achievements to the healthcare industry. Nanoparticle-based carriers to deliver various anti-cancer drugs opened new doors to boost the efficiencies of conventional chemotherapeutic approaches and decrease serious side effects. Although some challenges like drug resistance, instability, inappropriate accumulation, and drug leakage have remained, some delivery systems have achieved hopeful results in clinical trials, and consequently, some of them were approved by U.S Food and Drug Administration (FDA). In this review, the most essential and promising anticancer drug delivery systems for cancer treatment, particularly non-small cell lung cancer (NSCLC), are described. The primary emphasis was on evaluating different FDA-Approved ones in order to get a comprehensive grasp of their benefits and drawbacks for future research and industrial uses.

Keywords: *Cancer therapy, Drug delivery systems, NSCLC, Lipid nanocarriers, Nanomedicine, Targeted delivery*

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1. Introduction

Cancer is characterized by abnormal and uncontrolled Cancer is characterized by abnormal and uncontrolled growth of cells in the body. In fact, when some disorders happen in the crucial processes of cell proliferation, the cells are provoked to have some mutations in an unusual way which ultimately results in emerging cancerous cells. Some of the roots related to this unusual behavior of cells are smoking and the rising effects of some risk factors for instance stress pressure, and being overweight [1].

Recently, cancer incidence has been known as a gradually increasing issue. World Health Organization (WHO) reported cancer as the second most serious cause of death worldwide with approximately 7.6 million death every year which is 13% of total death. According to their findings, lung cancer ranks first or second among malignant tumors, with death and morbidity rates of 18% and 11.4%, respectively [2]. Furthermore, cancer after cardiovascular diseases is known as the most challenging issue with a heavy burden of economic and social effects globally [3]. On the other hand, by considering the current situation and main causes of cancer, it is predicted that cancer-related mortality will reach 13.1 million by 2030 [4].

Histologically lung cancer is divided into two major groups: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC accounts for about 85% of all cases.

Surgery, chemotherapy, and radiotherapy medications, as the three main systemic methods, were used in therapeutic approaches for cancer treatment for years. Despite various side effects from these methods and dramatic damage to patients' bodies, particularly in metastatic cases, they still are used for cancer therapy solely or sometimes in combination forms. However, chemotherapy is the most preferred method for lung cancer treatment as surgery and resection did not show satisfying results in more than 75% of the patients [5].

In recent years, scientists have been working on novel methods to mix some approaches that may get the highest efficiency. In this path, while many new anti-cancer agents have been emerging with higher effectiveness, some challenges, such as drug resistance, low drug solubility and stability, and poor delivery of anti-cancer drugs to the determined points (target cancer cells) make it difficult to get the permission from U.S Food and Drug Administration (FDA) to commercialize the final product(s) because of severe problems for human health. In general, chemotherapeutic drugs include toxic compounds that attack cancer cells and inevitably affect normal cells. They also are spread via the body non-specifically. Hence, it can be estimated to see various harmful side effects [6]. Therefore, these issues push researchers to find novel strategies to improve efficiencies. One of the most important methods is applying drug delivery systems (DDSs) to carry the specific drug by increasing its properties with the help of nanomedical approaches. The main mission of these carriers is to deliver drugs to the cancerous tissue/cells [7,8].

Nanomedicine is defined as a tool that uses nanotechnology to solve medical issues. In fact, nanotechnology plays a key role in medical science. Moreover, in today's world, nanotechnology has gained significant attention for cancer therapeutic goals and impressed drug delivery and diagnostics in an outstanding way [9].

Nanoparticles in terms of their special size (10-100nm) and surface area illustrated valuable properties as drug carriers, especially regarding the circulation and accumulation in the bloodstream. The enhanced permeability and retention (EPR) effect helps nanoparticles remain in the tumor cells. Besides, many pieces of research showed nanocarriers could increase the water solubility of drugs alongside improving biodistribution, and biological and pharmacological features [6,10,11]. They can deliver medicines to tumor cells with a little amount of drug leakage into healthy cells. Thus, targeted therapy has emerged to specifically target cancerous cells using useful tools, such as promising nanocarriers [10]. While several nano-drug delivery systems were studied so far, there is a need to improve their structures with beneficial methods which not only can improve their efficacy, but also make them available in the market at a reasonable price. In this review, various types of potential anti-cancer drugs and nanocarriers are described to have a better understanding of their applications and functions. Moreover, the strong capability of the popular nano drug delivery systems for cancer treatment, especially NSCLC, is explained from scientific and economic viewpoints.

2. Anti-cancer drugs

In general, there are different categories of anti-cancer drugs, and one of the best categories is divided into seven groups: alkylating agents, antimetabolites, topoisomerase inhibitors, antitumor antibiotics, mitotic spindle toxic agents, targeted therapies, and immunotherapies [12].

2.1 Alkylating Agents

Alkylating agents produce alkylation via the formation of covalent links among DNA strands. They result in abnormal nucleotide sequences, miscoding of messenger RNA, blockade of DNA replication, and breakage of DNA strands.

This category is divided into six groups:

- The nitrogen mustards (mechlorethamine, cyclophosphamide, ifosfamide, melphalan, and Chlorambucil);
- Ethylenamine and methylenamine derivatives (altretamine, thiotepa);
- Alkyl sulfonates (busulfan);
- Nitrosoureas (carmustine, lomustine);
- Triazenes (dacarbazine, procarbazine, temozolomide);
- Platinum compounds. Agents similar to alkylating agents crosslink with DNA (cisplatin, carboplatin, and oxaliplatin) [13,14]

Although the reactions of such alkylating agents are not specific to one phase of the cell cycle, their toxicity is particularly strong in the late 1st Gap phase (G1 phase) and synthesis phase (DNA duplicate) (S phase). They are also known as carcinogens and can cause hematologic malignancies [15]. Alkylating agents and platinum derivatives are useful to manage solid tumors because of their broad anticancer spectrum. Hence, they suffer from acute systemic toxicity, suboptimal treatment schedules, intrinsic or acquired resistance, and inadequate routing at the cellular level [16]. Despite major clinical side effects in terms of inhibiting the metabolic processes of normal cells, chemotherapy is still the most common treatment for many types of cancer in terms of its long-term therapeutic effectiveness [13,17,18]. Neutropenia and lymphopenia, for instance, are well-known as chemotherapy's side effects [19]. Zhou et al., who investigated the resistance mechanisms in platinum-based chemotherapy, showed a decrease in the accumulation of cellular drugs and apoptosis and autophagy. They also reported an increase in DNA repair process and in the detoxification system, a decrease. Platinum is used following the initial treatment period with these drugs [20]. Combined treatment with other drugs is one of the research projects which were done to reduce the side effects and improve the effectiveness of the drugs of this family. In this regard, Paz-Ares et al. showed that in squamous NSCLC, Pembrolizumab as an option for immunotherapy led to an improvement in the median OS (overall survival) in combination with carboplatin and taxane chemotherapy [21]. In the study of Gadgeel et al., it was seen that Pembrolizumab combined with pemetrexed and platinum chemotherapy as a treatment for non-squamous NSCLC without EGFR or ALK

mutations led to an improvement in median overall survival [22].

2.2 Antimetabolites

This group of materials competes with the natural substrate to reach the active site of an essential enzyme or receptor which interferes with DNA synthesis. They include three popular categories as follows:

- Antifolates (methotrexate and pemetrexed)
- Pyrimidine analog (cytarabine, 5-fluorouracil, and gemcitabine)
- Purine analogs (6-mercaptopurine, azathioprine) [23]

Methotrexate decreases the concentration of tetrahydrofolate (THF) in the cells by inhibiting dihydrofolate reductase (DHFR) enzyme and reducing the purine nucleotide and DNA synthesis [24]. Among the side effects of folate, the main antagonists are bone marrow suppression, gastric and intestinal mucositis, as well as kidney failure in high doses [25]. Gemcitabine is used against various solid tumors, including lung and pancreas cancers [26,27]. Neutropenia, proteinuria, increased hepatic transaminase levels, nausea, vomiting, and skin rash are side effects of high-dose gemcitabine include [28]. Overexpression of ribonucleotide reductases is one of the causes of gemcitabine resistance [29]. Pemetrexed is a folic acid analog and a potent inhibitor of pyrimidine and purine [30]. This drug inhibits vital enzymes, such as glycinamide ribonucleotide formyltransferase (GARFT), aminoimidazolecarboxamide ribonucleotide formyltransferase (AICARFT), and thymidylate synthase (TS) [30-32]. Resistance mechanisms of pemetrexed include overexpression of TS, suppression of the folate transporter SLC19A1, and Akt activation [33,34]. To reduce the side effects and improve the anti-tumor properties of these drugs, anti-PD-1 or anti-PD-L1 drugs, including durvalumab, pembrolizumab, and nivolumab, are the preferred options for immunotherapy. Nucleotide antimetabolites, such as Gemcitabine, 5 FU, Pemetrexed, Decitabine are also used along with anti-PD-1 and/or anti-PD-L1 [35,36].

2.3 Topoisomerase Inhibitors

Topoisomerases are enzymes that control the changes in DNA function by catalyzing the phosphodiester structure of DNA strands during the cell cycle. On the one hand, Camptothecin derivatives (irinotecan, topotecan) exert their cytotoxic effect by inhibiting topoisomerase I. On the other hand, Epipodophyllotoxin derivatives (etoposide, teniposide) inhibit topoisomerase II.

Typically, the topoisomerases are considered important targets for therapeutic intervention because they play a significant role in DNA replication and recombination, as well as transcription and repair [37,38]. They show poor solubility, prolonged half-life in plasma, and accumulation in target tissues or organs. Furthermore, complications can arise in terms of the overproduction of enzymes by the target cells, conformational changes in the enzyme structure, and gene mutations leading to drug resistance [39,40]. DNA topoisomerase inhibitors are valuable instruments that allow us to investigate the biological roles of topoisomerases [41]. Topoisomerase inhibitors come in two different varieties: Topoisomerase poisons that predominantly inhibit type I topoisomerases include topotecan, irinotecan, belotecan, and camptothecin. In general, topoisomerase poisons or Type I topoisomerase inhibitors stop strand rotation after which the link between topoisomerase and DNA is firmed. Etoposide, teniposide, doxorubicin, and mitoxantrone are topoisomerase poisons that primarily affect type II topoisomerases [42]. Since topoisomerase inhibitors, such as camptothecin suffer from low solubility, selectivity, and high systemic toxicity, as well as fast clearance from blood circulation, these nano-delivery systems may provide an excellent opportunity to improve their characteristics for potential clinical applications [43].

2.4 Antitumor Antibiotics

Antitumor antibiotics act by several mechanisms: DNA strand breaks, intercalation between DNA base pairs, and inhibition of topoisomerase 2. Anthracyclines (daunorubicin, doxorubicin, liposomal doxorubicin, epirubicin, idarubicin), bleomycin, mitomycin, and mitoxantrone are known as antitumor antibiotics. Mitomycin C is FDA-approved for the treatment of adenocarcinomas of the stomach and pancreas, while bleomycin is employed in squamous cell cancer, Hodgkin's disease, and germ cell tumors. Doxorubicin is an anthracycline glycoside antibiotic that intercalates between DNA bases and DNA

topoisomerases inhibitor. It is also used for many cancer types but is primarily applied in breast carcinoma, ovarian cancer, and Hodgkin's disease [44]. Antibiotics, such as actinomycin D, anthracyclines, and the anthracenones were approved as anticancer agents [45]. The most constricting steps in this process are the toxic side effect, poor solubility, and decreased efficacy due to derivatization [46].

2.5 Mitotic Spindle Toxic Agents

Vinca alkaloids and Taxanes are two major groups of compounds in this category:

- Vinca alkaloids

These drugs bind to microtubular proteins (Mitosis phase (M-phase) of the cell cycle), which dissolve the mitotic spindle structure. Some of the drugs in this group are vinblastine, vincristine, vindesine, and vinorelbine [47].

- Taxanes

These drugs not only bind to microtubules but also help to form non-functional microtubules and resist depolymerization. Paclitaxel, docetaxel, and cabazitaxel are in this group. Some experimental evidence described the role of p53, bcl-2, and bcl-x and other gene products which are directly linked to the regulation of the equilibrium between cell proliferation and apoptosis. However, the antiproliferative cascade triggered by vinca alkaloids at the molecular level is not known yet [48].

2.6 Targeted Therapies

- Oldest targeted agents

Endocrine agents can slow down and stop the synthesis of hormones or prevent the action of hormones by blocking their receptors. These endocrine therapies are mainly prescribed in hormone-sensitive cancers, such as breast cancer (including tamoxifen, aromatase inhibitors, and luteinizing hormone-releasing hormone analogs) or prostate cancer (including antiandrogens and luteinizing hormone-releasing hormone analogs).

- Recently targeted therapies

According to the extensive studies that have been done so far, targeted treatments can be known as a key to the recovery of cancer patients. Various studies were conducted concerning the mechanisms of increasing EGFR signaling in cancer cells [49]. Many researchers studied different drugs that reduce EGFR activity. However, developing resistance to EGFR tyrosine kinase inhibitor drugs has become a challenge for researchers.

a. Kinase proteins

Protein Tyrosine kinases (PTKs) are enzymes that regulate the biological activity of proteins by phosphorylation of certain amino acid residues. This reaction causes a conformational change from an inactive form of the protein to an active form, which is one of the most important regulatory mechanisms of the cell cycle. Dysregulation of protein kinase activity is implicated in the processes of carcinogenesis and the progression of various solid cancers [50].

Tyrosine kinases (TKs) are enzymes that selectively phosphorylate the hydroxyl groups of a tyrosine residue in different proteins with adenosine triphosphate (ATP) as the source of phosphate. They play a role in regulating the most fundamental cellular processes, such as growth, differentiation, proliferation, or programmed cell death [51]. TKIs can block some of the tyrosine kinases involved in cell growth, like epidermal growth factor receptors (EGFR), vascular endothelial growth factor receptors (VEGFR), placket-derived growth factor receptors (PDGF), and fibroblast growth factor receptor (FGF).

Ceritinib, neratinib, osimertinib, pemigatinib, geftinib and erlotinib are some drugs in this group. Cycline-dependent kinases (CDK) are a family of serine - theronine which regulate the cell cycle and other important cell functions like gene transcription and metabolism [52]. Abemaciclib, Ribociclib and Palbociclib are from this group.

In solid tumors, the unnormal activity of different parts of the signaling path occurs with activating multi-kinases. Multi-kinase inhibitor targets a group of structural kinases and blocks their activity simultaneously [53]. Palbociclib, Brigatinib, Afatinib, and Axitinib are among the famous drugs in this group.

The purpose of research in the anti-cancer drug discovery field, particularly for NSCLC cancer, is to understand the mechanisms of drug resistance in patients and improve treatment methods. Various research studied different drugs in the subgroups of NSCLC cancer, showing the importance of knowing these mechanisms and the initial examination of

patients to prevent drug resistance. For example, the study by Soria et al. studied Osimertinib in removing exon 19 or L858R as the most important EGFR mutations in advanced NSCLC [54]. The study of Shaw et al. examined Crizotinib in positive rearrangements for ROS1 [55]. Moreover, the research work of Planchard et al. examined the two drugs Dabrafenib and Trametinib in BRAF mutation [56], and the study by Peters et al. examined Alectinib in ALK-positive NSCLC [57]. It was proved that a specific mutation of exon 20 of EGFR tyrosine kinase domain, known as T790M, causes acquired resistance of NSCLC patients in 50% to 60% of cases, especially in the first and second generation of tyrosine kinase inhibitors [58-61]. Other studies showed that this resistance spreads after 9 to 14 months from the start of treatment [62,63]. Contrary to the initial idea regarding the creation of this mutation by tumor cells during treatment, recent studies showed that T790M could be identified in a subgroup of NSCLC [64]. Therefore, it is hypothesized that the cells with this mutation remain after the first period of treatment and continue their activity. Thus, they may be responsible for the recurrence of the disease. In NSCLC patients with mutated EGFR, increased VEGF concentrations were observed via multiple mechanisms [65-68]. Over the past decade, there were several studies related to the combination of VEGF inhibitor and EGFR inhibitor. In the studies of Herbst et al. and Johnson et al., it was shown that the combined treatment of Bevacizumab plus Erlotinib improves patient survival compared to Erlotinib alone or Bevacizumab alone [69,70]. The clinical results of JO25567 trial showed an improved survival rate using these two drugs [71,72]. Several other studies showed similar results in the simultaneous use of EGFR and VEGF inhibitors [73-75]. The results of the above studies show the high efficiency of using two drugs, Erlotinib, and Bevacizumab. On the other hand, treatment with anti-EGFR monoclonal antibodies slows down the proliferation of tumor cells as a result of blocking this receptor. Anti-EGFR antibodies have been shown to improve the efficacy of other treatment methods in many investigations [76]. As a monoclonal antibody, cetuximab targets EGFR by blocking its ligands competitively [77,78]. In the studies of Gomes et al. and Iida et al., it was shown that the acquired resistance to cetuximab is related to the activation of the mTOR/PI3K/AKT signaling axis [79,80]. This axis is suppressed in treating EGFR tyrosine kinase inhibitors, especially Erlotinib. Considering the mechanism of activity and resistance of this drug and EGFR tyrosine kinase inhibitors, especially Erlotinib, it seems that using these two drugs in combination with each other can greatly help to prolong the resistance process of both drugs.

b. Monoclonal Antibodies (mAb)

Monoclonal Antibodies (mAb) are a special kind of antibody that bond to observed antigens. They attach to cell surfaces and activate the immune system. Their activities include blocking growth signals, preventing angiogenesis, and delivering radiation to cancer cells. The activity of mAbs leads to normalize growth rates and induces cancer cells' death via various mechanisms. Monoclonal antibodies are composed of two heavy and two light chains, which form three functional protein domains: two identical fragments for antigen binding (Fab regions) and one constant fragment (Fc region) [81]. Rituximab-abbs (CD20). Tafasitamab-cxix (CD19) and Isatuximab (CD38) are two examples of this group.

2.7 Immunotherapies

One immunotherapy approach is to block the activity of certain proteins that limit the strength of immune responses. Immunotherapy works by harnessing an anti-tumor immune response that is normally suppressed within the tumor microenvironment. CTLA-4 and PD-L1 are two pathways of the immune system that lead to tumor cell suppression. They are normal self-control mechanisms in the immune system which work to avoid autoimmunity and maintain tolerance to self-antigens. Tumor cells upregulate both inhibitory pathways to help evade the immune system [82,83]. Nivolumab and pembrolizumab are among the drugs in this group. Immunotherapy methods are mostly cell therapy, cancer vaccine, and monoclonal antibodies [84]. A phase 3 study conducted by Socinski et al., compared a quadruple combination regimen of bevacizumab, atezolizumab (anti-PD-L1), carboplatin, and paclitaxel chemotherapy with a triple regimen of this system without atezolizumab in non-squamous NSCLC. In the median PFS, the results showed improvements in the regimen with atezolizumab [85]. Figure 1 gives an overall view of different anti-cancer drugs' mechanisms of action.

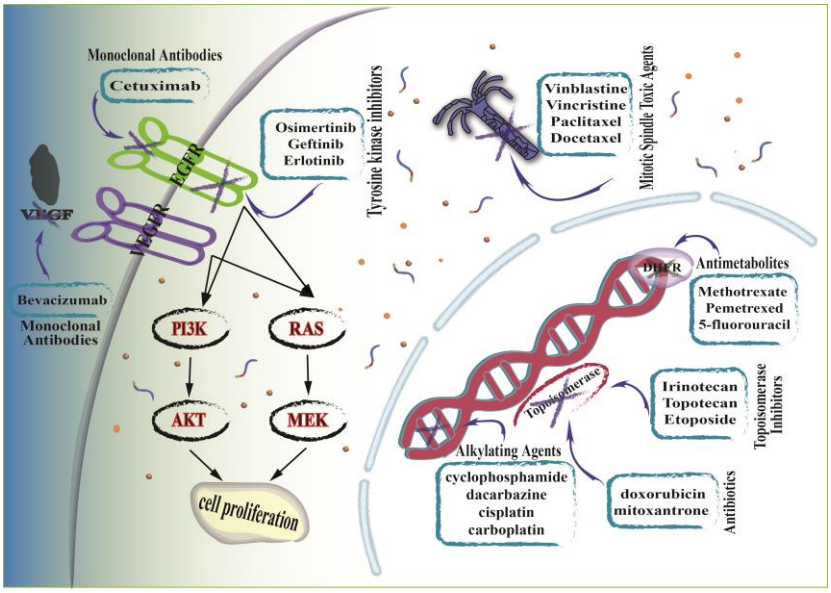

Figure 1. Schematic illustration of anticancer drugs mechanism of action

3. Potential nano drug delivery systems

3.1 Application of drug delivery systems in cancer therapy

Nanotechnology is a potential platform that innovates new approaches to discover novel applications of sciences such as molecular chemistry, pharmaceutical science, molecular science, and nutrition science.

Nowadays, nanotechnology has significant advances in cancer therapy, and it can be counted as a reliable method for cancer diagnosis and treatment.

One of the characteristics which make nano drug delivery unique for cancer treatment is providing a high surface-to-volume ratio. This feature can facilitate the absorption and transportation of small biomolecules, such as RNA, DNA, drugs, and proteins [86]. Nano-based drug delivery systems have more efficiency than traditional drug delivery systems. These systems are not only effective to boost the dugs' half-life, but also help to improve the solubility of hydrophobic drugs. Moreover, it allows for the controlled and targeted release of drugs in diseased sites [87]. The tumor targeting strategy appeared as an extraordinary method to access tumors. This method was divided into two categories, active and passive targeting. However, the process of active targeting occurs after passive accumulation in the tumor domain [88]. A passive targeting mechanism recommends the kind of transport in which nanoparticles can have paracellular transportation from compromised blood vessels [89]. Nanoparticles preferentially accumulate in neoplastic tissues [90], consequently, EPR in this kind of targeting will increase [91]. In fact, the main cause of this phenomenon is the speedy formation of hyper-permeable complicated tumor vasculature characterized by impaired lymphatic drainage of diseased tissue (tumor). It will be followed by the extravasation of 100 nm nanoparticles into the tumor microenvironment and stopping their clearance [92]. In addition to reaching tumors passively via EPR effect, the engineered nanocarriers can target particular tumor cells by binding to receptors that are over-expressed in cancer cells, such as transferrin (TR), folate (FA), epidermal growth factor, and nucleolin receptors. When these overexpressed receptors are targeted by anticancer agents in a cancer microenvironment, the absorption of the agents by cancer cells will increase [93]. Although a passive targeting mechanism facilitates the efficient localization of nanoparticles, their absorption by cancer cells still has not been increased. In this case, using active targeting can be an effective approach [94].

In contrast to passive targeting, active targeting was designed based on the interaction between the carrier's surface and overexpressed tumor cell receptors like

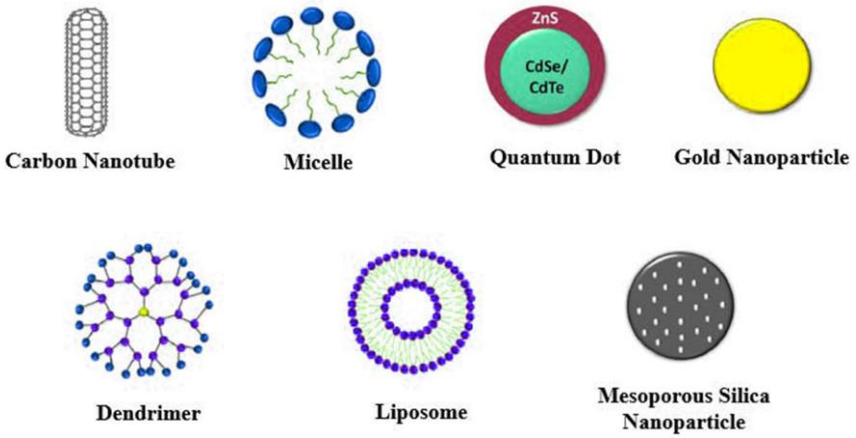

Figure 2. Various groups of nano drug delivery systems for cancer therapy [97]

antibodies and aptamers [95]. Cellular absorption of drug-containing nanoparticles and therapeutic efficacy will rise by active interaction between ligands and surface cell receptors [96]. If the nanoparticle binds to vascular endothelial cells via a non-internal epitope, high local concentrations of the drug will be available to the target cell [98]. However, this type of drug delivery is highly efficient but only some fractions of the released drug reach the target cell [99]. In most cases, nanoparticle internalization is important for the effective delivery of some anticancer drugs, especially in gene silencing and biotherapy [100]. So, it is necessary to find optimization methods for targeted therapy.

3.2 Popular drug delivery systems

There was a lot of research focused on drug delivery systems development for cancer therapy like liposomes, micelles, cyclodextrin (CD), mesoporous silica nanoparticle (MSNs), gold nanoparticles, dendrimers, carbon nanotubes, quantum dots, etc. [101-103]. Some group's schematics were shown in figure 2. This review will briefly discuss four groups of the most popular delivery systems, including liposomes, micelles, CDs, and mesoporous silica nanoparticles (MSNs).

3.2.1 Liposome

Liposomes are one of the most popular nanoparticles of the lipid family used for drug delivery systems. They are made to imitate the cell membrane and consist of phospholipids (Phosphatidylethanolamine, phosphatidylcholine from soybean, egg yolk, or lecithin), which are amphiphilic cholesterol to control fluidity, stearylamine (positively charged) and ordicetylphosphate (negatively charged) [104-106]. These phospholipids set up themselves by hydrophobic interactions. They shape bilayer membranes that include an inner aqueous compartment that allows for the incorporation of hydrophilic or lipophilic pharmaceuticals that may be placed in the hydrophilic section or on one of the sides of the bilayer membrane [107]. Some interesting properties of the liposome's structure include non-toxic nature, physical stability, high-vascular density, good maintenance time at the target site, and surface-changing ability by external stimuli [108]. Liposomes were classified based on their size, the number of layers, and how they are synthesized [109]. A liposome that is smaller than 100 nm can be classified as a single liposome vesicle (SUV), and if it is bigger than 100 nm it is known as unilamellar liposome vesicle (LUV) [110]. Targeted drug delivery strategies by liposomes include active and passive targeting, magnetic-responsive, thermo-responsive, and stimuli-responsive targeting which results in reducing the toxicity of soluble drugs [93]. Conventional liposomes known as C-liposomes are beneficial groups of liposomes that can get readily omitted from the blood by opsonins and the reticuloendothelial system. So, the encapsulated drug can be consequently released in plasma easily [111]. Smart or intelligent liposomes are the kind of liposomes that represent more efficiency for lung cancer therapy. They consist of bilayer phospholipids, surface modifiers, and some other covering molecules

[112]. This type of liposome enables target mitochondria and PH-sensitivity to prevent energy production in the cell and finally induce apoptosis. It also reduces the chance of MDR (Multi-drug resistance) in the cells [113]. The first FDA-approved liposome was the PEGylated liposomal doxorubicin or in short Doxil (in 1995). Doxil was used to treat some types of cancers, such as metastatic ovarian cancer and AIDS-related Kaposi's sarcoma [114]. In this structure of doxorubicin, a member of the anthracycline group is enclosed in a single-layered liposome. Meanwhile, the liposome is coated by PEG (Distearoyl-phosphatidyl-ethanolamine-PEG (DSPE-PEG) anchored into the phospholipid bilayers made of hydrogenated soy phosphatidylcholine and cholesterol) with a size of 80-90 nm [115]. This structure permits the drug to remain in the bloodstream for a longer period. Consequently, a larger amount of the drug reaches the target cell. Moreover, this product is designed to balance the efficacy and toxicity ratios of doxorubicin therapy [116]. Doxorubicin is loaded in liposomes by the ammonium ion gradient method. It is estimated that through intravenous injection each liposome can contain 10,000 to 15,000 DXR molecules with a lipid-in-drug ratio of 0.125 [117]. Another FDA-approved drug is a cytotoxic agent known as cisplatin (cis-diamino dichloro-platinum).

Some studies showed when cisplatin was encapsulated with liposome new products were produced in various clinical steps. They were named nanoplatin or OSI-211(clinical trial phase 1), SPI-77(clinical trial phase 2), and Lipusu (clinical trial phase 4). The last compound has been approved by the European medicine agency and now it has been tested as the first line against NSCLC [115,118,119]. Lipoplatin's average diameter is 110 nm, and the cisplatin is encapsulated in a liposome shell consisting of soy phosphatidyl choline dipalmitoyl phosphatidyl glycerol, cholesterol, and methoxy-polyethylene glycol-distearoyl phosphatidylethanolamine lipid conjugate. In this structure, the cisplatin's ratio to lipid is 8.9%: 91.1%(w/w) [120]. Lipoplatin works as a topoisomerase I inhibitor with very low hematological and digestive toxicity. Unlike cisplatin, lipoplatin did not show any nephrotoxicity or neurotoxicity [121]. Liposomal Paclitaxel or LEP-ETU with an average particle size of 150 nm which is in phase 2 of the clinical trial is considered one of the useful nanoparticles in NSCLC therapy. LEP-ETU is synthesized by a modified thin film hydration method. In this method, hydrophobic excipients, such as lipids (phosphatidylcholine, cholesterol, and cardiolipin), paclitaxel, and TAS, are dissolved in ethanol and transferred to a round bottom flask. The development of paclitaxel utilizing a novel liposomal formulation demonstrated that ideal physical and chemical properties are possible. The basic results from clinical trials phase 1 and 2 have proved that LEP-ETU is administered easily without any pre-medication. Therefore, the patient can tolerate up to a dose of 325 mg with minimal side effects [122]. One of the newest methods to treat lung cancer via inhalation is bacteriotherapy, where paclitaxel is placed in a liposome and the liposome is located inside the bacteria (E. coli or L. casei). This compound was called the LPB complex. LPB's test is still in the in vivo stage, however, this drug has succeeded significantly to inhibit the proliferation of type A549 cancer cells via the induction of apoptosis [123].

Liposomal vaccines were studied for cancer treating. Stimuvax is a liposomal vaccine with BLP25 lipopeptide to target MUC1 tumor-associate antigen. BLP25 composition is monophosphoryl lipid A, cholesterol, DMPG, and DPPC. It showed a 31% rate of 3-year survival in non-small-cell lung carcinoma in phase 3 of the clinical trial. Furthermore, no significant toxicity was observed in the cancer treatment using this drug [124]. Liposomes can be functionalized with different components like aptamers which are single synthetic strands and short chains produced from DNA or RNA [125]. The docetaxel liposome surface modified by CD133 aptamer showed a significant anti-tumor activity for lung cancer targeting in mice models and in vivo conditions [126]. The liposomes were encapsulated by functionalized triptolideencapsulated which are anti-CA IX (conjugation of anti-CA-IX with DSPEPEG-Mal micelles and postinsertion with preformed liposomes). They showed high efficacy against lung cancer. In fact, after only eight treatment doses, it had the strongest anti-tumor effects. Furthermore, treated mice lived twice as long as the control group with an average survival time of up to 90 days [127]. Tables 1 and 2 illustrate various drug delivery systems based on liposomes used for cancer therapy.

3.2.2 Micelles

Micelles are self-assembled microstructures that are formed by surfactants in an aqueous medium. Their size ranges from less than 50 nm to more than 100 nm. This flexibility in size (especially when they are smaller than 50 nm), counts as one of their unique features [128]. Polymeric micelles are described as auto-assemblies in liquid shape. They are composed of amphiphilic macromolecules, in generic amphiphilic di- or tri-block copolymers fabricated from solvophobic and solvophilic blocks. Micelles can be widely used as physiological transport systems for hydrophobic drugs with low molecular mass, genes, and proteins [129]. Because micelles are often manufactured for injection in normal blood and the physiological milieu of the body, one of their weaknesses as drug carriers is their very poor stability when they are exposed to environmental changes. If the concentration of the environment in which the micelle floats is lower than the critical micelle forming concentration (CMC), it will lead to the phenomenon of explosive release of the drug before reaching the desired environment [130]. The early release of the drug can affect the duration of stability in the blood circulation and the high drug loading at the site on which our nanocarrier is designed. So, the result of treatment, in this case, will be completely similar to unprotected drugs. Micellar drug Taxotere is one of these kinds of micelles that quickly leave the bloodstream after intravenous injection [131]. Despite the mentioned weakness, the positive feature of micelles, i.e. flexibility in size, cannot be ignored. Strategies, such as covalent crosslinking were implemented to increase the stability of micelles. This method includes shell-crosslinked micelles and core-crosslinked micelles [132]. Docetaxel (DTX) like paclitaxel (PTX) was approved by FDA for clinical application and it is widely prescribed to treat lung cancer. One of the noteworthy nanoparticles that can load PTX or DTX well is composed of polyethylene glycol (PEG) and cholic acid (CA)-based micellar

Table 1. Liposomal nanodrugs in the clinical trial

TRADE NAME	CARRIER TYPE	INDICATION(S)	DEVELOPMENT STAGE
ONCO-TCS	Liposomal Vincristine	Non-Hodgkin Lymphoma	Phase I, II [133]
LEP-ETU	Liposomal Paclitaxel	Ovarian cancer Breast cancer Lung cancer	Phase I, II [134]
AROPLATIN	Liposomal Cisplatin analog	Colorectal cancer	Phase I, II [135]
SPI-77	Stealth Liposomal Cisplatin	Lung cancer	Phase III [136]
NAREKT -102	Irinotecan, PEGylated liposome	Breast cancer Colorectal cancer	Phase III [137]

Table 2. Liposomal nanodrugs in in-vitro/vivo experiments

DRUG TYPE	CARRIER	INDICATIONS	STUDY STAGE
DOXORUBICIN	Liposome	Colorectal cancer	In-vitro In-vivo [138]
OLEUROPEIN	PEGylated liposome	Prostate cancer	In-vitro In-vivo [139]
CURCUMIN	Liposome	Liver cancer	In-vitro [140]
DNA PLASMID TUMOR PEPTIDES	Liposome-DNA	Gastric cancer	In-vitro [141]
DOXORUBICIN	Peptide-ligand Liposome	Lung cancer	In-vitro In-vivo [142]
TRIPTOLIDE	PEG-Mal micelles & postinsertion with preformed liposomes	Lung cancer	In-vitro [127]
PACLITAXEL & RAPAMYCIN	Liposome	Breast cancer	In-vitro [143]

system (PEG5K-CA8 telodendrimer (TD)). The CA-based micellar system has a great potential to carry hydrophobic drugs, such as DTX and PTX. It showed a high half-life in the bloodstream in in vivo environment as well [144]. One of the compounds that had a prominent inhibitory effect on CD 133+ lung cancer stem cells (CSCs) in in vivo environment and succeeded to inhibit tumor growth in the body was an amphiphilic prodrug (cisplatin-poly (ethylene glycol) - block-polycaprolactone). It was shown that this prodrug formed micellar nanoparticles NPPt (IV) [145].

Another common type of micelles used to transport the paclitaxel is Cremophor-Free (Genexol-PM), which is polymeric micelle-formulated paclitaxel, and its recommended dosage is 300mg/m^2. This nanocarrier successfully passed the first phase of the clinical trial and is in the second phase. The current result of these studies showed that the toxicity of paclitaxel is greatly reduced when transferred by micelle carriers [146]. Another type of micelles in which docetaxel (DTX) is loaded is polymeric mixed micelles that consist of Pluronic P105 and F127 copolymers. This compound was synthesized by thin-layer hydration method. In vivo pharmacokinetic study showed that this type of drug delivery inhibition rate of lung tumors is 69.05%. So, it seems that DTX-loaded P105/F127 mixed micelles can act as a potential system with relatively strong antitumor effects against multidrug resistance in lung cancer [147]. Estrasorb™ or micellar formulation of estradiol is the only FDA-approved micelle used for topical treatment of moderate to severe vasomotor symptoms of menopause. So far, apart from this composition, no other micellar composition was approved by FDA, and the rest are in various phases of clinical trials and/or in vitro/vivo phases [148]. Table 3 shows the list of popular FDA-Approved liposome and micelle-based nanodrugs used for different diseases.

Table 3. FDA-approved liposomal and micellar nanomedicines

pRODUCT NAME	TYPE (ACTIVE INGRIDIENT)	INDICATION(S)	APPROVED DATE
daunoxome	Liposome encapsulated Daunorubicin	HIV-related Kaposi sarcoma	1996 [149]
depocyt	Liposomal Cytarabine	Lymphomatous meningitis	1999 [150]
Myocet	Liposome encapsulated Doxorubicin	Breast cancer	2000 [151]
DOXIL	PEGylated Liposome	AIDs-related Kaposi's sarcoma Multiple myeloma Ovarian and breast cancer	1995 [152]
Marqibo	Liposomal Vincristine	Acute Lymphoblastic Leukemia	2012 [153]
ONIVYDE	PEGylated Liposomal Irinotecan	Metastatic pancreatic cancer	2015 [154]
VYXEOS	Liposomal Daunorubicin and Cytarabine	Acute myeloid leukemia	2017 [155]
AmBisome	Liposomal Amphotericin B	Fungal/protozoal infections	1997 [156]
DepoDur	Liposomal Verteporfin	Macular degeneration histoplasmosis	2000 [157]
Abelcet	Liposomal Amphotericin B lipid Complex	Fungal infections	1995 [158]
Curosurf	Liposome-proteins SP-B And SP-C	pulmonary surfactant for Respiratory Distress Syndrome	1999 [159]
Genexol-PM	Paclitaxel-loaded polymeric micelle	Breast cancer small cell lung cancer	Marketed in Europe & Korea (It is not FDA-Approved) [160]

3.2.3 Cyclodextrin (CD)

Cyclodextrin is a cyclic oligosaccharide formed by linking six or more glucose subunits through α- 1, 4 glycosidic bonds. The enzymatic hydrolysis of starch produces these CD. Each CD has external hydrophilic and internal hydrophobic properties. This special structure made CDs widely effective in cancer treatment, nano drug delivery systems, gene therapy, and immunotherapy approaches [161]. They are divided into three categories based on the number of glucose subunits, which are named α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD), respectively [162]. CRLX101 is a CD-based camptothecin nanoparticle with Olaparib which is in the stage of clinical trial phase 1 on lung cancer patients. However, the exact results of their tests are not fully known yet [163]. Topotecan Hydrochloride or CD-based Polymer- Camptothecin CRLX101 is another CD derivative that was tested in the clinical trial for lung cancer treatment. However, this system was stopped in phase 2 due to a lack of drug delivery ability [164].

3.2.4 Mesoporous Silica Nanoparticle (MSN)

Silica-based materials are considered safe by the FDA, and subsequently, it has made silica-based nanoparticles one of the suitable groups of candidates for targeted drug delivery in cancer therapy [165]. MSNs are particles with uniform and adjustable pore size and high pore volume surfaces, as well as the potential for large-scale production. These features all increase the efficiency of drug encapsulation significantly [166].

There is a lot of flexibility in drug delivery system design using MSNs. For example, so far PH/redox-responsive MSNs were designed to release chemotherapy drugs. Heat and ultrasound-responsive MSNs were studied. MRP-1 siRNA and myricetin can be loaded in MSN nanoparticles and also can be modified with folic acid to target lung cancer cells. In vivo tests showed that Myr-MRP-1/MSN-FA dramatically reduced the volume of lung tumors in the treated mice [167]. Although there are no FDA-Approved drug delivery systems based on MSNs for lung cancer treatment, research in this scope still is under process.

4. Social and economic effect of cancer treatment strategies

Cancer, as one of the main causes of death and disease in the world, not only causes great losses to the health of patients and survivors, but also imposes a heavy financial impact on societies [168]. In 2018, 9.6 million people died of various types of cancer worldwide. WHO estimates that 1 in 6 deaths globally is due to cancer, with approximately 70% of cancer deaths occurring in low- and middle-income countries, adjusted for income [169]. Cancer patients in the United States paid $5.6 billion out of pocket for cancer treatments in 2018 [168,169]. The national patient economic burden related to cancer care which was reported in 2019 in the United States, was $21.09 billion, consisting of patient-paid costs, $16.22 billion, and patient-time value costs, $4.87 billion [168].

The economic burden of cancer is significant in all countries, reflecting costs for patients and countries' healthcare systems, as well as lost productivity in terms of morbidity and premature death from cancer[170]. According to a report published in October 2021 in the Journal of National Cancer Institute (JNCI), across all cancer sites, average annual net out-of-pocket costs for medical services in early stage and end-of-life care for patients initially diagnosed with the localized disease were less compared to the disease in more advanced stages. Moreover, according to this analysis, the overall costs of cancer care and lost productivity in the United States were far greater than those borne directly by patients [168].

Although economic data are available in some countries, the global economic burden of cancer is still unknown. In the United States in 2017, cancer healthcare costs were estimated at $161.2 billion. Productivity loss in terms of tolls was US$30.3 billion, and premature mortality, was $150.7 billion; the economic burden of cancer in the United States was approximately 1.8% of the gross domestic product (GDP). In European Union, health care costs were 57.3 billion euros, and productivity losses in terms of complications and premature death were 10.6 billion euros and 47.9 billion euros, respectively, which increased to 141.8 billion euros with informal care costs, which is equivalent to 1.07% of the gross domestic product. The economic burden of lost

productivity due to complications and premature death from cancer accounts for nearly 60% of the total cancer-related economic burden in EU countries [170].

4.1. Ways to reduce the cost of cancer

As cancer treatment costs rise, prevention, screening, and early detection efforts have the potential to save money [170]. In 2019, national costs were highest for "cancers" of the breast ($3.14 billion), prostate ($2.26 billion), colorectal ($1.46 billion), and lung ($1.35 billion) which indicates a higher prevalence of these cancers [168]. In many cases, people use less cancer screening and may pay more for their cancer care. Therefore, prevention is the key to reducing payment costs, and access to the right screening tests at the right time is an effective step in this direction [168].

Economic analysis can be useful in minimizing costs and informing resource allocation decisions and investments in cancer control programs, including prevention, early detection, treatment, survival, and end-of-life care [168,170]. Approximately $183 billion was spent in the United States on cancer-related health care in 2015, and this amount is projected to increase to $246 billion by 2030. The reason for this 34% increase is aging and population growth [168,171].

Not all cancer patients experience these expenses and sufferings in the same manner, but some circumstances increase the likelihood that the patient may have financial difficulties. The numerous cancer types, the incidence of the illness, the patterns and length of therapy, and the cost of various forms of care for distinct cancer locations are all shown via cost difference analysis [168].

The most common cancers in terms of frequency and number of deaths are lung, breast, and colon [169]. Total U.S. national spending in 2019 for medical services and oral prescription drug spending was highest for the most common cancer sites. This figure was reported for women's breast cancer ($26 billion), colorectal ($21 billion), and lung ($20 billion) [171]. Overall, national prescription drug costs are highest for women's breast ($2.7 billion), leukemia ($2.4 billion), lung ($1.4 billion), and prostate ($1.3 billion) cancers [171].

4.1.1 Lung cancer / costs / smoking

Lung cancer is the leading cause of cancer deaths in the world. Gender differences in the incidence and mortality rates for different types of lung cancer were identified. So, new research incorporating this variable will potentially lead to the development of new therapies to treat this devastating disease [172]. Estimated rates of lung cancer in the United States for 2021 suggest that of the 235,760 new cases, 119,100 will be in men and 116,660 in women which causes the death of 69,410 men and 62,470 women with lung cancer every year [172].

Respiratory diseases impose a heavy burden on society in terms of disability and premature mortality, as well as direct costs of health services, prescription drugs, and indirect costs related to lost productivity [168].

A study estimated these costs in 28 current EU member states using WHO and European data collections. According to the reports, the total cost of respiratory diseases in 28 EU countries alone is more than 380 billion euros annually, of which at least 55 billion euros are spent on direct costs of primary health care and hospitals. Among them, the average direct costs due to asthma are 33.9 billion euros, and for each case of tuberculosis, it is about 7,500 euros. As for multi-drug resistant diseases (MDR-TB), this cost is 33,000 euros, and for highly drug-resistant diseases it rises to 47,500 euros [168].

In a study conducted in China in 2015, the total estimated smoking-attributable expenditure (SAE) for lung cancer was predicted at 5249 million dollars which is equivalent to 0.05% of the gross domestic product (GDP) of this country, of which 36.9% is related to direct costs and 63.1% is related to indirect costs. According to the results, it was evaluated that if there is a 20% reduction in smoking, the total SAE will decrease to 4.9% by 2030 [173].

Almost half of the economic burden of respiratory diseases is related to smoking [168,173]. Smoking is the number one risk factor for lung cancer as well as for other cancers [169,170]. The global cost of tobacco use is nearly $2.05 trillion annually, which is roughly 2% of global economic output [170]. On average, 14.4% of men and 11.7% of women are daily tobacco users, so the lifetime risk of developing lung cancer disease is about 1 in 15 for men and 1 in 17 for women [172].

4.2. Pharmacoeconomics

Pharmacoeconomics is a discipline that evaluates the relationship among clinical, economic, and human outcomes to determine products and services that maximize value for every dollar spent [174]. This knowledge is considered to be a branch of health economics that identifies, measures, and compares the costs and consequences of drug therapy for healthcare systems and society, in addition to provide fundamental guidance on resource management [175-177]. The United States of America is currently moving in this direction, and the FDA is considering conducting studies in the field of pharmacoeconomics in addition to the standard studies on the safety and effectiveness of drugs as the importance of this approach in oncology is seen when policymakers use research findings to make practical decisions [174].

From the pharmacoeconomic point of view, developing new pharmaceutical materials and products, such as nanosystems, and their introduction to pharmaceutical market can be far more economically effective. In particular, the potential for side effects reduction plays an important role in treatments with new nano-based systems that lead to reduced medical procedures, and personnel costs, and allow patients to return to professional life by increasing the chance of recovery [178,179]. Regarding limited financial resources, health economics and pharmacoeconomics are becoming widely used criteria for decision-making in modern health care policies. Moreover, research in this area is evolving to meet the needs of the individual patient and decision-makers in a payer group, healthcare system, or community [174,180,181]. Therefore, the study of new therapeutic options, such as nanocarrier-based drug delivery systems characterized by high efficacy with limited side effects, remains a highly desirable goal [182].

4.3. Nanocarriers / benefits / costs

While surgery, radiation therapy, and drug therapy are the three most widely-used ways to treat cancer, the rising cost of drug treatment for cancer patients brought heavy healthcare costs in the United States to continue to rise faster than the consumer price index [168,174]. The National Cancer Institute (NCI) of America conducts its programs to reduce cancer prevalence and improve cancer patients' lives through research in the field of developing new interventions, including new methods of drug delivery. Novel nano-based systems can be therapeutic agents themselves or be served as a vehicle to carry various active pharmaceutical agents to specific parts of the body .The promising development of nanomedicines leads to improving therapeutic efficacy, reducing the effective therapeutic dose, and reducing the side effect risks. These advantages make nanotechnology much more economical than conventional treatments because it can be reflected in the pharmacoeconomic aspect as a reduction of costs related to medicine (disease, medical equipment, treatment monitoring) and non-medical methods [169].

The effectiveness of selected drugs in terms of their equivalents in nanocarriers can affect the reduction or minimization of costs in pharmacoeconomic analysis, especially to shorten the hospitalization time or reduce the number of tests performed. For instance, reducing the days of hospitalization of a patient leads to a decline in the infection risks and side effects of drugs, and improves the quality of treatment, by which finally the efficiency of bed management and hospital profits increase [183].

All advantages presented in the application of nanocarriers, which make nanotechnology-based therapies much cheaper than conventional treatment methods, can be reflected in the expected medicinal efficacy. This can cause an outstanding cost reduction in cancer patient management. In other words, the effective treatment allows patients to return to their professional life [169]. Up to now, 224 nanocarriers, such as DDS are designed to reduce the cost of drug administration, improve compliance, and help patients recover as quickly as possible [169]. Hence, among various nanocarriers, the lipid category has received the most FDA approval which indicates the high potential of this category for industrialization.

All these aspects are reflected in pharmacoeconomics to provide reliable information about the cost of treatment and choose the best treatment methodology based on its effectiveness at the lowest possible cost [169]. This branch of science can be certainly justified in decision-making processes while evaluating the cost-effectiveness and availability of the right nanomedicine for the patient at the right time, comparing alternative drugs from the same therapeutic class or similar drugs with a similar mechanism of action [169].

Using pharmaceutical nanocarriers is a unique opportunity to improve the economic attractiveness of known drugs since the development of new nanoformulations, especially using the nanocarriers based on lipids, micelles, and cyclodextrins are much cheaper and faster than the discovery of new drugs.

In general, in recent years, the increase in health care costs has been a worrying issue for most developed and even developing countries. To maximize economic returns, it is critical that governments gain a deeper understanding of the cost-effectiveness of nanomedicines. The first step in developing this market in the modern era of cancer research is a standardized cost-effectiveness study that demonstrates whether the benefits of nano drugs can be worth the extra cost compared to standard formulations [184,185].

5. Conclusion

Cancer, as a lethal threat to people's health, has been always an international issue. Lung cancer, in particular, is a serious problem with high mortality and morbidity among malignant tumors. It imposed a heavy burden of cost, either economic or social aspects on governments. Different methodologies were used to find a cure or at least an effective treatment to solve this challenging issue. In summary, valuable results of different research showed that nano drug delivery systems can improve the efficacies of chemotherapy for cancer therapeutic approaches and reduce the severe side effects. Moreover, considering the pharmacoeconomic aspect, taking advantage of nanocarriers for cancer therapy could reduce hospitalization time and cost. Although some drawbacks like drug leakage, drug resistance, instability, and inappropriate accumulation, still remained in nano-based drug delivery systems, recent studies presented the great potential of using nanocarriers with some modifications for cancer therapy. Lipids achieved the highest attention among various types of nano-based carriers for cancer treatment, and some of them succeeded to be known as FDA-Approved compounds. However, more efforts need to be accomplished and various complementary pieces of research need to be done to enhance the application and effectiveness of these nanocarriers. Targeted smart nano drug delivery systems need to be constructed in a way that results in having enough stability and acceptance in the industrial aspect as well to be used on a large scale.

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