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Review Article

Cancer Nanomedicine: A New Era of Successful Targeted Therapy

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Cancer is considered as one of the most challenging health care problems. Though there are many approved drugs that can be used for cancer therapy, drug resistance and delivery are among of the barriers of the treatment. In addition, pathological characteristics of tumors and their abnormal blood vessel architecture and function also reduce the efficiency of the conventional cancer treatment. Therefore, looking for techniques that can increase the efficacy of the therapy such as nanoparticles (NPs) is vital. NPs have many properties such as their small size, ability to load various drugs and large surface area, and ability to increase the absorption of conjugated. Therefore, the NPs have been considered as excellent tumor-targeting vehicles. The recent nanoscale vehicles include liposomes, polymeric nanoparticles, magnetic nanoparticles, dendrimers, and nanoshells; lipid-based NPs have been used as conjugates. There are few examples of approved conjugated anticancer NPs including AmBisome® (amphotericin B liposomal) and Doxil® (liposomal doxorubicin). There are many other conjugated anticancer drugs at different stages of clinical trials for treatment of various cancers. This review will discuss the properties of different NPs in cancer treatment and their benefits of overcoming multidrug resistance. In addition, recent advances of using nanomedicine in different approaches of cancer treatment such as chemotherapy, radiotherapy, and immunotherapy will be highlighted in this review.

1. Introduction

There are several therapeutic methods that have been used to treat tumors and their surrounding environments. An example of these strategies is chemotherapy, which was first tried in 1942 when Louis Goodman and his colleagues tested using nitrogen mustard in treatment of non-Hodgkin's lymphoma. After that, many chemotherapeutic drugs have been used to eradicate cancer progression [1]. Nowadays, there are many examples of chemotherapeutic agents that have been used to control different cancers in clinic such as doxorubicin, paclitaxel, gemcitabine, and cisplatin [1]. However, chemotherapy has helped in the improvement of cancer therapy of patients; in most cases, cancer with a more progressive stage normally occurs, and usually, multidrug resistance takes place. Targeting the surrounding environment of tumors also has been tried, since cancer cells depend primarily on oxygen and angiogenesis for survival and metastasis [2]. Radiotherapy is another example of a method for eradicating cancer cells, since cancer cell is more susceptible for damaging compared to normal cells [3]. Gene therapy and immunotherapy have been also used for cancer therapy [4, 5]. However, most of them are associated with side effects, resistance, or recurrence after initial treatment [6].

The failure of chemotherapy in the clinic is mainly due to different extents of multidrug resistance (MDR) results with approximately 90% of cancer patients died [7]. MDR occurs when tumor cells develop resistance to structurally and functionally unrelated classes of chemotherapeutic agents leading to drug inactivation and/or drug efflux from cancer cells leading to obstacle of the treatment [8]. There are several report hypotheses of the molecular mechanisms of MDR, mainly including increasing efflux of membrane transport proteins, detoxification by reducing the drug activation and potentiating drug metabolism, alteration in drug targeting by enhancing the DNA repair mechanism, blocking apoptosis, and alteration of cell cycle regulation

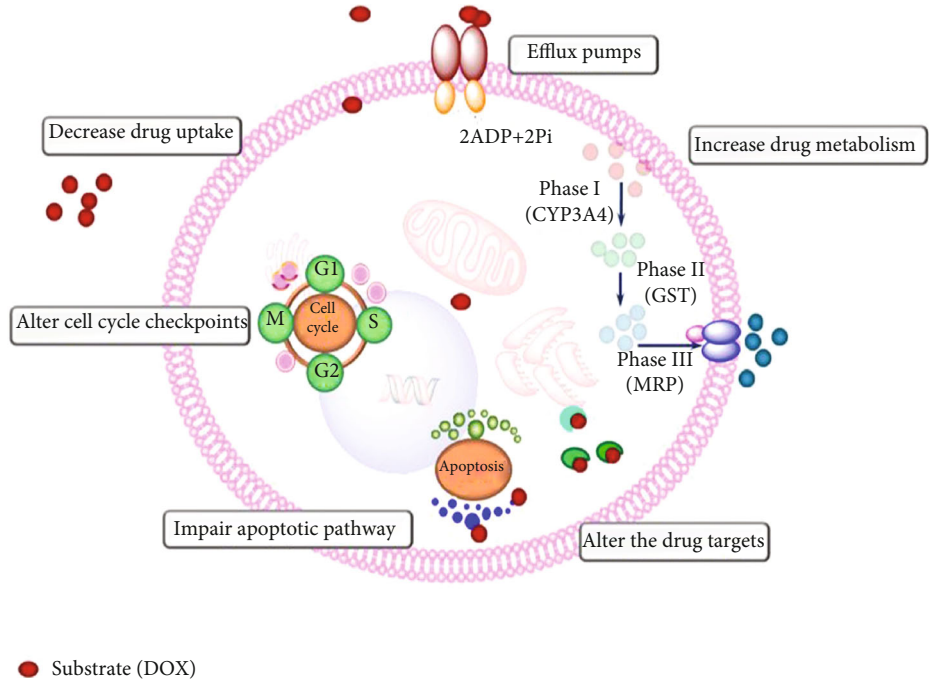

Figure 1: Molecular mechanisms of multidrug resistance in cancer.

(Figure 1) [9]. All these mechanisms synergistically interact together to produce MDR. The modulation of membrane transport protein is one of the most effective mechanisms of resistance against the commonly used anticancer drugs. There are two approaches to decrease the intracellular accumulation of cytotoxic agents inside cancer cells either by reducing drug uptake and/or increasing extrusion of the chemotherapeutic molecules. Both mechanisms are mediated by ATP-binding cassette (ABC) proteins and transmembrane transporters [10]. Overexpression of P-glycoprotein (P-gp, MDR1, or ABCB1) which is the most common member of ABC proteins is responsible for the development of MDR. P-gp is consisting of two homologous halves, each containing six transmembrane domains (TMD) and a nucleotide-binding domain (NBD) [10].

The common substrates of the P-gp transporter are including epipodophyllotoxins, *Vinca* alkaloids, taxanes, and anthracyclines that are currently involved in chemotherapeutic regimens [11]. Several approaches have been investigated to overcome the efflux pump either by inhibition of the function of P-gp using natural agents that act as P-gp inhibitors or by downregulation of MDR-1 gene expression [12, 13]. These approaches subsequently reverse MDR and inhibit the P-gp function, thus enhancing the therapeutic efficacy [14]. NP scan overcome all these mechanisms of MDR [15, 16].

Therefore, it is rational to find out a combination therapy with more precise technique to maximize the efficacy of the therapy and to overcome multidrug resistance in cancers. NP conjugation with chemotherapeutic drugs or using NPs during radiotherapy of cancer showed some promising outcome, with many of them approved for treatment of different cancer types [17]. The formulations of chemotherapeutical agents into nanoparticle have several advantages over the standard chemotherapy dosage form. The bioavailability of a low molecular weight drug is increased by its formulation in nanoparticle, whereas nanosized drug carrier minimizes their elimination through the liver and/or kidney [18]. The permeability and accumulation of chemotherapeutical nanoparticle are passively targeting the tumor tissue resulting in low systemic toxicity and increased drug concentration inside more than the treatment with standard chemotherapy [19]. This review will discuss the update of the use of NPs to overcome the resistance of cancer treatment.

2. Cancer Targeting with Conjugated Nanoparticles

NPs have been used to produce one or more of the followings actions. They prevent the degradation of the conjugated drug. They also improve its absorption through the epithelial diffusion that ultimately results in reaching the optimum concentration in a short time. NPs also alter the pharmacokinetic and distribution profile of the drug in the tissue and increase the intracellular efflux in cancer cells [20]. NPs are designed as active and passive targeting of anticancer drugs to deliver and elevate the intracellular anticancer concentration. Enhancing the permeability and retention effects of anticancer drugs is considered as passive targeting of NPs to the tumors. However, actively targeted NPs can be designed based on tumor microenvironment- and ligand-directed targeting to the tumor cells [21]. Therefore, as a unique inherent property of NPs to the solid tumors, the nanoparticle is considered as an excellent tumor-targeting vehicle. This effect makes the accumulation of NPs preferable

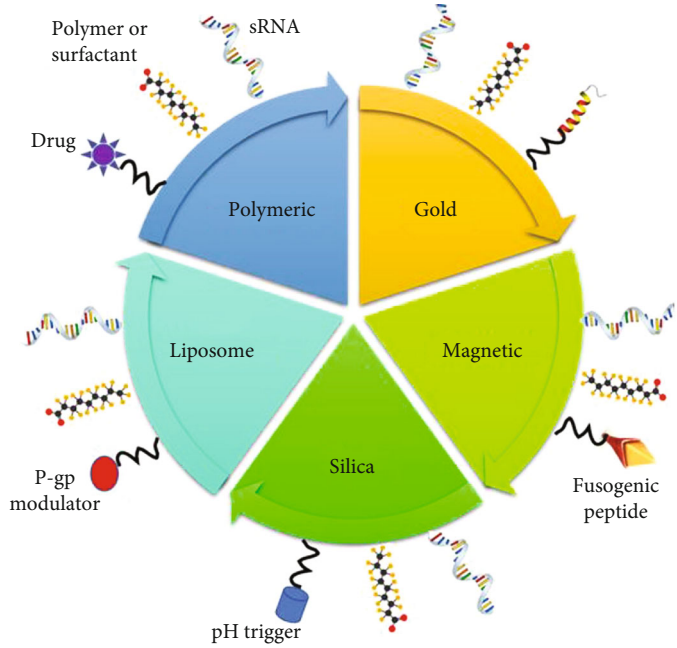

Figure 2: Common drug targeting technology.

at the tumor site. In addition, the multifunction of NPs allows targeting the tumor site that is directly connected to the main blood circulation [22]. This action considered as a major advantage of NPs against MDR mechanisms. There are several types of NPs which include lipid (NPs) and nanocapsules, polymeric (NPs), metal (NPs), dendrimers, and liposomes that will be discussed in detail in this review (Figure 2) [23].

3. Can Be the Barriers for the Treatment of Tumors Overcome by Nanoparticles?

At the cellular level, the drug resistance is considered as a physiological barrier to the success of the anticancer drug. The penetration of chemotherapy to the solid tumor is difficult due to the pathological characteristics of the solid tumors that include abnormal blood vessel architecture and function, interstitial hypertension, lack of lymphatics, and dilated angiogenesis [24].

This microenvironment to certain extent contributes to the drug resistance results in decreasing in the drug accumulation and/or penetration to the solid tumor [25, 26]. Nevertheless, chemotherapy encounters another major barrier, i.e., multidrug resistance even after its penetration to the tumors. MDR remains the main challenge towards conventional chemotherapy during treatment of the common tumors [26].

Pharmaceutical history of the development of nanoparticle started with the first discovery of liposome [27]. Particle size is the most important properties of NPs that allows the NPs to be safely dosed via intravenous administration and to be the main choice of therapeutical approaches; this ultimately allows increasing the specificity of effective drugs and overcoming the resistance of tumors [28].

The therapeutic index of NPs has improved the potential of commonly used drugs through increasing the efficacy and decreasing the toxicity of the drug and keeping its concentration in the steady state over a long period of time [29]. Thus, drug-coated NPs should have long half-life to give the maximum effect. NPs increase the chemical's solubility and stability to provide new effective drugs. The targeting of active sites of transporters or receptors is the main character of NPs because of their flexible surface chemistry that allows for potential conjugation of targeting ligands. Figure 3 shows the several mechanisms of NPs to improve drug delivery to the solid tumors [30]. On the other hand, several anticancer agents exhibit low specificity towards cancer cells. Hence, the adverse outcomes of chemotherapeutic agents diminish the effective dose to the tumor resulting in subtherapeutic to the toxic effects [31]. Therefore, the delivery of drugs to the solid tumors is still a difficult approach. The reticuloendothelial system (RES) that known as "mononuclear phagocytes" is the major defense system in the bloodstream of the body that rapidly removes NPs from the blood [32].

Therefore, it has been considered as a main obstacle for the circulated nanoparticles. RES recognizes the NPs as foreign bodies. Hydrophilic and flexible polymers can coat the NPs from the opsonins hence avoid the uptake of NPs by the RES [33]. Poly(ethylene oxide) and poly(propylene oxide) or their combinations are the most commonly used polymers that covalently grafted, entrapped, and adsorbed on the surface of nanoparticles. The degree of block binding of NPs to opsonins is variable depending on the thickness of the layer that coats the nanoparticles, coating strategies, polyethylene glycol PEG molecular weight, surface chain density, and conformation [34]. The development of lipid-based nanoparticle systems of anticancer drugs has advantages including the improved drug delivery, low toxicity, enhanced

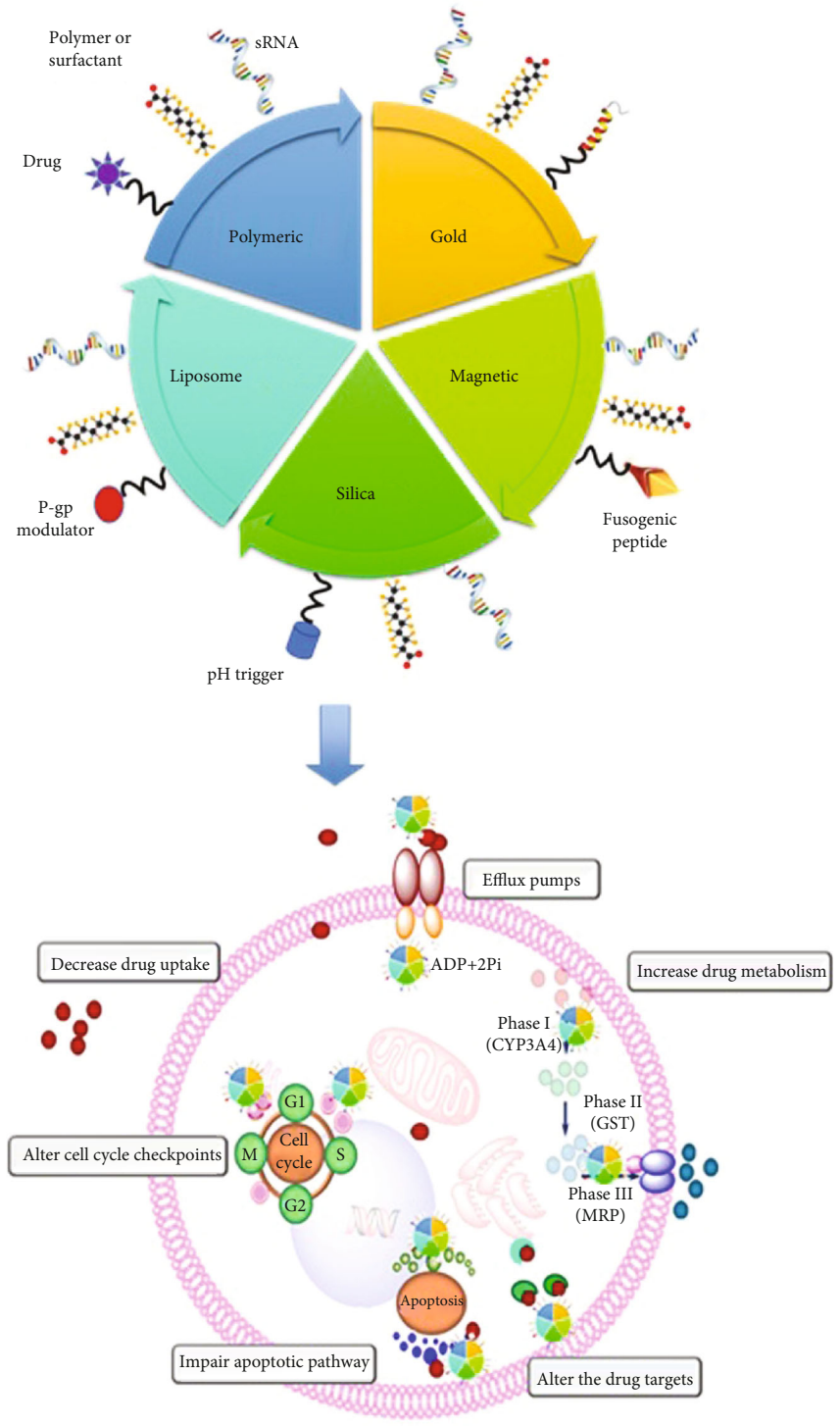

Figure 3: Nanotechnology against multidrug resistance.

solubility, increased loading and protection of drugs, prolonged circulation, targeting delivery, and controlled release [35]. Liposomes, micelles, nanoemulsions, nanocapsules, and solid lipid NPs are common types of lipid-based NPs that are administered by different routes, e.g., oral, topical, and parenteral [23]. NPs such as liposomes, polymeric, magnetic, silica, and gold NPs used to prepare MDR inhibitors through increasing drug efflux altered metabolism, activating DNA repair and changing apoptotic pathways (Figure 3).

4. Overcoming MDR Using NPs and the Possible Mechanisms

Several approaches attempting to overcome drug resistance have been developed including NPs (Figure 3). Some of the

Table 1: The formulated NPs of chemotherapy.

Nanoparticle	Medicinal ingredients	Generic name	Cancer type	Reference
Liposome NP	Doxorubicin	Doxil	Kaposi sarcoma, ovarian cancer, and multiple myeloma	[36]
	Doxorubicin	Myocet	Metastatic breast cancer	[36]
	Doxorubicin	MM-302	HER-2-positive breast cancer	[37]
	Doxorubicin	Anti-EGR liposome	Many solid cancers	[38]
	Doxorubicin	ThermoDox	Hepatocellular carcinoma	[39]
	Vincristine sulfate	Marqibo	Acute lymphoblastic leukemia	[36]
	Irinotecan	MM-398	Metastatic pancreatic cancer	[40]
	Irinotecan	CPX-1	Advanced colorectal cancer	[41]
	Paclitaxel	EndoTAG-1	Pancreatic cancer, liver metastases, and HER2-negative breast cancer	[42, 43]
	Cisplatin	Lipoplatin	Non-small-cell lung cancer	[44]
	siRNA against EPHA2	siRNA-EPHA2-DOPC	Late-stage cancers	[45]
	siRNA against PLK1	TKM-080301	Late-stage hepatocellular carcinoma	[46]
	MUC1 antigen	Tecemotide	Non-small-cell lung cancer	[47]
	HER2 antigen	dHER2+AS15	Breast cancer	
	Multicancer-associated antigens	DPX-0907	Ovarian, breast, and prostate cancers	[48]
	Melanoma antigens	Lipovaxin-MM	Malignant melanoma	[49]
Albumin NP	Paclitaxel	Abraxane	Breast, lung, and pancreatic cancers	[36]
Lipid NP	siRNA against PLK1	TKM-080301	Advanced hepatocellular carcinoma	[50]
	siRNA against MYC	DCR-MYC	Hepatocellular carcinoma	[51]
	siRNA against KSP	ALN-VSP02	Solid tumors	[52, 53]
	shRNA against stathmin 1	pbi-shRNA STMN1 LP	Late-stage cancers	[54]
Colloid gold NP	TNF, several chemotherapies	CYT-6091 AuNPs	Late-stage cancers	[55, 56]
Polymeric micelle	Paclitaxel	Genexol-PM	Breast cancer and non-small-cell lung cancer	[36]

common examples of preparation that formulated chemotherapy in NPs are summarized in Table 1.

5. Common NPs That Have Been Used in Cancer Therapy

5.1. Liposomes. Liposomes are colloidal drug delivery systems normally composed of phospholipids. It is consisting of the concentric bilayer vesicles with layers of aqueous media separating the lipid layers. The small unilamellar vesicles have particle size range of 20–80 nm and consist of a lipid outer layer with an aqueous core. The type of phospholipids determined the charge of the surface of the liposomes (charged or uncharged) [57]. Both hydrophobic and hydrophilic drugs are incorporated in liposomes. The hydrophobic drug is dissolved in the lipid layers, while hydrophilic drugs resided remain in the aqueous core. Several liposomal drugs are now marketed including AmBisome® (amphotericin B), Doxil® (doxorubicin hydrochloride), and Visudyne® (verteporfin). These preparations inhibit direct P-gp efflux or bypassing P-gp through an endocytosis pathway [58]. A liposome is a vesicle which consists of phospholipid membrane and can be filled with chemotherapy. Phospholipids have hydrophilic head and hydrophobic tail. Liposome is one of the most common NPs that is approved for treatment of cancer [59–61]. Liposomes are usually administrated as a potential targeting and delivery tool of the chemotherapy because liposomes able to minimize elimination, increase the targeting, and reduce the toxic side effect of the chemotherapeutical agents [62]. Doxorubicin is one of the commercial available chemotherapies in a liposome dosage form (e.g., Doxil and Myocet) [63]. Pharmaceutically, the liposome improves the pharmacokinetic and pharmacodynamic properties of the drug used; hence, the survival of cancer patients increases compared with parenteral drug treatment.

5.2. Polymer, Lipid Nanocapsules, and Nanoparticles. Nanocapsules have polymeric membrane (polymers or a combination of hydrophilic/lipophilic surfactants) that covers the liquid core (essential oils and triglycerides). The hydrophobic drugs are loaded in the lipid core and considered as a reservoir allowing a high drug loading with sustained release. Therefore, nanocapsules are ideal for lipid-soluble drug preparation [64]. Lipid NPs (or

nanocapsules) are commonly used to overcome P-gp-mediated drug resistance [65]; an example of that is the use of nanosponge [66]. *In vivo*, polyalkylcyanoacrylate NPs can reverse P-gp activity by an endocytosis process [67]. Polyisohexylcyanoacrylate (PIHCA) chemotherapy NPs showed more cellular uptake and cytotoxicity than free drugs in resistant cells. The mechanism of delivery of these NPs is by the changing the positive charge of drugs to ion pair with cyanoacrylic acid (a nanoparticle degradation product) increasing its diffusion across cell membranes [68]. A new polymer-lipid hybrid nanoparticle (PLN) system was used to bypass P-gp, leading to improved uptake and cytotoxicity of chemotherapy in resistant cells [67]. Drug-loaded sodium bis(2-ethylhexyl) sulfosuccinate (AOT)-alginate NPs significantly increased the chemotherapy cytotoxicity in resistant cells and overcome P-gp-mediated drug resistance [69].

5.3. Polymer-Drug Conjugates. Poly(N-[2-hydroxypropyl]-methacrylamide) (polyHPMA) and HPMA copolymers are water-soluble, nonimmunogenic synthetic polymers. HPMA copolymer-chemotherapeutic drug conjugates exhibit potent effect to overcome MDR [70, 71]. The endocytosis pathway is the mechanism of action whereas the conjugation of polymer-drug was hydrolyzed by enzymatic reaction in the lysosome of the cells, resulting in the release of the drug from the conjugate. The MDR1 expression was downregulated by HPMA conjugates and decreases the resistance against Taxol of resistant cells [72, 73]. Additional mechanisms are inhibition of detoxification genes encoding glutathione and UDP, induction of apoptosis signaling pathways, and downregulation of DNA repair [74]. The most commercially available albumin-based NP is paclitaxel (nab-paclitaxel; Abraxane) [75]. Albumin-based nanomedicine is able to formulate the hydrophobic chemotherapy in injection with broad-spectrum doses (high dose) and quickly reaches to the maximum concentration of drugs in plasma with higher bioavailability [76]. Thus, nab-paclitaxel (IV) is degraded into paclitaxel and albumin without any significant change in pharmacokinetic or tissue distribution of the chemotherapeutical agent [77]. In addition, by increasing the time of treatment with nab-paclitaxel (for several weeks), the rate of response and progression of the breast cancer patients were significantly increased more than the standard paclitaxel treatment [78].

5.4. Pluronic Micelles. The micelles are naturally present in the body that utilize the endogenous surfactant bile salts to complete lipid digestion [79]. Micelles functionally facilitate the absorption of water-insoluble fat and fat-soluble vitamins [80]. Their size is normally within in a range between 5 and 100 nm; amphiphilic molecules consist of a core: hydrophobic fragments and shell and hydrophilic moieties [81]. Water-insoluble drugs are usually intravenously administrated with an adjuvant solubilizing agent such as ethanol, which mainly has common toxic side effects [82]. The micelle nanoparticle formulation of these hydrophobic drugs is usually used to avoid the addition of the harmful adjuvant [83].

Folate-conjugated poly(ethylene glycol)-b-copolycarbonates and methoxy poly(ethylene glycol)-b-copolycarbonates loaded with doxorubicin improve the cytotoxicity of doxorubicin via FA receptor-mediated endocytosis [84]. Clinical trials were used to treat metastatic GIT adenocarcinoma using SP1049C-doxorubicin micelles of pluronic L61 and F127. The accumulation of doxorubicin in tumors was more than free doxorubicin with normal distribution of polymer in normal tissues [85, 86]. The mechanism of action of micelles is changing the structure of the membrane, decreasing membrane fluidization, and inhibiting function and expression of efflux transporters, such as P-gp and MRPs [87–90]. These subsequently sensitize resistant cancer cell to the chemotherapeutic agents [91], increasing the proapoptotic [92], decreasing the levels of glutathione (GSH) and glutathione-S-transferase (GST) activity, inhibiting the mitochondrial respiratory chain [92], decreasing oxygen consumption [93], and decreasing both mitochondrial membrane potentials [94], and the production of reactive oxygen species and release of cytochrome C in MDR cells are additional mechanisms [95, 96].

6. NPs in Chemotherapeutic Approaches of Cancer Treatment

Conjugated NPs have been applied in many disciplines of cancer treatment approaches. The followings are examples of the methods that have been combined with nanoparticles, in order to overcome multidrug resistance and/or to increase the sensitivity of the treatment.

6.1. NPs Conjugated with Topoisomerase Inhibitor Drugs. Topoisomerase inhibitors work through molecularly targeting topoisomerase enzymes that are essential for underwinding DNA during replication which leads to cell cycle arrest at G1 and G2 and apoptosis ultimately after failing DNA damage repair [97]. FDA has considered doxorubicin as one of the most effective chemotherapeutic drugs [98]. It introduces into DNA and RNA polymerase, which eventually stopped their actions. Doxorubicin can also induce apoptosis through activation of adenosine 5′ monophosphate-activated protein kinase (AMPK) that activates downstream targets such as p53, c-Jun N-terminal kinase (JNK), and mammalian target of rapamycin complex 1 (mTORC) [99–102]. Despite of anticancer effects of doxorubicin, resistance in some tumors has been shown. Another example of a chemotherapy drug that targets isomerase is irinotecan. It is a semisynthetic analogue of a camptothecin that is firstly obtained from the *Camptotheca acuminata* tree. It is a chemotherapeutic drug that initiates cell apoptosis through targeting topoisomerase I. It exhibits a potent antiproliferative activity against a different cancer types [103]. Same as doxorubicin, irinotecan interferes with the Topo-I-DNA complex resulting in twisting of DNA and DNA damage through double-strand breaks [104]. Conjugation of NPs with topoisomerase targeting drugs has shown successful in targeting many cancers; for example, Doxil is a liposomal doxorubicin conjugation that is approved by FDA for treatment of Kaposi sarcoma, ovarian cancer, and

multiple myeloma [36] and Myocet is approved by European and Canadian for treatment of metastatic breast cancer [36]. M-302 is in clinical trial for treatment of human epidermal growth factor receptor 2 (HER2) breast cancer [52] and anti-EGFR immunoliposome loaded with doxorubicin in clinical trial I for treatment of solid tumors [38], and ThermoDox, is liposome conjugated with doxorubicin for treatment of hepatocellular carcinoma in clinical trial III [39]. Another example for topoisomerase conjugated with NPs is MM-398 that is liposome conjugated with irinotecan, which is approved by FDA for metastatic pancreatic cancer treatment [40], and CPX-1 is in phase II for treatment of advanced colorectal cancer [41]. Conjugation of NPs with cisplatin has been used to increase the efficiency of cancer cell targeting and to reduce side effect of this drug. Lipoplatin, for example, is pegylated liposome that is conjugated with cisplatin for treatment of non-small-cell lung cancer (NSCLC), and it is now in phase III [44]. The combination of both chemotherapies such as doxorubicin and P-gp inhibitor such as verapamil in liposome formulation showed more cytotoxic effect than a single drug in both *in vitro* and *in vivo* resistant models [105]. Human transferrin (Tf) was used to potentiate the targeting effects of liposomes on Tf receptors. In resistant leukemia K562 cells (overexpressed with Tf receptor^{+}), Tf-conjugated coloaded liposomes showed highly cytotoxic than both nontargeted coloaded liposomes and Tf-conjugated doxorubicin liposomes. Hence, the TfR-targeted liposomes coloaded with doxorubicin and verapamil were able to reverse drug resistance and selectively target cancer cells [106]. pH-sensitive liposome doxorubicin (SpHL-DOX) has been reported to reduce the serious cardiotoxic effects of DOX in preclinical trial [107].

6.2. NPs Conjugated with Tubulin Assembly Inhibitor Drugs. Tubulin assembly targeting drugs are group of agents that interfere with mitotic assembly of tubulin and subsequently induce chromosome segregations and cell death eventually [108]. Paclitaxel is an example of these chemotherapeutic drugs that has been used for cancer treatment [108]. Vincristine sulfate (vincristine) is another example of a tubulin dynamic targeting chemotherapeutic drug that suppresses cancer cell proliferation through blocking mitosis via inhibition tubulin formation [109–111]. The inhibition of mitosis occurs between metaphase and anaphase of a cell cycle, which results in tubulin depolymerization [112, 113]. This leads to chromosome condensation and later dissociation but stay attached with the centromeres [114]. Vincristine (VCR) is used widely for lymphoma and leukemia treatment [115]. It has been reported that the overexpression of P-glycoprotein (P-gp) on several cancer cell membranes, e.g., leukemia, colorectal, and breast cancers, leads to cellular resistance to VCR [116]. Conjugation of paclitaxel with NPs augmented drug delivery, therefore, increases treatment effectiveness. Works on breast cancers with a metastatic stage shows the dramatic eradication of metastasis after administration of paclitaxel in complex with NPs and shRNA [117]. It effectively delivered the drug and RNA that suppressed metastasis [118]. Using paclitaxel loaded in pax NPs during ovarian tumor surgery effectively reduced tumor relapse. Combination of chemotherapy with NPs has shown promising result in boosting cancer treatment. For example, Abraxane is albumin bound to paclitaxel approved by FDA for treatment of breast, lung, and pancreatic cancers [36]. Genexol-PM, which is polymeric micelle conjugated with paclitaxel, is approved in Korea for breast cancer treatment [36], NK-105 conjugated with polymeric micelle is for metastatic breast cancer treatment in phase III [119], EndoTAG-1 is liposomal paclitaxel for pancreatic, hepatic, and breast cancers [42, 43], and Marqibo, which is vincristine sulfate conjugated with liposome, is approved by FDA for acute lymphoblastic leukemia treatment [36].

6.3. NPs Conjugated with Drugs That Target DNA Replication. There are many chemotherapeutic drugs targeting DNA replication. For example, cisplatin is a chemotherapeutic drug that has had a wide influence in cancer therapy [120]. It works through interfering with DNA replication primarily via its interaction with purine bases in DNA to form a DNA protein crosslink [120]. Cisplatin-induced DNA damage activates many cellular signaling. It activates cell cycle checkpoints that transitory induces the S phase and subsequently inhibits Cdc2-cyclin A to induce G2 arrest [121, 122]. It also induces cyclin-dependent kinase 4 (Cdk4) inhibitor $p16^{INK4A}$, which results cell cycle arrest at G1 [123].

The limitations of the therapeutic efficacy of cisplatin in cancer treatment are mainly due to drug resistance and systemic side effects in treated patients. Cisplatin resistance is correlated to the increase in the intercellular levels of glutathione (GSH). Recently, unique NPs composed of cisplatin prodrug and poly(disulfide amide) polymers with a high disulfide density which reverse cisplatin resistance in cancer cells were developed [124]. The suggested mechanism of this nanoparticle platform is GSH scavenging process by a disulfide group of polymers. Furthermore, TAT-ASA-MNPs@CDDP nanoparticle was prepared by condensation of aldehyde with the amino group and then coordinated with cisplatin which exhibited more cytotoxic and apoptotic effect than prodrug [125].

There are other few examples of conjugated cisplatin with NPs. Conjugation of cisplatin with polymeric micelle has been used under a NK-105 trade name. This compound has been tested for non-small-cell lung cancer, and it is in phase III [44].

7. NPs in Nonchemotherapeutic Approaches of Cancer Treatment

There are other strategies that have been used for cancer treatment other than chemotherapy. Radiotherapy, for example, has been used in cancer therapy for many decades that has shown a benefit for some cancer types and on cancer patient's survival [3]. For end-stage tumor cases, radiotherapy is a preferable treatment [126]. Radiation induces double-strand DNA damage either through ionization or through increasing free radical production within cells resulting in apoptosis [127]. It induces many

signaling pathways that are essentials for cell death, including the p53 pathway. Inhibition of upstream signaling proteins of DNA damage such as ATM and ATR has shown implication in increasing cancer cell sensitivity towards radiotherapy [128–130]. NPs, such as chlorin e6-loaded chitosan, improved photodynamic cancer therapy. The use of NPs in radiotherapy for cancer treatment has been tested before; Nanobiotix (NBTXR3) hafnium oxide is administrated systematically and once targeted cancer cells; they are activated by radiotherapy resulting in energy release and destroying cancer cells [131]. It is in phase III for soft tissue sarcoma treatment [131]. Highly biocompatible chlorin e6-loaded chitosan nanoparticles have been shown to improve photodynamic cancer therapy [132].

Immune therapy is also among the approaches that has been used for cancer treatment. After initial cancer transformation in premalignant tumors, immune cells can effectively eliminate these cells in a process called "immune surveillance." However, impairment in this mechanism could result in malignancy [133]. Since the immune system can clear cancer cells in an early stage, scientists tried to treat cancer through boosting of the immune system. Many immunotherapy strategies have been approved for treatment of different cancer types, for example, sipuleucel-T for prostate cancer treatment [5] and CTLA-4 antibody for melanoma [134]. Some immunotherapy includes stimulating immune cells through cancer antigen vaccination, such as interleukin-2 (IL-2) and interferon-α (IFNα), or using dendritic cells for therapy enhancement [135–137]. Combination of gene therapy and NPs has been tested for cancer therapy. Tecemotide, for example, for non-small-lung cancer treatment in clinical trial III, is a transmembrane glycoprotein Mucin 1 (MUC1) antigen conjugated with liposome to induce immune response against cancer cells [47]. dHER2+As15 is in clinical trial II; it is a recombinant HER2 and AS15 antigen for treatment of metastatic breast cancer [138]. DPX-0907 is polytumor-related antigens linked with liposome in clinical trial I for late-stage ovarian breast and prostate tumors [48]. Lipovaxin-MM is in clinical trial I, and it is a combination of a melanoma antigen conjugated with liposome for malignant melanoma treatment [49]. JVRS-100 is a conjugated drug between lipid nanoparticle and DNA for relapsed leukemia; it is in phase I [139]. CYT-6091 is another example of a combination between tumor necrosis factor (TNF) antigen and colloid gold nanoparticle for treatment of late-stage solid tumors, and it is in clinical trial I [55].

Gene therapy is a method of delete, modify, or replace mutated genes in target host cells. In cancer research, gene therapy has received attention since cancer cells have mutated gene(s) that results in uncontrolled proliferation [4]. Therefore, ability to introduce intact genes to cancer cells or dormant stem cells can modulate malignancy. Transferring genetic materials into host cells can be conducted using viral, bacterial vectors, or nonviral vectors such as liposome and nanoparticles [140]. There are examples of nanoparticle drug conjugation genetic materials for gene therapy of cancer. SGT53, for example, is Tfr-targeting liposome that is conjugated with plasmid coding for wild-type p53 for treatment of pancreatic cancer in phase II [141, 142], and PNT2258 drug is a liposome nanoparticle conjugated with oligonucleotide against BCL2 for non-Hodgkin lymphoma and diffuse B-cell lymphoma in phase II [143, 144]. SNS01-T is polyethylenimine NPs linked with eIF5A plasmid for recurrent B cell malignancies in phase I/II [145]. Atu027 is a liposomal particle conjugated with small interfering RNA (siRNA) N3 kinase for pancreatic cancer treatment in phase I/II [50]. TKM-080301 is a lipid nanoparticle conjugated with polo-like kinase (PLK1) siRNA for hepatocellular carcinoma and neuroendocrine tumors in phase I/II [46, 146], discontinue clinical development of DCR-MYC; it is also lipid nanoparticle conjugated with siRNA against MYC for hepatocellular carcinoma treatment in phase I/II [51]. CALAA-01 is polymeric nanoparticle conjugated with siRNA against ribonucleotide reductase M2 for many solid tumor treatment in phase I [147]. ALN-VSP02 is a lipid nanoparticle conjugated with siRNA against kinesin spindle protein (KSP) and vascular endothelial growth factor A (VEGFA) for solid tumor treatment in phase I [52, 53]. siRNA-EPHa2-DOPC is a liposome conjugated with sirRNA against ephrin type-A receptor 2 (EphA2) for late-stage solid tumor treatment in phase I [45]. pbi-shRNA STMN1LP is lipid nanoparticle against stathmin 1 for many solid tumor treatment in phase I [54]. Chen et al. reported that the multidrug delivery devices by combination of novel liquid crystalline self-assembled nanocarriers with baicalin (BAI) and *Brucea javanica* oil (BJO) synergistically enhanced the anticancer activity through induction of apoptosis in human lung carcinoma cell line A549 [66].

Recently, novel pH-sensitive prodrug nanoparticles were prepared using self-assembly of a synthetic amphiphilic macromolecular prodrug resulting in the improvement of the selective codelivery of doxorubicin (Dox) and curcumin (Cur) into the human breast cancer cell line MCF-7 with an improved cardiotoxicity profile on an in vivo zebrafish model compared to free Dox [148]. Furthermore, novel disulfide-crosslinked sodium alginate nanoparticles with doxorubicin were prepared and enhanced the doxorubicin release by triggered glutathione and showed a selective cancer cell cytotoxicity on Hep-G2 and HeLa cells, safe on healthy human liver L-O2 cells, and no cardiotoxicity in an in vivo zebrafish model [149].

8. Conclusions

Overcoming the drug resistance in cancer treatment is an important approach and has become the greater interest in the last years. The fast improvement of the drug delivery system and development of the nanotechnology provide the possibility of a more potential strategy for drug resistance in cancer. The development of NPs might provide a new strategy for the treatment cancer therapy. However, there are several challenges that should be overcome, for example, off targeting of normal cells that share the same surface proteins of cancer cells; hence, selective targeting of cancer cells is not guaranteed. Therefore, identifying the specific surface marker for cancer cells is crucial for a targeted therapy of tumor [150]. An example of high specific NPs is MM-398, which successfully targets cancer cells via the acidity of the

tumor microenvironment. This drug inhibits the DNA replication machinery of highly dividing cells such as cancer cell. On the other hand, some normal cells are dividing in the acidic environment such as epithelial cells of the stomach. This explains the digestive associated side effects of the drug. Therefore, high selective ligands of cancer cells could limit these side effects. The challenge of nanomedicine also is extended to its production quality. Reproducibility of NPs at large-scale production is still difficult, especially synthesis of homogenous sets of the drug. Further, NPs need a special circumstance for production and storage. Hence, at each phase of NP production quality control should be performed to check the efficacy and reproducibility of NPs. Moreover, during the development of drugs in the laboratory, some changes in law sometimes take place. Therefore, groups such as Nanotechnology Characterization Laboratory should increase the collaboration between committees, scientists, and laboratories to support the assessment of nanomedicine legislation [151]. So, more work should be conducted in order to overcome these challenges. The solution is possible, but it requires a collaborative work between scholars, governments, and pharmaceutical companies to pave the way for the successful usage of NPs in cancer therapy. Nanoparticle formula loaded with chemotherapy has been designed to overcome the limitations associated with conservative drugs such as severe cytotoxic side effects and the variation in therapeutical response. Many nanomedicines have been approved by FDA and shown acceptable performance in clinical practice. However, the therapeutic efficacies cannot be improved. The future perspective of stimuli-responsive nanoparticles can be achieved by wide array of desirable properties including pH variations, redox potential, enzymatic activation, thermal gradients, magnetic fields, light, and ultrasound (US) or can even be responsive to dual or multicombinations of different stimuli that can be eventually developed for safe and efficient cancer therapy.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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