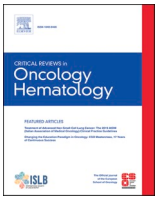
Critical Reviews in Oncology / Hematology 174 (2022) 103677

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc



Nanomedicine tactics in cancer treatment: Challenge and hope

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ARTICLE INFO

Keywords:
Anti-cancer
Nanomedicine
Cytotoxicity
Liposomal Nanoparticles

ABSTRACT

Defeating cancer is the ultimate challenge and goal of oncologists, facing various obstacles along with finding effective anti-cancer therapies and understanding drug delivery mechanisms. Additionally, the translation of the experimental findings to the clinical outcomes such as specificity, delivery, toxicity, clearance, and bioavailability is another health concern. Nanomedicine is a branch of nanotechnology that has been drastically developed in the last decades. Due to the fact of various nanomaterial formulas, different nanomedicine drug delivery tactics have been developed as anti-cancer therapies. The most effective and less toxic approaches involved the active targeting drug delivery tactic, which relies on the recognition of the drug nanoparticle carriers and the cell surface marker. Accordingly, FDA approved such a group of nanomedicine drug delivery systems while other formulas are still under the clinical trial phases. Nanomedicine is showing a bright future in the treatment of cancer. Oncologists learned from cancer research the possible drug resistance that could be developed. Consequently, researchers need to be prepared for the possible adverse effect of the nanomedicine approach.

1. Introduction

Cancer disease is a very challenging disorder with no decline in prevalence and incidence worldwide (Kulkarni et al., 2020; Sharma, 2021). Substantial research efforts and health service facilities are still under pressure to develop effective treatments for reducing mortality and morbidity hoping to defeat this chronic disease worldwide (Traub et al., 2021). However, cancer-curing therapy is still way from reach due to many reasons such as the diversity of cancer types and subtypes (Parris, 2020). Many clinical trials have been conducted with various proposed anti-cancer treatments; however, the successful outcomes are very limited. The major concern when there is an effective treatment is the side effects as well as the delivery to the target site. In addition, drug resistance and toxicity raise another challenge against the new anti-cancer therapies (Housman et al., 2014; Kaur et al., 2020; Vasan et al., 2019). In the last decades, there was a notable development in the nanotechnology field that highlighted the possible solution to overcome the toxicity, delivery and resistance of anti-cancer therapies (de la Torre et al., 2020; Yao et al., 2020). Nanotechnology is a highly revolving biotechnology approach with a wide range of applications including in medical and environmental fields. The promising outcomes of nanotechnology research especially on chronic diseases such as cancer treatment encourage the scientific community to evaluate the toxicity of these products (Al-Trad et al., 2019; Aljabali et al., 2018a; Aljabali et al., 2019; Aljabali et al., 2020; Aljabali et al., 2018b; Alomari et al., 2020; Wang et al., 2017b). In particular, In cancers and diabetes diseases, scholars are keen to find safe and effective treatments with the lowest side effects (Agarwal et al., 2020; Arvanag et al., 2019; Bisht and Rayamajhi, 2016; Farooq et al., 2018; Liu et al., 2018; Peng et al., 2019; Wang et al., 2017b, 2017c; Yang et al., 2018). However, different studies showed contradictory results of the toxicity of the nanomaterials as treatments of chronic diseases. The uncertainty report by the Royal Society and Royal Academy of Engineering warned the need for biosafety evaluation of nanomaterials application in diseases treatments (Bowman, 2017; Maynard, 2014; Pidgeon et al., 2004). Accordingly, there were national plans for the assessments of the manifestations of the nanoparticles used in clinical approaches (Handy and Shaw, 2007). In this review, we are aiming to emphasize the role and the effectiveness of

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https://doi.org/10.1016/j.critrevonc.2022.103677
Received 23 January 2022; Received in revised form 31 March 2022; Accepted 31 March 2022
Available online 3 April 2022

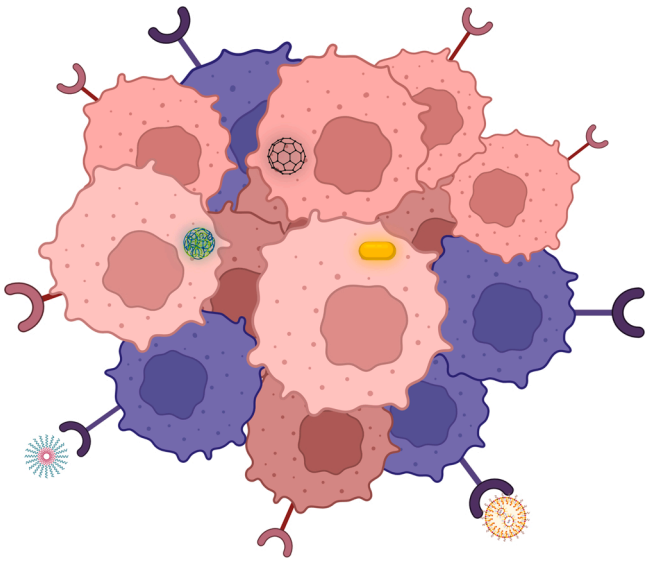

Fig. 1. A representative diagram showing the difference between passive and active nanoparticles through cancer tissue. (*Created by BioRender*).

nanoparticle use in cancer treatment and to underscore the importance of toxicity assessment of this new approach.

2. Why nanoparticles (NPs) in cancer treatment?

For many years, the major challenge of effective treatment against cancers is the translation of in vitro and in vivo results to clinical applications due to many obstacles such as toxicity, delivery, stability, targeting, and resistance (Gewirtz et al., 2010; Sun et al., 2014; Vasan et al., 2019; Vasir and Labhasetwar, 2005). Therefore, nanoparticles drug delivery systems have been proposed and developed in many formulas to overcome those barriers (Cho et al., 2008; Haley and Frenkel, 2008; Phillips and Mousa, 2022; Rehman et al., 2022; Vasir and Labhasetwar, 2005). For instance, the immune checkpoint blockades (ICBs) showed a potential anti-cancer drug, however, the life-threatening adverse effects limited their application in cancer treatment. Therefore, the development of nanotechnology delivery approaches showed an effective combination of nanotechnology and ICBs anti-tumor agents (Sanaei et al., 2021). Furthermore, a combination of immunogenic cell death (ICD) inducers with immune checkpoint inhibitors showed the prevention of tumor metastasis and recurrence. In addition, the capability of nanoparticles to generate immunogenic cell death can help to turn "cold" tumors into "hot" ones which increase the sensitivity of patients to anti-cancer therapies (Qi et al., 2021).

Despite the vast number of developed nanoparticles as anti-cancer treatments, passive targeting and active targeting are the two major systems or mechanisms for nanomaterial drug delivery routes (Fig. 1) (Alavi and Hamidi, 2019; Bazak et al., 2014; Hirsjarvi et al., 2011). The passive nanoparticle targeting mechanism depends on the high permeability of the target tumor vascularization tissues and the absence of lymphatic drainage which provides a retention effect (Bazak et al., 2014). The enhanced permeability and retention effect (EPR) is a characteristic feature of the tumor microenvironment in which the lymphatic system is unable to drain tumoral fluids leading to the accumulation of those components, including nanoparticles, in the tumor site (Fig. 2) (Kalyane et al., 2019; Rodallec et al., 2018a). Different reports showed the employment of EPR in targeting the tumor tissues either as therapeutic or diagnostic approaches (Maeda, 2012; Sykes et al., 2016). In addition, the neovascularization of tumor tissues is characterized by the absence of a supportive basement membrane and leaky structure with large pores (Siemann, 2011). The huge space, 15 times the normal tissue barriers, allows the large nanoparticles to invade the tumor microenvironment without affecting normal tissues and reduces the cytotoxicity of certain anticancer drugs like chemotherapies (Drummond et al., 1999; Heo et al., 2012; Kalyane et al., 2019; Mundra et al., 2015; Tang et al., 2012).

The active targeting therapy relies on the binding of certain ligands,

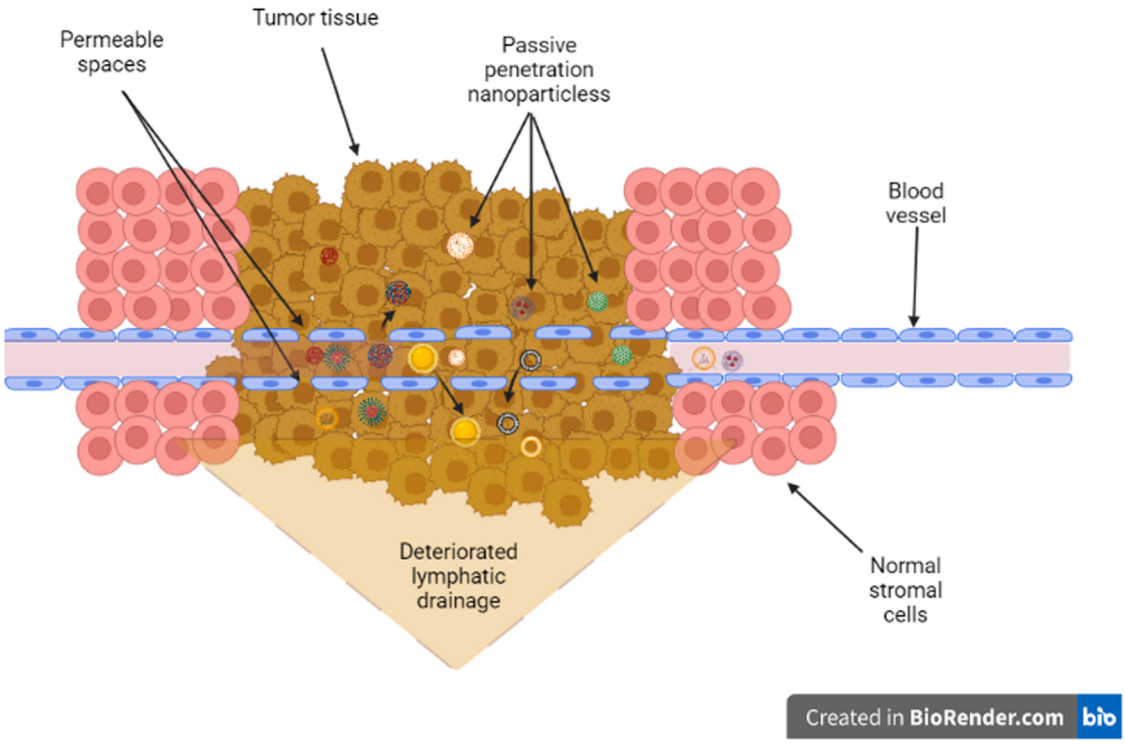

Fig. 2. : A schematic representation of the enhanced permeability retention effect in tumor microenvironment tissue showing the passage of nanoparticles (< 200 nm) through the highly permeable vascular spaces and the retention due to the deteriorated lymphatic drainage (*Created by BioRender*).

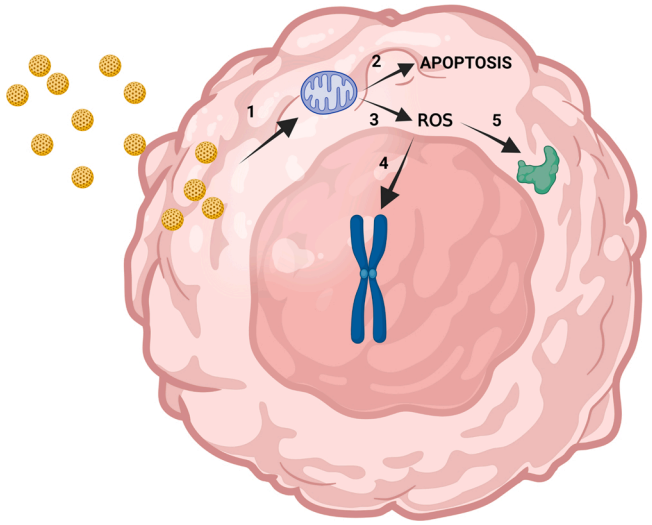

Fig. 3. A representative diagram showing the intracellular cytotoxic effect of nanoparticles treatments (ROS: reactive oxygen species). 1. Mitochondrial dysfunction. 2. CytC leads to apoptosis. 3. Generation of ROS. 4. DNA Damage. 5. Oxidative stress and protein denaturation (*Created by BioRender*).

that can be linked to the nanoparticles, which will recognize certain cell surface markers. Many ligand structures have been generated depending on the target site such as antibodies, aptamers, carbohydrates, and peptide molecules (Fig. 1B) (Byrne et al., 2008; Cho et al., 2008). This specific targeting mechanism is overcoming many issues of specificity of the anticancer treatment and cytotoxicity side effects (Rao et al., 2015).

Despite the mechanism of the nanomaterial-based anti-cancer treatment approach, a new tactic that depends on endogenous and exogenous stimuli-responsive systems developed to defeat cancer growth. For instance, cancer microenvironment endogenous properties such as hypoxia, ATP, and acidic conditions have been proposed to be manipulated by nanomaterials to affect cancer growth (Kumari et al., 2020; Li et al., 2018). Moreover, physical properties such as heat, light, and MRI can be applied as well to affect cancer growth (Raza et al., 2019). Different studies showed the efficacy of hyperthermia application using metal nanoparticles to generate heat upon reaching the target site after stimulation by certain wavelengths (Chen et al., 2011; Wang et al., 2012a).

3. Types of drug delivery NPs in cancer therapy

Whether it is passive or active nanoparticle targeting therapies, the types of anti-cancer nanomaterial delivering systems can be one of four major forms depending on their structure and composition materials (Fig. 2) (Cho et al., 2008). These types are known as 1) Organic nanoparticles (Liposomal, Polymeric, and Dendrimers NPs), 2) Inorganic nanoparticles (Gold, Carbon, Silica, Magnetic and other metals NPs) 3), Viral nanoparticles and 4) Hybrid nanoparticles (lipid-polymer NPs, Organic-inorganic NPs, and Cell membrane coated NPs) (Cho et al., 2008; Yao et al., 2020).

3.1. Organic nanoparticles

3.1.1. Liposomal Nanoparticles

Liposomal encapsulation is expected to offer a safer and more effective anti-cancer therapy as conventional chemotherapies have been associated with adverse effects. Chemotherapeutics for treating cancers are non-specific treatments that can be disseminated into many organs and tissues with inefficient pharmacokinetics (Danhier et al., 2010; Olusanya et al., 2018). Therefore, different nanomaterials have been developed to overcome the non-specific delivery and pharmacokinetic issues of effective chemotherapies (Balzus et al., 2017; Kieler-Ferguson et al., 2017). Penetration of encapsulated nanoparticles is a challenge to the delivery of the anti-cancer treatment to the target site, and therefore, the structural properties of the liposomal nanoparticles are very advantageous. In particular, the basic structure of nano-liposomes is composed of a phospholipid bilayer that facilitates the solubility of the encapsulated particles in the aqueous systems. This cellular mimic structure makes the liposomal nanoparticles less toxic and less immunogenic (Mohammed et al., 2004). In addition, sustainable drug release, lowering drug toxicity, increasing drug shelflife, lowering drug degradation are other advantages of nano-liposomal encapsulation (Allen et al., 2006; Allen and Martin, 2004; Cristiano et al., 2017; Mohammed et al., 2004; Park et al., 2011). However, some studies have shown an immune response against certain types of nano-liposomes such as PEGylated liposomes which is suggesting immunogenicity screening as a requirement (Mohamed et al., 2019). The immunogenicity of PEGylated liposomes can lead to accelerated blood clearance (ABC) i.e. enhanced clearance of the later doses due to the formation of anti-PEG antibodies (Dams et al., 2000). Moreover, some reports showed the potential use of nanoparticles localization in tumor tissue as a boosting immunogenic agent (Rodallec et al., 2018b).

In some specific examples, liposomal doxorubicin or liposomal paclitaxel-nanoparticles showed higher anti-cancer efficacy with lower toxicity compared to the free treatments in prostate and breast cancer (O'Brien et al., 2004; Satsangi et al., 2015; Yari et al., 2019). The drug combination is another option that can be offered by liposomal encapsulation, enhancing the efficacy and reducing the resistance to certain anti-cancer therapies (Chen et al., 2017; Meng et al., 2016).

3.1.2. Polymeric nanoparticles

Polymer nanoparticles are another type of organic nanoparticle that can be generated for drug delivery systems (Amreddy et al., 2018). For instance, polylactic-co-glycolic acid (PLGA) is commonly used for drug delivery systems owing to its reasonable biodegradation and biocompatibility (Acharya and Sahoo, 2011; Saneja et al., 2019). In addition, polymeric micelles are another example of high efficient anti-cancer drug delivery particles that increase the solubility of certain drugs by encapsulation into a hydrophobic core surrounded by a hydrophilic surface (Yao et al., 2020; Zhou et al., 2018).

3.2. Inorganic nanoparticles

Despite the poor biocompatibility and degradation of inorganic nanoparticles, they are characterized by a facile chemical preparation. Inorganic nanoparticles include many types such as AuNPs, AgNPs, FeONPs, and many others (Al Zoubi et al., 2021; Yao et al., 2020).

Metal nanoparticles have shown good efficacy in cancer treatment relying on different approaches such as drug delivery or magnetic hyperthermia. However, these particles need to be coated with a protective layer to improve their stability and efficacy (Basoglu et al., 2018).

AuNPs are the most common studies nanoparticles for the treatment of cancers due to the inert and non-toxic core that enhances the efficacy against cancer tissues. In addition, some studies used AuNPs for delivering different therapeutic formulas such as photothermal therapy (Yao et al., 2020).

Silica nanoparticles are another example of an effective drug delivery system due to their ability to form highly porous structures that are loaded within a high amount of anti-cancer drugs in addition to their efficient release (Almeida et al., 2014; Cheng et al., 2019; Xu et al., 2019; Zhang et al., 2017a).

Moreover, carbon nanotubes have been used in anti-cancer drug delivery systems containing doxorubicin or paclitaxel, or hyperthermia targeting (Luo et al., 2013; Madani et al., 2011).

3.3. Mixture (Hybrid) nanoparticles

Efficacy, biocompatibility, biodegradation, stability, and toxicity are the major challenges of developing drug delivery nanoparticles. Normally, each type of organic and inorganic nanoparticle has its advantages and limitations. Therefore, the fusion of these two types has been suggested to overcome most of the drug delivery obstacles (Mottaghitalab et al., 2019). Different reports showed better efficacy of combined polymer core and lipid outer layer nanoparticles in many cancer treatments (Gao et al., 2017; Hu et al., 2010). The improved efficacy of the hybrid nanoparticles has been attributed to the better biocompatibility of the lipid shell and integrity of the polymeric core (Wang et al., 2017a; Zhang et al., 2017b). In addition, other reports showed better cellular internalization and lower clearance of the hybrid nanoparticles (Hu et al., 2015; Su et al., 2013). In a group of studies on breast, pancreatic, and prostate cancer, silica-liposomal nanoparticles showed an efficient anti-cancer delivery mechanism (Colapicchioni et al., 2015; Meng et al., 2015; Wang, et al., 2017a). Other hybrid nanoparticles showed better anti-cancer properties such as carbon nanotubes and chitosan nanoparticles (Cirillo et al., 2019).

3.4. Cell membrane coating nanotechnology

Recently, mimicking the natural structure is achieved by a novel approach of coating the nanoparticles with a natural cell membrane from different cellular resources such as RBCs (Fang et al., 2018; Liu et al., 2019; Parodi et al., 2013). This new approach is expected to increase the safety and efficacy of drug delivery and cancer therapeutics (Fang et al., 2018; Yao et al., 2020).

4. Toxicity of anti-cancer nanomaterials

Normally, using different nanoparticle approaches in the treatment of cancer is expected to have different outcomes in clinical applications. For instance, metal oxide nanoparticles have been found to induce cancerous cytotoxicity compared to the null effect on normal cells (Vinardell and Mitjans, 2015). In the next subsections, we are exploring the different types of nanomaterials, their efficacy and cytotoxicity.

4.1. Liposomal nanoparticles

A few liposomal therapies against cancer such as Doxil or Caelyx and DaunoXome have been approved by the FDA. While Myocet, a non-pegylated doxorubicin liposomal particle, is approved in Europe (Haley and Frenkel, 2008). For safety concerns, the cytotoxicity of the liposomal nanoparticles has been investigated. It is found to be related to their structural and physical properties. Generally, the positively charged liposomal nanoparticles showed hepatocellular toxicity. Different mechanisms have been reported to explain the molecular mechanism of hepatocellular toxicity. For instance, Kedmi et. al. demonstrated the overexpression of IF-γ and TNF-α by leukocytes, (Kedmi et al., 2010) while others showed reactive oxygen species (ROS) over-production (Bae et al., 2009; Soenen et al., 2009; Takano et al., 2001). However, the non-pegylated liposomal nanoparticles showed some advantages over the pegylated liposomal nanoparticles. In particular, the pegylated showed a prolonged half-life with low clearance compared to the non-pegylated liposomal nanoparticles which were attributed to the opsonization and degradation of non-pegylated liposomal nanoparticles by the reticulum-endoplasmic system vis Kupffer cells which is a desire when liver diseases are the target. On the other hand, the pegylated liposomal nanoparticles showed some side effects such as palmar-plantar erythrodysesthesia syndrome, stomatitis, mucositis, immunologic reactions due to its stealth behavior (Haley and Frenkel, 2008; Ko et al., 2013; Zhu et al., 2021).

4.2. Metal nanoparticles

Gold nanoparticles (AuNPs) are widely investigated as an anti-cancer treatment in vitro and in vivo. However, the exact mechanism of the anti-cancer activity of gold nanoparticles is not fully understood. Cellular uptake of AuNPs was proposed to explain the mechanism of action. For instance, Huang et.al. found that AuNPs of less than 6 nm in size showed nuclear localization compared to larger ones (Huang et al., 2012). Receptor-mediated endocytosis has been reported in vitro (Zhang et al., 2013). The different routes of AuNPs uptake can be explained by the presence of small size (4–10 nm) of AuNPs in the kidney, liver, brain, and spleen (Hillyer and Albrecht, 2001). *In vitro* study showed low toxicity of AuNPs against leukocytes with a size smaller than 18 nm (Connor et al., 2005). Moreover, RBC hemolysis was demonstrated upon exposure to a high concentration of large-size AuNPs (30 nm) (Love et al., 2012). Consequently, the AuNPs application in clinical trials has some health concerns. Love et al. reported that using a large size of AuNPs (27 nm TNF-α-AuNPs) demonstrated an absence of AuNPs in the parenchymal cells.[94] Another study did not show any sign of toxicity of AuNPs within the first 24 h (Glazer et al., 2011). Interestingly, Zebrafish embryonic study reported a lack of toxic and lethal effects of AuNPs (Asharani et al., 2011). Alternatively, animal injection with AuNPs supported the low toxicity findings of AuNPs.(Gad et al., 2012) The reticuloendothelial system showed an accumulation of the cleared AuNPs with limited presence in the kidneys and adrenal glands and notable pigmentation in Kupffer cells tissue (Gad et al., 2012). Moreover, Libutti et. al. reported the presence of AuNPs in normal and tumor liver cells (Libutti et al., 2010).

Silver nanoparticles cytotoxicity has been evaluated in different studies (Ahamed et al., 2008; Arora et al., 2009; Braydich-Stolle et al., 2005; Carlson et al., 2008; Choi et al., 2009; Griffitt et al., 2009; Kawata et al., 2009; Kvitek et al., 2009; Navarro et al., 2008; Roh et al., 2009; Santoro et al., 2007; Sereemaspun et al., 2008). In an in vivo study using the zebrafish model, the results showed size dependent toxicity that affected the hatching period and heart rate (Asharani et al., 2011). other scholars showed DNA damage and apoptosis when mice are exposed to AgNPs especially the ones are coated with polysaccharides (Ahamed et al., 2008). Carlson et. al. reported the cellular interaction of AgNPs in ROS and inflammatory response in lung macrophages (Carlson et al., 2008). The investigators found that AgNPs induce an anti-oxidative mechanism with mitochondrial pigmentation (Arora et al., 2009). Kvitek et. al. investigated the toxicity of AgNPs,[104] authors found that the exposure of *P. caudatum* to 25 mg/mL of AgNPs did not show any toxic effect compared to 0.4 mg/mL of Ag ions (Kvitek et al., 2009). These findings were also supported by other studies that attributed the toxicity of AgNPs to the dissolution of Ag ions from the AgNPs (Beer et al., 2012;Kittler et al., 2010;Navarro et al., 2008).

CuONPs are also studied in the literature. An in vitro study using the human cancer cell line (A549) and breast cancer cell line (MCF7) showed significant growth inhibitions, which is believed to be attributed to the activation of the apoptosis mechanism (Sankar et al., 2014; Sivaraj et al., 2014; Wang et al., 2012b). Another in vivo study of CuONPs was found to inhibit tumor metastasis and rapid clearance (Wang et al., 2013). Moreover, severe acute inflammation of CuONPs has been related to the high doses in the lung of treated rats (Yokohira et al., 2009). Generally, the toxicity of CuONPs has been attributed to the induction of oxidative stress (Wang et al., 2012c). A study showed that CuONPs administration reduces the activity of antioxidant enzymes such as catalase and glutathione reductase with significant induction of glutathione peroxidase activity (Fahmy and Cormier, 2009). In another report, Cu was found to activate apoptosis and necrosis of the branchial chloride cells (Li et al., 1998). Other environmental studies showed the toxic effect of CuONPs in aquatic animals, algae, plants, and bacteria (Aruoja et al., 2009; Gomes et al., 2012; Griffitt et al., 2007; Grosell et al., 2007; Pelgrom et al., 1995; Shi et al., 2011; Bondarenko et al., 2012).

Different in vitro studies showed the effectiveness of ZnONPs cancer cell lines with low cytotoxic effect on human normal cells such as T98G glioma, Melanoma, squamous cell carcinoma cell lines (HNSCC), HepG2, and MCF7. Remarkably, the outcomes of those studies showed a similar mechanism of action, which relied on the induction of apoptosis in a dose-dependent manner (Wahab et al., 2013b; Wahab et al., 2014; Wahab et al., 2013a; Hackenberg et al., 2010). Nevertheless, a group of studies showed a similar toxic effect of ZnONPs and CuONPs (Chang et al., 2012; Franklin et al., 2007; Mortimer et al., 2008; Mortimer et al., 2010). The main route of ZnONPs entrance to the human body is skin due to its composition in sunscreens (Cross et al., 2007). Oral administration of ZnONPs showed significant toxicity to different organs (Wang et al., 2008; Zheng et al., 2009). Similar to other nanoparticles, ZnONPs showed cytotoxicity in a concentration-dependent manner and induction of oxidative stress mechanisms (Sharma et al., 2009; Brunner et al., 2006; De Berardis et al., 2010). In different studies, *C. elegans*, *Saccharomyces cerevisiae, microalga*, *E. coli* and some plants demonstrated a reduction in growth upon exposure to ZnONPs (Wang et al., 2009; Xiong et al., 2011; Franklin et al., 2007; Heinlaan et al., 2008; Jiang et al., 2009; Yamamoto, 2001; Kasemets et al., 2009; Brayner et al., 2006).

SiO_2NP provides another option for metal nanoparticles in variable formulas like delivering anticancer drugs such as paclitaxel against pancreatic cancer (Meng et al., 2015). A study indicated that camptothecin-loaded SiO_2NP has low toxicity (Lu et al., 2010; Bagwe et al., 2006). Like many other types of metal nanoparticles, the SiO_2NPs showed an anti-cancer effect in a dose and time-dependent manner combined with activation of oxidative stress (Lin et al., 2006a).

PtNPs are considered the golden approach in imaging contrasts. Moreover, PtNPs treatment showed an efficient anti-cancer effect in a xenografted lung cancer cell line (A549) (Yogesh et al., 2016). In addition, platinum-folate or photothermal targeting nanoparticles showed higher specificity against cancerous tissues (Mironava et al., 2013) (Samadi et al., 2018; Teow and Valiyaveettil, 2010). The effective anti-cancer activity of PtNPs was supported by some studies that showed a lack of toxicity of PtNPs on human endothelial and lung epithelial cells but inhaling of PtNPs has been linked with lung inflammation (Elder et al., 2007). On the other hand, a study showed a non-significant reduction in the viability of 4T1-luc2-tdTomato, HepG2, and NIH/3T3 cells when treated with PtNPs compared to normal organ functions and histological structures (Brown et al., 2018). In addition, delayed hatching of zebrafish and a reduced heart rate have been presented upon exposure to PtNPs (Asharani et al., 2011).

CeO_2 is another option for cancer treatment (Celardo et al., 2011). CeO_2 has shown induction of oxidative stress and apoptosis in cancer cells compared to normal cells, which is supported by multiple in vivo studies (Colon et al., 2010; Tarnuzzer et al., 2005; Alili et al., 2011; De Marzi et al., 2013; Sack et al., 2014; Wason et al., 2013; Lin et al., 2006b). Interestingly, the anti-cancer mechanism of CeO_2NPs has been attributed to their ability to induce oxidative stress and induction of apoptosis (Khorrami et al., 2019). However, different studies suggested the possible toxicity of CeO_2NP due to its capability to interact with biological molecules and cause adverse effects (Park et al., 2008). Other in vivo studies reported low concentrations with the toxic effect of CeO_2NP (García et al., 2011; Gagnon and Fromm, 2015). Additionally, DNA damage has been reported upon the use of CeO_2NPs (Alili et al., 2013).

Similar to PtNPs, the use of TiO_2NPs showed a long time availability and non-toxic photothermal therapy against cancer growth (Ou et al., 2016; Thevenot et al., 2008; Vinardell and Mitjans, 2015; García et al., 2011). However, the major challenge is the limited penetration of the triggering UV (Cui et al., 2013).

Iron oxide nanoparticles (Fe_3O_4NPs) are effectively used as anti-cancer therapy based on the principle of hyperthermia stimulation (Laurent et al., 2011). In the EU, Fe_3O_4NPs hyperthermia stimulation is approved as an anti-cancer against glioma, glioblastoma, and prostate cancer (Silva et al., 2011; van Landeghem et al., 2009). Using the MCF7 breast cancer cell line the Fe_3O_4NPs demonstrated induction of oxidative stress and apoptosis (Alarifi et al., 2014). Moreover, selective induction of ROS, autophagy, and mitochondrial damage has been presented in A549 (a lung cancer cell line and HepG2 (a human hepatocellular carcinoma) treated with Fe_3O_4NPs (Khan et al., 2012; Ahamed et al., 2013).

The toxicological impact of Fe_3O_4NPs has been suggested (Cho et al., 2010; Soenen and Cuyper, 2010). The toxicity effect of Fe_3O_4NPs is related to the application of usage and type of Fe_3O_4NPs (Liu et al., 2013). For instance, ROS and apoptosis induction are very common in MRI applications of the Fe_3O_4NPs (Kim et al., 2012; Schrand et al., 2012; Shubayev et al., 2009; Soenen and De Cuyper, 2010) (Könczöl et al., 2011; Murray et al., 2013). Magnetic Fe_3O_4NPs are found toxic in other studies (Berry et al., 2003; Kim et al., 2006; Liu et al., 2013; Mahmoudi et al., 2009; Martin et al., 2008; Müller et al., 2007; Müller et al., 2008; Pawelczyk et al., 2008).

5. Molecular bases of nanomaterials cytotoxicity

5.1. Passive targeting mechanism

As a mechanism, the passive targeting of nanoparticles relies on the EPR effect. Therefore, the accumulation of different types of anti-cancer nanoparticles could be associated with certain types of cytotoxicity. The molecular bases of the cytotoxicity of nanoparticles have been investigated in many studies. Generally, the major factors that have a role in the action of the nanoparticles include size and charge, metal structure, concentration, ionic dissolution, and the route of application. A systematic study assumed that the atomic number of the building element is proportionally associated with the cytotoxicity of NPs while the viability of the treated cells is related to the particle surface charge, availability of the binding site, and the dissolution of NPs (Huang et al., 2017).

In many examples, the size of NPs proved to have various effects on the target site. For instance, AuNPs and AgNPs showed a size and concentration dependant effect and are believed to be attributed to the cellular localization of these nanoparticles (Ahamed et al., 2008; Arora et al., 2009; Asharani et al., 2011; Braydich-Stolle et al., 2005; Carlson et al., 2008; Choi et al., 2009; Connor et al., 2005; Gad et al., 2012; Glazer et al., 2011; Griffitt et al., 2009; Huang et al., 2012; Kawata et al., 2009; Kvitek et al., 2009; Libutti et al., 2010; Love et al., 2012; Navarro et al., 2008; Roh et al., 2009; Santoro et al., 2007; Sereemaspun et al., 2008; Zhang et al., 2013). In other studies, bulk CuONPs and ZnONPs have shown lower cytotoxicity compared to smaller size NPs. In an in vitro study, thrombocyte and granulocyte activation, which is related to inflammation and RBCs hemolysis, was found to be correlated to the small size nanoparticles (Mayer et al., 2009). Generally, the specific surface area to size ratio is increased with the smaller-sized nanoparticles, which may affect the reactivity and dissemination of nanoparticles in the tissues and organs (De Jong et al., 2008). In addition, the surface charge has been demonstrated a role in the efficacy and elimination of nanoparticles which was attributed to low hydrodynamic diameters for improved renal clearance. PEG, cysteine, or thiolated polyaminocarboxylate improved renal clearance by neutralization the surface charge (Alric et al., 2013; Choi et al., 2007). Different studies indicated the accumulation of nanoparticles in the liver, kidney, and spleen organs. Nevertheless, certain nanoparticles such as AuNPs and FeNPs demonstrated better clearance while the hydrophobic nanomaterials proved less clearance (Brown et al., 2018).

Despite the physical properties of the nanoparticles, many studies showed that the ROS response is induced in the target cells (Jiang et al., 2008; Kai et al., 2011). Biochemically, ROS are highly reactive compounds that are associated with cellular damage due to the ability to attack nucleic acids, proteins, and proteins. Moreover, cell signaling pathways have been suggested to be involved in the activation of the ROS mechanism. For instance, a study showed that ROS induction by NPs treatment is linked with (Ca^{++}) release, leading to the activation of

Table 1
Some examples of ligand-surface target moieties used in nanomedicine anti-cancer therapy.

Nanoparticle Ligand	Cell Surface Binding Site
Folate	Folate Receptor (Lu et al., 2014; Shmeeda et al., 2006; Sun et al., 2019; Yang et al., 2014)
Transferrin	Transferrin Receptor (Iinuma et al., 2002; Li et al., 2009)
Hyaluronic acid	CD44 (Peer and Margalit, 2004; Ravar et al., 2016)
Anti-EGFR	EGFR (Mamot et al., 2005)
Anti-HER2	HER2 (Park et al., 2002)

different cell signaling cascades (Huang et al., 2010; Tang et al., 2013). In other studies, the mitochondrial potential membrane has been reduced in lung cell lines after exposure to ZnO/TiO_2 nanoparticles (Lai et al., 2015; Wang et al., 2015). Interestingly, protein degradation and cell cycle arrest were proven in certain reports after the exposure of cells to metal nanoparticles (Chang et al., 2012; Huang et al., 2017; Kai et al., 2011; Lai et al., 2015; Periasamy et al., 2016; Saptarshi et al., 2013; Wang et al., 2015; Wu et al., 2010).

5.2. Active targeting mechanism

Despite the variable efficacy of the passive targeting of nanoparticles, the nonspecific delivery of the loaded anti-cancer nanoparticles is a major limitation. Therefore, the active targeting delivery system has been investigated and showed more efficient outcomes of anti-cancer therapies (Leonor Pinzon-Daza et al., 2013; Pearce and O'Reilly, 2019; Yoo et al., 2019). However, the commercialization of active anti-cancer nanomedicines is limited to nab-paclitaxel which showed a significant improvement in the survival of aggressive pancreatic cancer (Bertrand, 2014). Despite the successful outcomes of the targeted nanomedicine in vitro, there are some challenges of the active anti-cancer therapy such as the lower diffusion, limited-expression and the localization of the target antigen before and during the treatment. In addition, cancer tissue is a heterogeneous structure that may develop resistance at a certain point of treatment which may need further monitoring toward personalized or precision medicine. The principle of active targeting drug delivery using drug-loaded nanoparticles relies on the membrane markers expressed by the target cells. Therefore, exclusive expression of certain antigens on the cancer cells is required to achieve the most efficient outcomes with minimum toxicity to the body (Yoo et al., 2019). Another challenge of the drug delivery upon reaching the target tissue is the internalization of the loaded drug (Cho et al., 2008). The endocytosis process is the major route of internalization of the conjugated nanoparticles which will lead to the release of the drug after fusion with the cellular lysosomes, thereafter, the change in the pH will release the drug inside the cells (Leamon and Reddy, 2004). Certain cell ligand-cell surface moieties have been reported in targeted nanomedicine anti-cancer treatments (Table 1) (Yan et al., 2020). These approaches rely on the following strategies: 1) Folate/Folate receptor. 2) Transferrin/transferrin receptor. 3) Hyaluronic acid/CD44. 4) Anti-EGFR/EGFR and 5) Anti-HER2/HER2.

5.2.1. Therapeutic approaches of active targeting

Clinical trials have been conducted using different nanoparticle targeting mechanisms, all of these nanoparticles are summarized in Fig. 4. Several approaches have been approved by the FDA as described in Table 2.

6. Conclusions

Oncology research is aiming to create safe, specific, less toxic, and

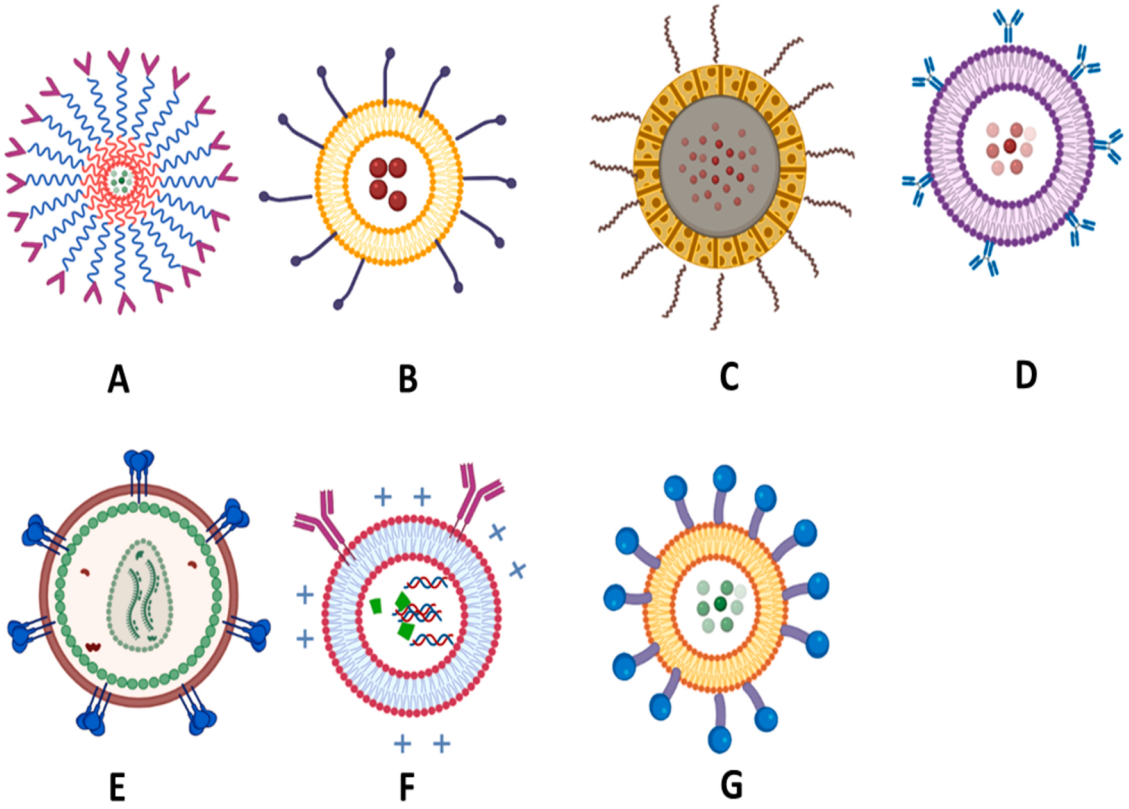

Fig. 4. Some examples of targeted drug-loaded liposomal nanoparticles as anti-cancer therapy. A. PEG-glutathione liposome. B. PEG-ligand liposome. C. Aptamer liposome. D. Anti-body coated liposome. E. Retroviral expression vector. F. Cationic immune liposome (Gene loaded). G. PEG-peptide liposome (*Created by BioRender*).

Table 2
Some examples of ligand-surface target moieties used in nanomedicine anti-cancer therapy.

FDA Approved Nano-Anticancer (Structure)	Phase INano-Anticancer (Drug)	Phase IINano-Anticancer (Drug)	Phase IIINano-Anticancer (Drug)
Doxil (Liposomal doxorubicin) (Barenholz, 2012)	Alocrest (Vinorelbine) (Semple et al., 2005)	EndoTAG-1 (Paclitaxel) (Awada et al., 2014; Fasol et al., 2012)	CPX-351 (Cytarabine andDaunorubicin)(5:1) (Cortes et al., 2015; Feldman et al., 2011)
DaunoXome (Liposomal daunorubicin) (Krauss et al., 2019)	ATI-1123 (Docetaxel) (Mahalingam et al., 2014)	LEP-ETU (Paclitaxe) (Slingerland et al., 2013)	Lipoplatin (Cisplatin) (Boulikas, 2009; Stathopoulos et al., 2010)
Myocet (Liposomal doxorubicin) (Mross et al., 2004)	MCC-465 (Doxorubicin) Terminated (Hamaguchi et al., 2004)	MBP-426 (Oxaliplatin) (van der Meel et al., 2016)	MM-398 (PEP02) (Irinotecan) (Kang et al., 2015)
Onivyde (Liposomal Irinotecan) (Drummond et al., 2010)	NanoVNB (Vinorelbine) (Yang et al., 2012)	BIND-014(Poly(lactide)- poly(ethylene glycol (Docetaxel)) (Pearce and O'Reilly, 2019)	ThermoDox (Doxorubicin) (May and Li, 2013)
DepoCyt (Liposomal cytarabine) (Koller-Lucae et al., 1997)	HL-305 (Irinotecan) (Infante et al., 2012)	REXIN-G(Retroviral expression vector) (Pearce and O'Reilly, 2019)	
Marqibo (Liposomal Vincristine) (Zhigaltsev et al., 2005)	SGT-94(Cationic liposome) (Pearce and O'Reilly, 2019)	2B3–101 (PEGylated liposome) (Pearce and O'Reilly, 2019)	
Abraxane (Albumin-bound paclitaxelNanoparticles) (Nyman et al., 2005)	MESOMIR 1(Nonliving bacterial minicells) (Pearce and O'Reilly, 2019)	SGT 53 (Cationic liposome) (Pearce and O'Reilly, 2019)	
Eligard (Leuprolide acetate andpolymer; PLGH (poly (DL-Lactide-co-glycolide)) (Ohlmann and Gross-Langenhoff, 2018)	LIPOVAXIN-MM(Liposome) (Pearce and O'Reilly, 2019)	ANTI-EGFR-IL-DOX(PEGylated immunoliposomes) (Pearce and O'Reilly, 2019)	
	MM-302(Liposome) Terminated(Pearce and O'Reilly, 2019)	CORNELL DOTS(PEGylated silica) (Pearce and O'Reilly, 2019)	
	CALAA-01(PEGylatedcyclodextrin) Terminated (Pearce and O'Reilly, 2019)		

effective anti-cancer therapies. Currently, some effective anti-cancer treatments, especially, chemotherapies are under limited use and clinical benefits due to many reasons such as delivery, solubility, and specific targeting. Nanomedicine offered various options of drug delivery models to overcome the mentioned obstacles. Some of these drug delivery systems are actively targeting the cancer cells depending on specific binding between the ligand attached nanoparticle and the cell surface receptors. A group of these active targeting anti-cancer therapies is approved by the US-FDA while others are still under clinical trial phases. Active targeting anti-cancer nanomedicine will accumulate in the target cancer tissue, however, the challenge is the presence of specific cell surface moiety. Therefore, molecular dissection of different cancers is required to reveal those tumor-specific targets. For instance, HER2 and EGFR showed effective outcomes using an active targeting drug delivery system in anti-cancer therapies. The effectiveness of targeted nanomedicine has been shown in different studies, however, the cytotoxicity and drug resistance are underestimations which encourages oncologists to urge the need for more investigations about the future approaches to this new technology.

Funding

The article-processing charges (APCs) for accepted open access articles are generously funded by Qatar National Library (QNL) for authors affiliated with Qatar-based non-profit institutions. The authors would like to thank QNL for the generous APC funding.

CRediT authorship contribution statement

Mazhar S. Al-Zoubi: Data curation, Writing – original draft. **Raed M. Al-Zoubi:** Writing – review & editing, Submission.

Acknowledgments

We are very thankful to Dr. Murtaza Tambuwala for his help in the production of Figures through his license on BioRender. Open Access funding provided by the Qatar National Library.

Conflict of interest

We declare there is no conflict of interest in this work.

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