A review on application of nanoparticles for cancer therapy

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Abstract

In recent years, scientific societies had warmly embraced nanotechnology as an emerging field in cancer therapy. Nanotechnology has had a profound influence on almost every aspect of the twenty-first century’s diurnal life. During the past years, nanomaterials have been successfully applied in different biomedical fields; especially in cancer therapy. While cancer is one of the deadliest disorders worldwide, there is a need to develop novel anticancer approaches. In this review, we explained various kinds of nanoparticles such as liposome-based and polymeric nanoparticles and dendrimers along with their applications in cancer therapy.

Introduction

With the emergence of more than 10 million new cancer cases every year, the worldwide incidence of cancer has rapidly increased in the past decades. Treatment of cancer is hard delivering malignancies as major causes of morbidity and mortality in populations (1). Although anticancer drugs can be efficient in cancer therapy, their activities and effective dosages are generally manipulated by various factors. Traditional anti-cancer agents such as chemotherapeutic drugs nonspecifically target both cancerous and normal cells in the body. This event limits the dose of drug delivered to tumors resulting in suboptimal therapeutic efficiency.

Targeted therapy has been appeared as an approach to overcome unspecific targeting of cancer cells by traditional chemotherapeutic agents (2). After reaching tumor cells, drugs should release their active forms in a controlled way to selectively target tumor cells without influencing normal tissue. This phenomenon is critical for improving both quality of life and survival of patients by increasing the intracellular concentration of drugs and limiting dose-related toxicities. As efficient drug carrier systems, nanoparticles seem to fulfil both specificity and efficiency requirements of cancer therapeutics (3). During recent years, researchers have tried to develop new diagnostic strategies for cancer. In this regard, nanotechnology has been under focus as one of the most promising fields to diagnosis and treat cancers.

Nanotechnology is the knowledge of engineering substances and practices at molecular measure. In medicine, comprehensive studies on nanomaterials have culminated in their application as drug-release vehicles. These nanocarriers are mostly <100 nm in size and have the capability to carry and supply the therapeutics agents to intended cells (4). In cancer treatment, the efficiency of nanoparticles depends on their penetrability and ability to be stored and retained in tumor tissues (5). As mentioned, intravenous injection of noxious chemotherapeutic drugs poses a critical risk to healthy tissues limiting their tolerable doses (6). In brief, nanoparticles can increase the intracellular absorption of drugs by cancer cells and prevent toxicity against normal cells by recruiting both passive and active targeting approaches (7, 8). Moreover, after binding to particular receptors, nanoparticles can penetrate into cells as endosomes through receptor-mediated endocytosis. In this way, they can bypass the action of P-glycoprotein as one of the major drug resistance
mechanisms in cancerous cells (9). In this review, we discussed various nanoparticles used in cancer therapy.

Materials and Methods
For this review, we used a variety of sources including PubMed, Web of Science, Embase, EBSCO, Google Scholar and Scopus. The search was conducted, using combinations of the following key words and or their equivalents; cancer, nanoparticles, liposomes, dendrimers, albumin, endocytosis, photoluminescence, carbon nanotubes and nanomedicine.

Liposomes
Liposomes were introduced by Bangham et al in 1965. Liposomes are among very first nanoparticle-based platforms utilized for therapeutic purposes (10). They consist of amphiphilic lipid molecules gathered into bilayer spherical vesicles with an aqueous core and a vesicle shell (4,6).

Depending on their designs, liposomes vary in diameter ranging from tens of nanometers to micrometers. Features such as biocompatibility and biodegradability, in addition to the unique capability to encapsulate both hydrophilic (inside the aqueous core) and hydrophobic (inside the lamellae) drugs deliver liposomes as brilliant drug carriers. Likewise, to enhance their constancy and half-life in circulation, liposomes can also be covered with polymers like polyethylene glycol (11).

Liposomal medicine formulations usually amend the pharmacokinetics and biodistribution of a drug. There are currently more than 11 liposomal formulations permitted for clinical application, and many other formulations are in clinical and preclinical phases (4). The liposomal formulations currently used in cancer therapy include DepoCyt (12, 13), ONCO-TCS (14), Doxil (15,16) and DaunoXome (17,18) which are formulations of doxorubicin, daunorubicin, cytarabine and vincristine respectively (6).

Another liposome-based formulation has been used to co-deliver SiRNAs and chemotherapeutics. SiRNAs are developing classes of cancer therapeutics interfering with gene expression through targeting mRNAs. In 2008, Saad et al developed a liposome system to transport SiRNAs targeting BCL2 (a protein responsible for resistance of cells to apoptosis) and MRP, (a multifunctional defiance-associated protein) in combination with doxorubicin into human H69AR lung cancer cells (19). Table 1 provides a brief description regarding anti-cancer liposome-based combinational treatments.

Polymeric nanoparticles
Biodegradable and biocompatible polymeric nanoparticles have been under investigations to transport and target drugs (6). Many polymeric nanoparticles have been investigated in comprehensive clinical and preclinical studies as biocompatible and biodegradable drug carriers (26).

As polymers propose higher synthetic freedom, they allow various particles to be tailored for particular clinical needs. Due to these unique properties, polymeric nanoparticles have attracted enormous interests among scientific and industrial societies even though they are still in the early phases of investigations (6). The hydrophobic core of polymers is able to carry high amount of drugs whereas the hydrophilic shell supplies a steric defense for the nanoparticle. Polymeric nanoparticles have also been able to encapsulate either micro or macromolecules (such as nucleic acids and proteins) with hydrophilic or hydrophobic properties (27).

In comparison with liposomes, polymeric nanoparticles generally have better stability, sharper size distribution, more advantageous physicochemical attributes, sustained and more manageable drug-release profiles, and better loading capacity for water-insoluble drugs (6).

Dendrimers
Dendrimers are a new class of nanoparticles developed as drug-delivery vehicles in cancer therapy. They are well described branched spherical macromolecules (28). Dendrimers are produced in a stepwise and iterative method. The structure of dendrimers constitutes from a core surrounded by layers of branched repeated units with functional groups on the outmost layer (6).

They are commonly derived from either synthetic or natural elements like nucleotides, sugars, and amino acids. These nanoparticles can be simply conjugated to therapeutics. Through holes in their cores, dendrimers can be loaded with drugs via hydrophobic interactions.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Indication</th>
<th>Reference</th>
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<tbody>
<tr>
<td>CPX-351</td>
<td>Acute myeloid leukemia</td>
<td>(20)</td>
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<tr>
<td>Liposome co-encapsulating 6-mercaptopurine and daunorubicin</td>
<td>Acute lymphocytic leukemia</td>
<td>(21)</td>
</tr>
<tr>
<td>Liposome co-encapsulating quercetin and vincristine</td>
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<tr>
<td>Transferrin-conjugated liposome co-encapsulating doxorubicin and verapamil</td>
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<td>Cationic liposome co-encapsulating SiRNA and doxorubicin</td>
<td>Lung cancer</td>
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<tr>
<td>CPX-571</td>
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</tbody>
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as well as hydrogen, and chemical bonds. The preclinical studies on dendrimers have largely focused on developing dendrimer-drug conjugates (4).

Collectively, the unique attributes of dendrimers make them suitable platforms for simultaneous delivery of water soluble and insoluble agents. For example, the hydrophobic core of dendrimers includes a hole encapsulating hydrophobic drugs. On the other hand, the multivalent outer layers can be conjugated with hydrophilic medications (6).

Although several attempts have been made to deliver multiple drugs using dendritic platforms (6), dendrimers have not attracted as much notice as liposomes and polymeric nanoparticles. So far, a dendrimer-based compound (i.e. 5 poly-propyleneimine) has been utilized to co-encapsulate methotrexate (a hydrophobic chemotherapeutic) and all-trans retinoic acid (a hydrophilic drug with mild anticancer activity) (29,30).

**Nanoparticle albumin-bound (nab) technology**

Albumin is a vital plasma protein carrying hydrophobic molecules by forming reversible noncovalent bonds. Albumin is highly concentrated in tumors, and therefore nanoparticle albumin-bound (nab) platforms can be promising carriers to deliver hydrophobic chemotherapeutics to tumors (31).

The traditional formulations for constructing hydrophobic remedial agents use toxic solvents and surfactants such as Cremophor EL and Tween. These agents can deter the dispersal and delivery of the active drug component by micellar sequestration. On the contrary, the “nab” technology allows combination of hydrophobic molecules with albumin through noncovalent hydrophobic interactions to build 50–150 nm colloidal nanoparticles (32). These nab-paclitaxel nanoparticles have a narrow size distribution with an average particle size of round 130 nm as verified by dynamic laser light scattering (32, 33).

Briefly, the “nab” technology is a nanoparticle-based drug delivery platform constructed on the unique functional attributes of albumin which permits efficient diffusion of drug in tumor tissues and obviates the need for using toxic solvents (32).

Recent research based on the maximum-tolerated dosage showed that antitumor activity of nab-paclitaxel was superior or at least equal to that of polysorbate-based docetaxel in prostate, breast, colon, and lung cancer xenograft models (34). In preclinical investigations on pancreatic cancer models, the combinational therapy with nab-paclitaxel and gemcitabine showed strong antitumor activity with higher concentration of gemcitabine within the tumor which may be attributed to either the capability of nab-paclitaxel to disturb tumor stroma (35) or reduce the activity of cytidine deaminase, the primary gemcitabine metabolizing enzyme (36).

**Metal nanoparticles**

In recent years, metal oxide nanoparticles have grabbed significant attentions in biomedical fields (37), in particular developing nanovaccine scaffolds. Due to their tendency to penetrate into a wide range of cells, these nanoparticles have also been interesting candidates for cancer therapy (38,39).

Metal oxide nanoparticles have unique physical (e.g. fluorescent enhancement and plasmonic resonance) and chemical (e.g. catalytic activity) properties delivering them appropriate agents as drug carriers (40-47). Metal nanoparticles have larger surface area, higher surface area to volume ratio, and characteristics physicochemical properties (such as high toxicity against cancer cells due to structural properties and inducing reactive oxygen species, as well as photothermal, and hyperthermia effects) which make them potential platforms for cancer therapy. Regarding their unique properties such as photoluminescence and superparamagnetic attributes, metal nanoparticles have also been investigated in diagnostic and imaging procedures (41-43). Metallic nanoshells which usually contain metals such as gold (Au) or titanium (Ti) have been employed to control the gradual release of chemotherapeutic agents in tumor tissues (45-47).

**Silica nanoparticles**

Silica is a critical constituent of human cells. Amorphous silica is a nontoxic, biocompatible and biodegradable agent that is widely distributed throughout the human body and excreted in urine (48).

For the first time, Unger-K et al, conjugated drugs to sol-gel derivative of silica (SiO$_2$) in 1983 (49). Since then, silica-based substances have been well characterized as drugs and molecules carriers (50,53), gene transfection elements (51) and cell identifiers (52).

A challenging problem in cancer treatment is the unavailability of efficient biocompatible systems to transfer many hydrophobic remedial anticancer drugs (54). Amongst various drug-delivery methods, mesoporous silica substances (55) have been effective in transferring water-insoluble medicines. The large surface area and spongy interiors of silica substances potentiate them for loading large quantities of hydrophobic therapeutics (54). On the other hand, mesoporous silica nanoparticles including fluorescein isothiocyanate (a widely used fluorescence color) are highly biocompatible promising an efficient system to deliver hydrophobic anticancer medicines (56).

In this regard, in vitro investigations showed that mesoporous silica nanoparticles were effective in simultaneous delivering of doxorubicin and SirNA to cancer cells promoting the efficiency of chemotherapy (6).
of surface holes of the particles. Furthermore, the capacity of mesoporous silica nanoparticles to absorb drugs can also be promoted by optimizing medicine incorporation environment (57, 58).

Carbon nanotubes
In recent years, carbon nanotubes (CNTs) have gained increasing interests by many scientists worldwide. The drug and gene delivery capacities of CNTs along with their surface properties and unique physicochemical attributes beacon novel and efficient nanomaterial-based systems for cancer treatment (59).

Single-wall carbon nanotubes (SWNTs) present notable opportunities to address progressive challenges of drug delivery methods (60, 61). Some approaches have been introduced to link biological molecules such as proteins, DNA, and smaller molecules to SWNTs (62, 63). Based on their biocompatibility, excretion properties, and minor toxicity, chemically functionalized SWNTs have been effective in combinational cancer-targeted therapy in mice (64).

Overall, functionalized and solubilized SWNTs can carry proteins, peptides, DNA, and genes (65, 66) by penetrating through cell membranes with minor cytotoxicity (67, 68). SWNTs present large surface area per unit of weight delivering great drug loading capacity (69). In addition, in vivo and in vitro studies on cancer cells viability have clarified that oxidized SWNTs bio-conjugated with cisplatin and epidermal growth factor (EGF) receptor ligand can selectively and effectively target squamous carcinoma cells overexpressing EGF receptor (59).

Discussion
Targeted delivery
Numerous novel biotechnological methods have been developed in the past decades to treat cancer. Nanomedicine represents a filed aiming to develop diagnostic and therapeutic instruments and approaches based on nanoparticles (70). Because of providing safe and effective platforms, nanomedicine is rapidly getting recognition especially in anticancer therapy (71).

Although chemotherapeutic agents encapsulated within nanoparticles are highly powerful against cancer cells, they may inflict collateral harms on adjacent healthy tissues as well. Therefore, targeted delivery of these compounds toward tumor cells is highly important in the development of nanoparticle-based therapeutics. Although nanoparticles can passively be accumulated at the tumor site because of their high permeability and stability, active targeting of these compounds can further facilitate the process (6).

Conclusively, nanoparticles encapsulated drugs (such as Genexol- PM 1 and Doxil 1) boost pharmaceutical solubility and pharmacokinetic properties of drugs and lessen the cytotoxicity of chemotherapeutics in used for cancer therapy (71).

Recent studies have confirmed that liposomes, polymeric nanoparticles and dendrimers have surface functional groups which can be conjugated with target ligands such as antibodies (4, 6, 72, 73), peptides (Lyp1 and RGD) (74), oligonucleotides (aptamers) (75) and antibody variants (single-chain changeable pieces and diabodies) (76) to specifically target drugs toward tumors. Although nanoparticles as drug carriers have many benefits, there are still many limitations such as poor oral bioavailability, week traceability in circulation, insufficient tissue supply, and toxicity which need to be resolved.

Conclusion
As mentioned, the unique attributes of nanoparticle-based drug carriers generate suitable agents for therapeutic purposes in oncology. While nanomedicine is a comparatively novel science, it is rapidly transforming into a practical field in medicine. nanoparticle-encapsulated chemotherapeutics are expected to attain widespread applications as cancer therapeutics in the future. In spite of this, limited number of them have been approved for clinical use, and there are still disadvantages needed to be resolved before their widespread clinical application. More clinical studies are required to completely understand the benefits and harms of nanoparticle remedies.

Author’s contribution
Mohamad Ali Dayani is the single author of the paper.

Conflicts of interest
The author declared no competing interests.

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