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REVIEW ARTICLE

Novel drug delivery systems based on silver nanoparticles, hyaluronic acid, lipid nanoparticles and liposomes for cancer treatment

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Abstract

Drug delivery is a method to control the delivery of pharmaceutical compound to achieve therapeutic effect in humans or animals. Several active pharmaceutical ingredients (APIs) used in chemotherapy are cytotoxic to both cancer and normal cells. The combination of anticancer immunotherapy and conventional therapy is attractive as the new strategy to treat cancer whilst reducing cytotoxic side effects on the normal, healthy cells. Silver nanoparticles (AgNPs) have been developed as active drug delivery agents with anticancer, antibacterial, antiviral, antifungal, and antioxidant activities. The AgNPs exhibit enhanced physicochemical, optical, electrical, thermal and catalytic properties as compared to the bulk material. There are advantages as drug carriers including adjustable size and shape, high-density surface ligand attachment, enhanced stability for surface-bound nucleic acids, protection of the attached therapeutics from degradation, transmembrane delivery without harsh transfection agents, and high potential for improved timed/controlled intracellular drug delivery. However, AgNPs are toxic to normal cells and synergistic applications with natural products have been explored. Hyaluronic acid (HA) is a polysaccharide that has been widely explored for the development of anticancer therapies due to its ability to target CD44 receptors on cancer cells. HA can be used as a carrier and form conjugates with other drugs or for the delivery of multiple drugs to various pathological sites, for timing and targeted release. A novel HA-based strategy for the green synthesis of AgNP utilizes HA as reducing agent and stabilizer. Other most studied carrier systems to enhance drug delivery are lipid-based nanoparticles and liposomes. In pharmaceutical and cosmetic industries, liposome has been used to transport various molecules, and liposomal encapsulation of anti-cancer drugs is a stable platform for targeted delivery of anti-cancer drugs for cancer treatment. This review provides an overview of major development for novel delivery of drugs, highlighting the application of newly developed nano-carriers in combination therapies, immunomodulation, and theranostics, for encapsulating and targeting active molecules.

Keywords Drug delivery system · Silver nanoparticles · Hyaluronic acid · Liposomes · Co-application · Anticancer

Introduction

During chemotherapy, anti-cancer drugs such as doxorubicin (DOX), paclitaxel (PTX), tamoxifen (TMX), SN-38, or cisplatin (cis-diamminedichloroplatinum (II) or CDDP) enter the body to target the cancer cells or tissues by decreasing the cell viability or accelerating specific immune response to remove the cancerous tissues. However, these can damage both the normal and cancerous cells, leading to various side-effects. Moreover, the drugs can be easily broken down by physiological or immune reactions in the body (Lee et al. 2020). It is therefore imperative to control the drugs to affect only the cancer tissues, without affecting normal, healthy cells and preserve stable condition in vivo microenvironments until the delivery of the drugs (Lee et al. 2020). Drug delivery system (DDS) controls the delivery of pharmaceutical compound to obtain therapeutic effect in humans or animals. These include the nasal and pulmonary path of drug delivery, as alternatives to parenteral route, especially for peptide and protein therapeutics, for the treatment of human diseases. Several DDSs have been developed which include

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nanoparticles, liposomes, proliposomes, prodrugs, cyclodextrins, micro/nanospheres, micelles, gels, biopolymers and dendrimers (Tiwari et al. 2012; Gul-e-Saba and Abdullah 2015). Biosilica of diatoms is highly effective as a carrier for delivering targeted drugs in cancer treatment due to its high surface area, nanopore, biodegradation, and biocompatibility (Hussein and Abdullah 2020a). Liposomes are stable formulation strategies to enhance drug delivery and are among the most studied carrier system. Liposomes are used in the pharmaceutical and cosmetics industries to transport various therapeutic molecules (Patra et al. 2018). Gradual development of nanovectors with drugs using different bonding, are examples of the DDSs based on rational design, and well established nanotechnologies. Nanovectors have multiple nano-components, each designed to accomplish specific task to address multi-drug resistance or directed delivery of therapeutics to the target site (Zhang et al. 2013).

The main drug delivery routes include intravenous (IV), intranasal (IN), intramuscular (IM), intradermal (ID)/transdermal and oral administration, and others like ocular delivery, have been developed for topical drug administration without undesirable systemic side effects (Homayun et al. 2019). Drugs with low solubility in aqueous system however have limited bio-accessibility after oral intake, less ability to spread to the outer membrane, and requires more quantity for intravenous intake, with potentially undesirable effects, before the traditional vaccination process. All these limitations can be overcome by nanodrug delivery mechanism (Patra et al. 2018). The delivery mechanism can be affected by factors such as temperature, pH, osmotic controlled delivery and enzymes. For heat sensitive DDSs, temperature could influence the delivery of a drug. Normally, temperature can affect the solubility as well as the movement/spread of the drug. These are usually increased with an increase in temperature. Likewise, pH can affect drug solubility and thus the delivery rate of the active ingredients (Ficai et al. 2015). In the DDS design, both pH and temperature can be used to trigger the release of therapeutic drugs, at the specific target diseased-site and in a controlled-release manner.

The use of large-sized materials as DDS are facing challenges such as poor bioavailability, in vivo instability, poor solubility and absorption in the body, non-target-specific delivery, dosage effectiveness, and potential adverse effects of drugs. Novel nano-based DDS for targeting drugs to specific body parts could overcome those challenges, Nanotechnology plays a critical role in advancing medicine/drug formulations by targeting the diseased area with controlled drug release (Patra et al. 2018). HA is a naturally occurring biopolymer with no physiological toxicity, and has many advantageous properties as DDS including biocompatibility, mucoadhesion, and target-ability to CD44, the HA receptors which are overly-expressed in different tumor (Sabir et al. 2021). Liposomes are also considered as suitable drug carriers due to their bioavailability, high stability, and scalability (Sabir et al. 2020). The in vitro and in vivo nano-DDS based on AgNPs, HA and liposomes have been reported. However, the reports on synergistic applications of HA-AgNPs or AgNPs-natural products with chemotherapeutic drugs are scarce. To improve the efficiency of drug delivery to cancer cells, the combined mode of action of the drug with HA and AgNPs must be understood before clinical application. The HA-based, lipid-based and liposome-based synergistic drug application could achieve better therapeutic efficacy with minimal side-effects.

This review discusses the applications of AgNPs, HA, lipid nanoparticles and liposome as novel DDSs for improved drug delivery in cancer therapy. The combination of AgNPs with natural product or anticancer drug, and the AgNPs-coated HA with potent anti-cancer activity are highlighted as potential novel chemotherapeutic agents.

Silver nanoparticles

Nanomedicine uses nanomaterials and applies nanotechnologies in diagnostics, treatment and prevention of diseases (Satalkar et al. 2016). These include the applications of medical nanosensor, biochip, needleless injector, insulin pump, and nanoparticles (NPs) as DDSs (Ivanova et al. 2018). Nanostructures as DDSs could overcome the problems of stability and solubility of anti-cancer drugs; preserve the drug from the proteases and other enzymatic degradation, thereby prolonging the half-life of the drug in the systemic blood circulation; enhance the targeting and distribution of the drug; assist the potential release of drugs at the targeted cancer sites; and deliver multiple drugs to assist in decreasing drug resistance (Navya et al. 2019). Based on the studies of molecular mechanism, the delivery of nanomaterials affects cellular morphology, mitosis, intracellular trafficking, cytokine release, cell cycle progression, and cell viability. Nanomaterials with drugs stimulate cancer cell apoptosis in vitro and in vivo, with increased cell death rate, enhanced tumor growth inhibition, and changes in Caspase, NF-κB and Bcl-2 expression (Zhang et al. 2013). AgNPs have been used as active drug delivery agents and have exhibited anticancer activity against different cancer cell lines (Benyettou et al. 2015; Hussein et al. 2020a, b), antibacterial, and antioxidant activities (Hussein et al. 2020b, c), and antiviral and antifungal activities (Zhang et al. 2016a, b); Hussein and Abdullah 2020b). AgNPs possess enhanced physicochemical, optical, electrical, thermal and catalytic properties, as compared to the bulk material (Ivanova et al. 2018). These are advantageous as drug carriers with adjustable size and shape, high-density surface for ligand attachment, enhanced stability for surface-bound nucleic acids, protection of the attached therapeutics from degradation, potential for transmembrane

delivery without harsh transfection agents, and improved timed/controlled intracellular drug-delivery (Prashob 2017; Ivanova et al. 2018) (Fig. 1).

The AgNPs provide passive or active targeting on the tumor tissue. Active targeting involves molecular recognition where the receptor-mediated endocytosis can enhance cellular uptake of the drugs, and the aggregation of drugs at the target sites increases the activity of the anticancer therapy in vivo (Wicki et al. 2015). The biogenic AgNPs properties can be optimized through surface functionalization with targeting molecules, or coating with biodegradable and biocompatible polymers (Blanco et al. 2012; Jeyaraj et al. 2013), for intracellular trafficking of the therapeutics. The gene expression based therapies may require nuclear accessibility. Beyond enhanced cellular uptake and delivery of high drug concentrations, metallic NPs could control the release of bound therapeutic molecules from the particle surface. The attachment of the ligands via specific interactions to the metal NP surface offers a high degree of engineering precision with the potential for ligand/receptor-targeted delivery and controlled release of the particle payload (Qureshi 2013). The anti-cancer activity of synthesized AgNPs through green and eco-friendly route provides new treatment possibilities with specific nanostructures, properties and biocompatibility from the developed DDSs (Ivanova et al. 2018; Hussein and Abdullah 2020b). Several studies have shown that the incorporation of the drug with the AgNPs have the cytotoxic activities much improved. For example, Alendronate (Ald) has exhibited limited inhibition of cancer cell growth, with a maximum inhibition of 47% at 500 µM. The Ald@AgNPs however have resulted in significantly higher toxicity with IC_{50} 10.1 µM, potentially due to the higher lipophilicity and increased cellular uptake as compared to the free Ald (Benyettou et al. 2015) (Fig. 2).

AgNPs have intrinsic anticancer activity and can induce apoptosis in HeLa cells (Kim and Hyeon 2014). Clinical use of AgNPs as active antimicrobial solutions in wound care, and in in vivo studies have suggested the positive safety estimate for systemic exposure, and supported the biomedical applications of the AgNPs (Qureshi 2013). Minimal induction of secondary markers of liver damage has been reported even in the presence of chronic oral AgNPs doses greater than 300 mg/kg/day for 28 days (Qureshi 2013).

The AgNPs synthesized using different concentrations of *Setaria verticillata* extract and loaded with hydrophilic anticancer drugs including doxorubicin (DOX) and daunorubicin (DNR) show anticancer activity with significant adsorption ability and activity to reduce the side-effects of the chemotherapy drugs (Naz et al. 2017). The efficacy of endocytic delivery of the drug to the cells may depend on the NPs size and shape. The spherical shaped AgNPs of 5.7 nm size have been biosynthesized using *Aerva javanica* extracts and loaded with gefitinib as anti-cancer drug. The AgNPs-gefitinib exhibit more than 50% reduction in the viability of the MCF-7 cells, as compared to the gifitinib alone, with enhanced apoptosis in the cancer cells (Khalid and Hanif 2017). The imatinib-loaded silver nanoparticles (IMAB-AgNPs) also show dose-dependent cytotoxicity against MCF-7 cell line with the IC_{50} of 9.63 µM, 3.02 µM, and 1.69 µM for AgNPs, IMAB, IMAB-AgNPs respectively, where up-regulation of apoptosis has been exhibited by the IMAB-AgNPs. The AgNPs synthesized through *Eucalyptus procera* extracts, are therefore suggested to be a promising DDS (Shandiz et al. 2016). Methotrexate-AgNPs (Ag-MTX) coated with polyethylene glycol (PEG) have shown enhanced anticancer activity against MCF-7 cells with IC_{50} 258.6 µg/mL for PEG-Ag-MTX as compared to the MTX alone (512.7 µg/mL). The result suggests that PEG-Ag-MTX

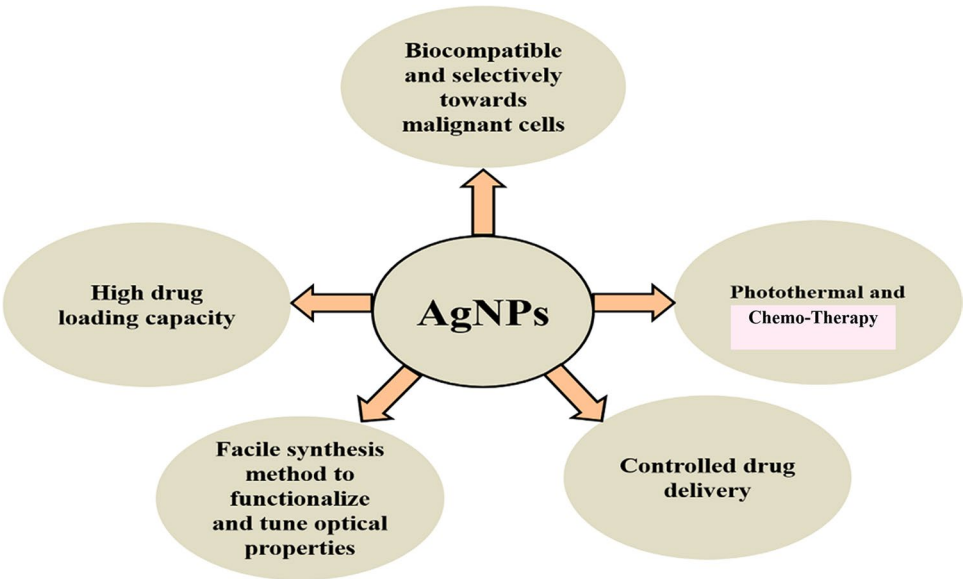

Fig. 1 Major highlights of drug delivery using multi-functional AgNPs (Modified from Prashob 2017)

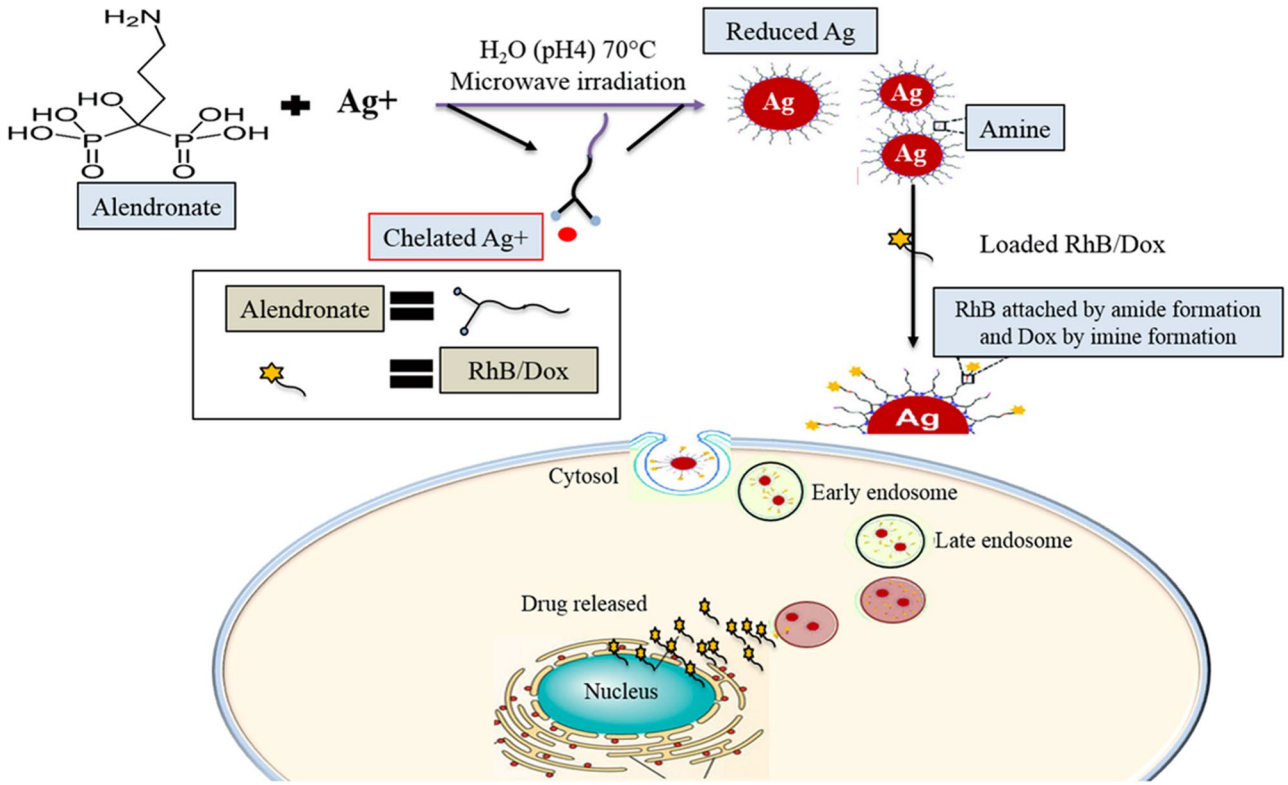

Fig. 2 Formation of Ald@AgNP and dye/drug conjugation. The uptake of the drug-Ald@AgNPs into the cells and the drug cargo release (Modified from Benyettou et al. 2015)

may provide the MTX-based cancer therapy with reduced side-effects (Muhammad et al. 2016). The AgNPs at 26 nm size, synthesized in a sodium citrate system, exhibit dose-dependent toxicity against human glioma cells (U251) when applied in combinations with Temozolomide (TMZ), an imidazotetrazine derivative of the dacarbazine alkylation factor. The induction of apoptosis in cancer cells is higher with combined treatment as compared to the AgNPs and TMZ alone, suggesting the potential of the AgNPs in improving the efficiency of the chemotherapy drug for glioma (Liang et al. 2017).

AgNPs-natural product synergistic application

The synthesis of a chitosan (CS) nanocarrier (NC)-based delivery of the AgNPs achieves the IC_{50} of 0.33 µg/mL against human colon cancer cells (HT29). The Ag-CS-NCs induces apoptosis with the activation of Caspase and the production of reactive oxygen species (ROS) elevated, higher than with the AgNPs alone (Fig. 3). The chitosan-based nanocarriers of AgNPs to cancerous cells are proposed as promising for therapeutic application (Sanpui et al. 2011). Microalgal Crude Extracts (MEs) and AgNPs synergistic applications have been investigated for their cytotoxicity on MCF-7 and 4T1 breast cancer cells, and against the non-cancerous Vero cells. The AgNPs-*Tetraselmis suecica*-chloroform extract at the 2:1 ratio achieves the highest cytotoxicity against MCF-7 (IC_{50} = 6.60 µg/mL) and 4T1 cells (IC_{50} = 53.7 µg/mL) as compared to the *T. suecica*-CHL single application (IC_{50} = 46.77 and 83.17 µg/mL, respectively) (Hussein et al. 2020a). The AgNPs-*Nannochloropsis oculata*-CHL at the 1.5:1 and 2:1 ratios exhibit the IC_{50} of 10.47 and 17.78 µg/mL against MCF-7 cells; and 79.43 and 52.7 µg/mL against 4T1 cells after 72 h treatment, respectively. The AgNPs-*Chlorella*-CHL at the 1:1 and 2:1 ratios exhibit the IC_{50} of 19.05 and 14.45 µg/mL against MCF-7 cells; and 79.43 and 50.11 µg/mL against 4T1 cells after 72 h treatment, respectively (Hussein et al. 2020b). However, none of the AgNPs-MEs treatments show any cytotoxicity against Vero cells. The synergistic applications exhibit higher incidence of early and late apoptotic events and a significant increase in the sub-G1 phase as compared to the single-applications against cancer cells, but with no apoptotic events in the Vero cells (Hussein et al. 2020a, b).

Apoptosis is an energy intensive event requiring high availability of ATPs and accompanied by the activation of caspase. Proper functioning of the caspases allows the upstream tumor-suppressor genes to activate the apoptotic pathway. As shown in Fig. 4, for the MCF-7 cell lines, the ADP/ATP ratio of the breast cancer drug Tamoxifen

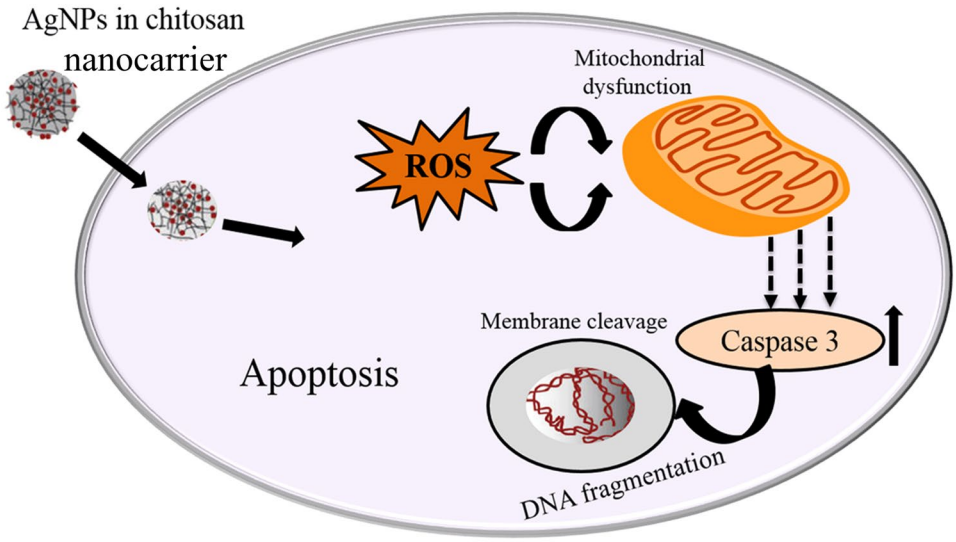

Fig. 3 The AgNPs in chitosan nanocarrier induce apoptosis in HT 29 cancer cells (Modified from Sanpui et al. 2011)

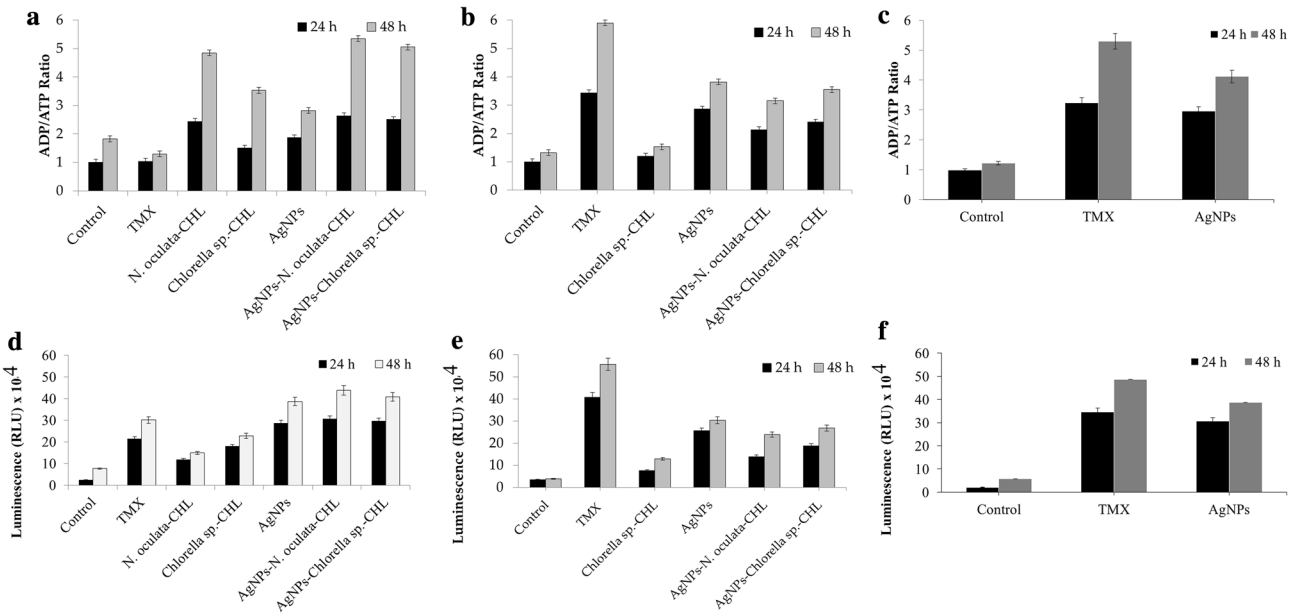

Fig. 4 Effects of MEs-CHL and AgNPs single and co-application at the IC_{50} levels against MCF-7, 4T1 and Vero cell lines, in comparison to the untreated cells, after 24 and 48 h treatments: **a**–**c** ADP/ATP ratio; **d**–**f** Caspase 3/7 activities

(TMX) was comparable to the untreated control after 24 h, and was slightly lower after 48 h, while the AgNPs was only slightly higher than the control. These results suggest cell growth arrest and that both TMX and AgNPs were more inclined towards early apoptosis. The ADP/ATP ratio was however much higher with AgNPs-*N. oculata*-CHL, and AgNPs-*Chlorella* sp.-CHL indicating that the co-applications were more inclined towards late apoptosis or necrosis. For 4T1 cell lines, TMX and AgNPs exhibited a much higher ADP/ATP ratio than the untreated control while the AgNPs-MEs-CHL showed slightly lower or a comparable level to the single AgNPs. For Vero cells (Fig. 4c), the ADP/ATP ratios attained with the TMX and AgNPs were much higher than the untreated control, confirming the early and late apoptotic events in the treated Vero cells, but none of the MEs or AgNPs-MEs treatment exhibited any induction of ADP/ATP ratio, suggesting the lower or absence of apoptosis. The MEs and AgNPs single and co-application exhibited significantly increased activities of caspases 3/7 in MCF-7 cells that were much higher than in the untreated cells. The AgNPs-*N. oculata*-CHL and AgNPs-*Chlorella* sp.-CHL treatments

(Fig. 4d) also showed the highest caspase activities. In the 4T1 cell lines, the highest activity of Caspase was observed with TMX, followed by AgNPs, and the co-applications (Fig. 4e), while for the Vero cells, the Caspase activities were significantly increased with the TMX and AgNPs treatments, but none with the MEs or AgNPs-MEs treatments (Fig. 4f).

A study to evaluate the effects of microalgal crude extracts with water (W) and ethanol (ETH) as green solvents, in synergistic applications with elevated level of AgNPs against breast cancer MCF-7 and 4T1 cells, and non-cancerous Vero cells, has been reported. The AgNPs-MEs-W at the 4:1 and 5:1 ratios after 48 and 72 h treatment, respectively, exhibit the IC_{50} values of 83.17–95.49 and 70.79–91.20 µg/ml against Vero cells, 13.18–28.18 and 12.58–25.7 µg/ml against MCF-7; and 16.21–33.88 and 14.79–26.91 µg/ml against 4T1 cells. The AgNPs-MEs-ETH formulations attain the IC_{50} values of 10.47–19.95 and 13.48–26.61 µg/ml against MCF-7; 14.12–50.11 and 15.13–58.88 µg/ml against 4T1 cells; and 56.23–89.12 and 63.09–91.2 µg/ml against Vero cells, respectively. Both the AgNPs-MEs-W and ETH have shown low apoptotic events in the Vero cells after 24 h but with very high early and late apoptotic events in the cancer cells (Hussein et al. 2020d). Significant antimicrobial activities against pathogenic microbes have been exhibited by the synergistic effects of the AgNPs-MEs. The AgNPs–MEs–methanol (MET) and hexane (HEX) show higher activities against *Streptococcus uberis, Bacillus subtilis*, and *Salmonella* sp.; and the AgNPs–*T. suecica*-HEX and MET and AgNPs–*Chlorella* sp.-HEX show activities against *Klebsiella pneumoniae* at the 1.5:1 ratios. The formulation could be useful in the fight against multidrug-resistant bacteria (Hussein et al. 2020c). The use of microalgal extracts in synergistic application with the AgNPs have been proven successful to kill breast cancer cells but not the healthy non-cancerous cells, and the presence of AgNPs could enhance antimicrobial activities of the microalgal extracts. The application of algal biomolecules in the DDS is therefore promising as the simultaneous lipid, carotenoids and antioxidant compounds can be harnessed for high bioactivities with minimal or no side-effects, especially for cancer treatment. During production stage, the variation of phytochemical compounds in the algal extracts can be modified or enhanced using two-stage cultivation and stress strategies (Ali et al. 2021). The economics of algal biocompound synergistic application with drugs or bioactive molecules can be made more competitive with the economies-of-scale, implemented through integrated algal biorefinery set-up involving biopharmaceuticals production with bioenergy and multiple bioproducts co-generation (Abdullah and Hussein 2021).

Hyaluronic acid

Hyaluronic acid (HA) is a negatively charged, high-molecular-weight glycosaminoglycan biopolymer, biocompatible, and is one of the major components of the extracellular matrix (Lapčík et al. 1998). HA is found in most biological fluids and tissues (Kogan et al. 2007). As the extracellular matrix component, HA facilitates cell proliferation and locomotion (Evanko and Wight 1999). Due to the solubility of HA, there are several modification techniques or conjugation of HA. The chemical modification is possible on the three functional components—carboxyl, acetamido, and hydroxyl groups. The HA carboxyl group can be targeted for controlled chemical modification with various hydrazides to produce polymers that can be used for application such as the development of primary drugs. The HA and its derivatives have been developed as nanoparticle DDS, gel DDS, cationic polymer gene carrier system, nano-emulsion delivery system (DS), polyelectrolyte microcapsule DDS, microsphere DDS, and film DS (Huang and Huang 2018). The hydroxyl group of anticancer drug such as paclitaxel (PTX) can be activated with carbodiimide for coupling with 4-bromobutyric acid, leading to a 4-bromobutyric-PTX linked to the ester (Kim et al. 2018). The HA-modified nanoparticles are of great interest to be used in the detection and treatment of cancer (Patra et al. 2018). Some examples of the applications are shown in Table 1. Due to the difference in molecular weight, HA can provide different bioactivities affecting changes in metabolism, receptor affinity, and clumps. HA may act as a nanocarrier itself or as an additive, but its precise role in signaling with respect to its size and localization must be understood. HA can be synthesized from different sources using one-pot synthesis, solvent-free methods, or click methods. The preparation of HA derivatives should be optimized to attain desirable properties such as strong stability, low dosing frequency, and versatility for its delivery for a broader market and clinical acceptance (Vasvani et al. 2020).

The common limitation of drug delivery into solid tumors is poor penetration of anticancer agents into the tumor mass. The aim of DDS development is to improve penetration efficiency by simultaneous targeting of the tight junctions that are present in the solid tumors (Kutova et al. 2019). There are three essential groups of cell receptors for HA:- CD44, Intercellular Adhesion Molecule-1 (ICAM-1) and Receptor for HA-Mediated Motility (RHAMM). The affinity histochemistry for HA and the expression profiles of CD44, ICAM-1, RHAMM and different surface markers have been determined by the Western blot, Flowcytometric, Fluorescence-activated cell sorting (FACs), Immunofluorescence (IF) and 2-dimensional

Table 1 The application of hyaluronic acid as drug delivery systems (Huang and Huang 2018)

Dosing system type	Loaded drug	In vivo characteristics
Hyaluronic acid-methylcellulose hydrogel	α-Chymotrypsin, IgG	Slow release of drugs within 28 days
	Nimodipine	Nanoparticles with slow release of drug in 2–3 days
Hyaluronic acid microsphere	Recombinant human insulin	Elongation of retention time and half-life of the drug in vivo
Hyaluronic acid-aminoethyl iso-butylenate nano-gel	Insulin, PEGylated glucagon-like peptide-1 (GLP-1), erythropoietin (EPO)	The release of the drug is affected by the cross-linking density and deterioration rate of the gel, with the continuous release properties
Thiolated hyaluronic acid microhydrogel	EPO	The stable release of drug within 7 days is maintained, and the blood concentration is higher than 0.1 μg/L

LC–MS/MS analyses (Wang et al. 2012; He et al. 2012; Cui et al. 2019). Both CD44 and ICAM-1 are known as cell adhesion molecules with alternative ligands before HA binding. HA can link to the CD44 receptor, which is mainly over expressed in different cancerous cells, by the receptor linker interaction. The HA-CD44 binding is common due to the presence of CD44 in the body and can be easily recognized by the HA cell surface receptor. CD44 mediates its cellular interaction with HA, thus linking the two functions as a biosynthetic half in diverse physiological events such as cellular endocytosis of HA (Fraser et al. 1988). CD44 also plays a supportive role for HA binding during cell proliferation, aggregation, migration, and activation, along with cell–cell and substrate-cell adhesion (Vasvani et al. 2020). Elevated level of High-molecular weight (HMW) HA promotes malignant cell growth and cancer development. The antagonists to HA-CD44 signaling could interfere with the HMW HA-CD44 interaction and inhibit tumor cell growth (Misra et al. 2015). ICAM-1 is a metabolic cell surface receptor for HA. ICAM-1 is also responsible for the removal of HA from body fluids and plasma which accounts for most of its circulation in the whole body. Binding to ICAM-1 receptor triggers a finely arranged series of events that fuel intracellular vesicles. Fusion with lysosomes leads to catalyze their digestion into monosaccharides, their active transmembrane transport, catalytic deacetylation, and phosphorylation. In addition, ICAM-1 may also act as a cell adhesion particle, and thus binding of HA to ICAM-1 contributes to the regulation of ICAM-1-mediated inflammatory activation (Vasvani et al. 2020). The combination of HA with RHAMM mediates cell proliferation and migration (in both normal and cancer cells) besides participating in the modulation of severe and chronic inflammatory responses in humans (Liao et al. 2008). RHAMM overexpression is connected to cancer progression, and the loss of RHAMM is linked to the malignant peripheral nerve sheath tumor growth. The interactions of HA with RHAMM play a role in inflammatory responses and tumor development and progression. Therapeutic strategies can be developed to block these key inflammatory and tumorigenic processes (Misra et al. 2015).

The development of many nano-constructs and their drug and transdermal delivery has been explored for biomedical

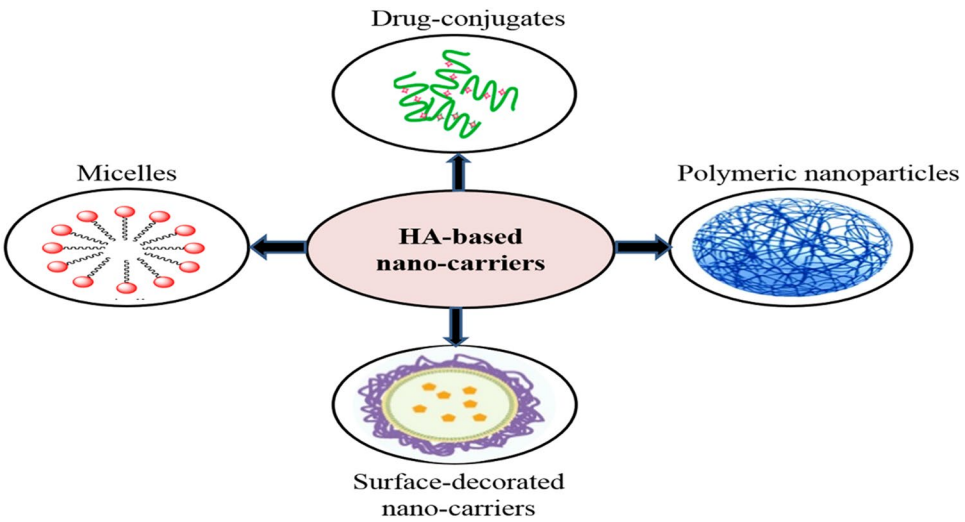

Fig. 5 The HA-dependent nanocarriers as anticancer drug delivery (Modified from Cadete and Alonso 2016)

Table 2 HA-dependent nanocarriers prepared for delivery of drugs (Modified from Cadete and Alonso 2016)

Nanocarrier type	Structure	Drug	Cancer types	Results	References
HA–drug conjugates	HA	Quercetin	Hepatoma xenograft	Elongated plasma half-life (2.5-fold) and inhibition of tumor growth (62%) as compared to free drug (25%)	Pang et al. (2014)
		SN 38	Intraperitoneal ovarian cancer	Increase in survival time from 66 days (free drug) to 71 days	Montagner et al. (2015)
		Paclitaxel	Brain metastasis of breast cancer	Increase in survival time from 42 days (free drug) to 49 days	Mittapalli et al. (2013)
		Paclitaxel	Hepatoma xenograft	Enhanced tumor uptake and reduction (fourfold) in tumor volume compared to the free drug	Xu et al. (2015)
	HA-MWCNTs-DOX	Doxorubicin	Human lung adenocarcinoma cells (A549 cells)	The MWCNTs-hyaluronic acid conjugated to doxorubicin is efficiently internalized into A549 cells by cellular endocytosis leading to 3.2 times higher cytotoxicity of the MWCNTs-HA-DOX than free DOX at the same concentration	Datir et al. (2012)
	HA-PTX	Paclitaxel	Human colon cancer (HCT-116) and MCF-7	HA-PTX shows higher cytotoxicity as compared to PTX formula, indicating that it could actively deliver the drugs to cancer cells expressing HA receptors	Lee et al. (2008)
Stimuli-responsive-HA		Paclitaxel	Hepatoma xenograft	Enhanced tumor uptake (2.8-fold as compared to drug conjugates with free drug) and decreased tumor size from 83 to 51% for the free drug	Yin et al. (2015)
		Cisplatin	Lewis lung cancer xenograft	Enhanced tumor uptake (2.5-fold as compared to free drug)	Fan et al. (2015)

Table 2 (continued)

Nanocarrier type	Structure	Drug	Cancer types	Results	References
Self-assembled micelles	HA–PLGA	Docetaxel	Breast cancer xenograft	Elongated plasma half-life (twice) and decreased of tumor size from 92 to 77% as compared to the free drug	Huang et al. (2014)
	HA–cholanic acid	Paclitaxel	Squamous cell carcinoma xenograft	Tumor growth inhibition is three-fold higher than the free drug	Thomas et al. (2014)
	HA-cholesteryl	Docetaxel	Mammary carcinoma xenograft	Enhanced plasma circulation time (12.6-fold), tumor accumulation (twofold) and significant tumor growth inhibition as compared to free drug	Song et al. (2014)
	HA–α-Tocopherol succinate (TOS)	Docetaxel	Breast carcinoma xenograft	Improved tumor accumulation (3.7-fold) and tumor inhibition (67%) as compared to free drug (57%)	Liang et al. (2015a, b)
	PTX-loaded HA-ss- deoxycholic acid (DOCA) micelles	Paclitaxel	MDA-MB-231 (in vivo)	Enhanced cytotoxicity of PTX-HA-ss-DOCA with IC_{50} of 25.6 ng/mL, confirm that redox-sensitive HA-ss-DOCA micelles have potential efficiency as targeted intracellular delivery-carriers of lipophilic anti-cancer drugs	Li et al. (2012)
Stimuli-responsive self-assembled micelles	HA–ss-PLGA	Doxorubicin	Breast carcinoma xenograft	Improved tumor accumulation	Park et al. (2015)
	HA–ss-PCL	Doxorubicin	Squamous cell carcinoma xenograft	Improved tumor accumulation	Han et al. (2015a, b)
	HA-Lys-LA	Doxorubicin	Breast carcinoma xenograft	Enhanced tumor accumulation (20-fold) leading to remarkable tumor inhibition (16-fold) as compared to free drug	Zhong et al. (2015)
	HA– PDSMA-N3	Doxorubicin	Squamous cell carcinoma xenograft	Inhibited tumor growth (60 and 40%) as compared to HA-micelles and free drug, respectively	Han et al. (2015a, b)

Table 2 (continued)

Nanocarrier type	Structure	Drug	Cancer types	Results	References
Nanoparticles	HA– methacrylate	Doxorubicin	Hepatoma xenograft	Improved biodistribution (four-fold) and higher plasma half-life (four-fold) leading to higher tumor growth inhibition (67%) as compared to free drug (57%)	Yang et al. (2015)
	HA-PTX	Paclitaxel	Lung (A549), breast (MCF-7) and colorectal (HT-29) cancer cells	Enhanced cytotoxic effects 2–3fold more than free PTX	Abdullah et al. (2014)
	HMSNs-SS-HA-DOX	Doxorubicin	Murine mammary carcinoma (4T1) cells	Stimulate apoptosis in vitro and suppress tumor growth in vivo	Huang et al. (2018)
	DOX/GHH	Doxorubicin	Liver cancer	The DOX/GHH nanoparticles exhibit higher antitumor effect as compared to free DOX	Tian et al. (2019)
	DOX-HA-MSNs	Doxorubicin	4T1 breast cancer and GES-1 gastric mucosa cells	The HA-MSNs nanocarriers show an effective new paradigm to treat cancers due to active targeting to the tumor cells and reduce side effects	Fang et al. (2019)
	HA Co-NPs (co-encapsulated DTX + TMX)	Docetaxel and Tamoxifen	AC16, MCF7, A549 and S180 cells	The drug co-encapsulated can be especially beneficial to treat tumor with CD44, and which is estrogen receptor-positive because of its capacity to reverse drug discrepancies	Zhu et al. (2017)
HA-decorated nanocarriers	GAGs	Doxorubicin	Ovarian adenocarcinoma xenograft	Improved tumor accumulation (23.5%) as compared to free drug (0.45%) and significant tumor growth inhibition	Cohen et al. (2014)
	Lipid NPs	Paclitaxel	Ovarian cancer xenograft	Enhanced tumor inhibition rate (85%), followed by PTX-NLCs (73%) and PTX solution (25%)	Wang and Jia (2016)
	Silica NPs	5-Fluorouracil	Colon tumor xenograft	Significant tumor growth inhibition	Liu et al. (2015)
	BCL/DOX-NLC	Baicalein and Doxorubicin	MCF-7/ADR cells	The HA-BCL/DOX-NLCs exhibit highest cytotoxicity and synergistic effect of two drugs against cancer cells in vitro. The in vivo study shows the highest anti-tumor activity as compared to other formulations in MCF-7/ADR cells	Liu et al. (2016)

applications. The main HA-dependent anticancer drug delivery including as drugs conjugate, micelles, polymeric NPs, and surface-decorated nanocarriers are shown in Fig. 5. Table 2 summarizes the HA-dependent nano-carriers produced for anti-cancer drug delivery. HA can interact ionically with other polymers to form polymeric NPs, and it can be used to decorate the surface of the fatty systems such as the liposomes, magnetic nanoparticles or nanoparticles (Cadete and Alonso 2016). HA reacts with other drugs to form conjugates, which can target the delivery of multiple drugs to various pathological sites, for the timing and targeted release (Chen et al. 2014). HA may be chemically associated with therapeutic drugs to form HA-dependent drug conjugates or with a hydrophobic molecule to self-gather in micelles. Moreover, HA is easily degraded in the human body (Bot et al. 2008). Thus, a nitroxide-containing substance must be added to protect the HA from being degraded, or a hyaluronidase inhibitor is added to stop the degradation of HA by inhibiting the activity of hyaluronidase (Sung et al. 2014). HA is a promising transdermal delivery carrier of nano-constructs for diagnostic and therapeutic applications. HA is advantageous to enhance the transdermal penetration of nano-constructs by the synergetic effect. The hygroscopic HA molecules hydrate skin tissues and open the transdermal pathway of conjugated cargos. The structural hydrophobic area domains in the HA molecule help the penetration of HA, and its cargo could destroy the lipid structure of stratum corneum (SC). The highly expressed HA receptors on the skin cells and cancerous skin cells also assist the penetration of HA and its derivatives by the HA receptor-mediated internalization to the cells (Jung et al. 2014).

HA has been modified by glycyrrhetinic acid (GA) and L-histidine (His) to enhance the selectivity of NPs based on HA copolymers (GHH). The DOX-loaded GHH has shown enhanced anticancer activity against liver cancer with reduced toxic side effects as compared to the free DOX (Tian et al. 2019) (Fig. 6). PTX is conjugated with HA using amino acids linker, which offer more stability in vivo. The HA-amino acid-PTX conjugates show improved cytotoxicity against breast cancer cell-lines and therefore may have possible application as therapeutic agents. The HA-leucyl-PTX exhibits higher cytotoxicity against MCF-7 cells (IC_{50} of 0.253 nM PTX equivalent) than other conjugate and free PTX (0.795 nM). These confirm that HA-PTX could stay in the body for a longer period as compared to the free PTX, and enhance the activity of the PTX against breast cancer (Xin et al. 2010). The conjugates of HA-DOX have been reported using HA-adipic acid dihydrazide (ADH) derivative (Cai et al. 2010). The in vivo study of animal model group treated with HA-DOX has demonstrated a delay in cancer development for 10 weeks, with increased animal survival as compared to the group treated with DOX alone. The HA-DOX conjugates are synthesized by combining the carboxyl groups of HA with the amine groups of DOX, and

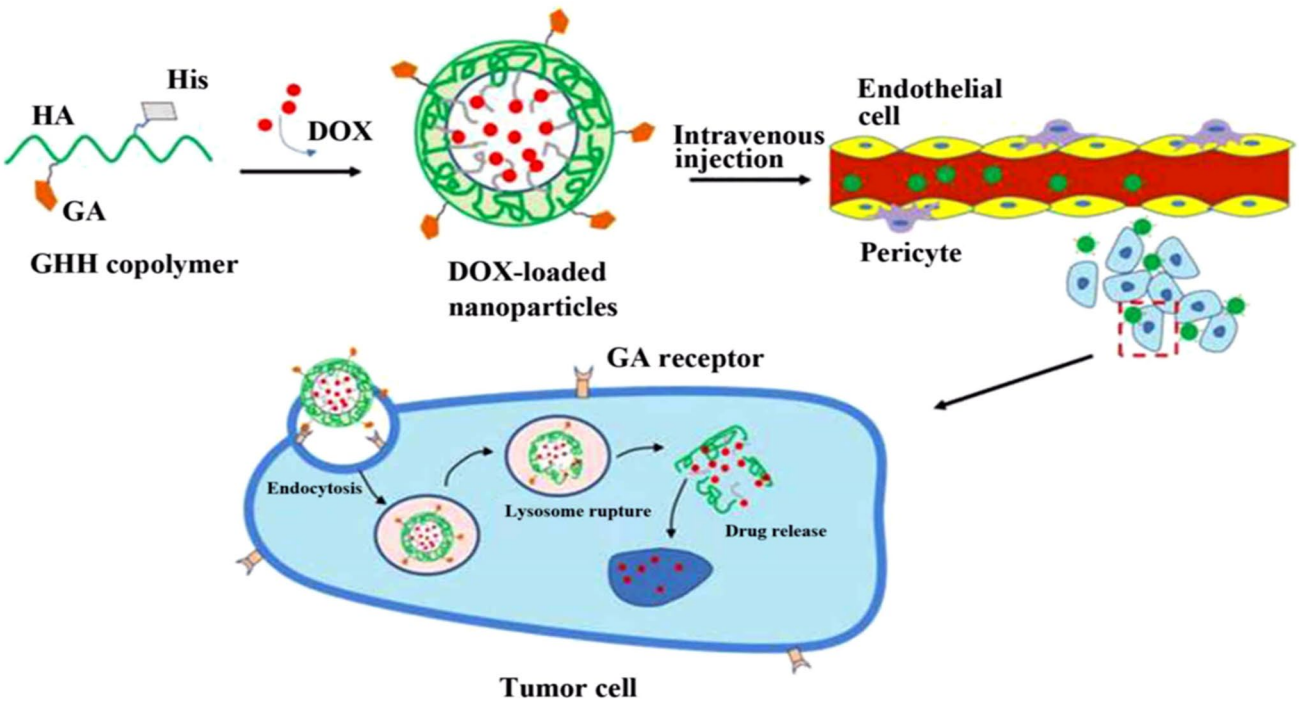

Fig. 6 Liver-targeting delivery and release of DOX from GHH NPs. The illustration represents self-assembly, aggregation in tumor tissue and intracellular uptake of GHH NPs (Tian et al. 2019) with permission from Spandidos Publications (Creative Commons Attribution License)

the methyl-like NPs, formed by self-assembly. However, HA-DOX molecules are stable in serum, as hyaluronidase activity is known to decrease significantly in the serum of cancer patients. This technique can also reduce the toxicity in animal models due to the early release of the drug in vivo (Lee et al. 2020). The HA conjugated cisplatin (CDDP) has also shown significantly enhanced tumor reduction with lower toxicity in the head and neck squamous cell carcinoma (HNSCC) as compared to the free CDDP. The mice group treated with HA-CDDP exhibits statistically significantly ($p = 0.003$) higher tumor reduction, while the control group shows tumor development (Cohen et al. 2013).

Hyaluronic acid-coated AgNPs

HA has a large number of negatively charged carboxyl groups, that could highly react with the Ag^+ ions, enabling the synthesis of stable AgNPs complexes (Abdel-Mohsen et al. 2012). HA is therefore a promising ligand for coating the AgNPs to get low cytotoxicity and increased stability. The AgNPs could eventually serve as a nano-platform for many biological applications (Zhang et al. 2016a, b). The HA-AgNPs formed by electrostatic interaction between negatively charged HA molecules and positively charged AgNPs have been developed via ultra-sonication. The synthesized HA-AgNPs display anti-leukemic activity with high ROS expression as compared to the single treatments. The leukemia cell viability is significantly inhibited by the HA-AgNPs through specific binding of HA with the CD44 receptors overexpressed on the cell surface, leading to apoptosis. The novel strategy of the HA-AgNPs in leukemia treatment is attributed to the modification of redox conditions in the cancer cells whilst decreasing systemic toxicity (Zhang et al. 2018). A novel HA-based route for the green synthesis of AgNPs has also been proposed, in which HA is used as the stabilizer and reducing agent. Moreover, HA is the ligand of the CD44 and the HA-based AgNPs can target the CD44 receptors that are highly expressed in the cancer cells. The CD44-based endocytosis can significantly enhance intracellular delivery of HA-AgNPs as compared to the AgNPs alone. The anti-cancer activity is significantly improved by HA modification potentially through the reduction of mitochondrial membrane potential and pyknosis, autophagy, cell cycle arrest, and apoptosis (Liang et al. 2015a, b) (Fig. 7). Another important aspect of the HA-AgNPs therapy is in reducing the damage to the cells whilst enhancing the antibacterial activity. The hyaluronidase-triggered photo-thermal platform for the elimination of bacteria has been reported based on graphene oxide (GO) and AgNPs, wherethe HAase-triggered GO-AgNPs exhibit antibacterial activity against *Staphylococcus aureus*. The GO-dependent nanomaterials locally increase the temperature, upon illumination of the Near-Infrared (NIR) light, leading to a higher death-rate of the bacteria. The HAase-triggered AgNPs releasing methods for antibacterial activity, allow the AgNPs to be covered by the HA template, for lower toxicity against the mammalian cells. As shown in Fig. 8, the GO-HA-AgNPs nanocomposites exhibit excellent antibacterial activity for the wound disinfection in the in vivo model (Ran et al. 2017).

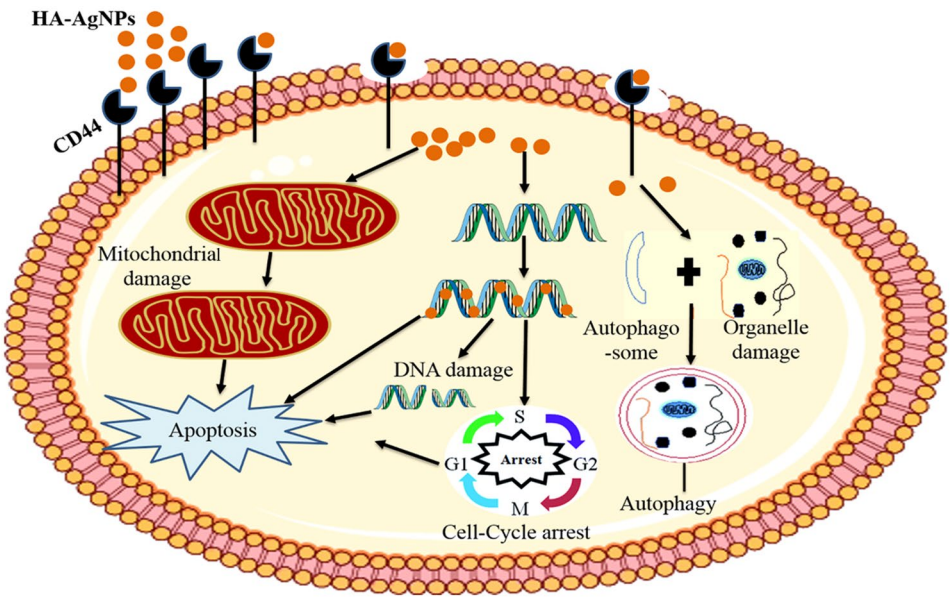

Fig. 7 The possible mechanisms of antitumor effect of HA-AgNPs (Modified from Liang et al. 2015a, b)

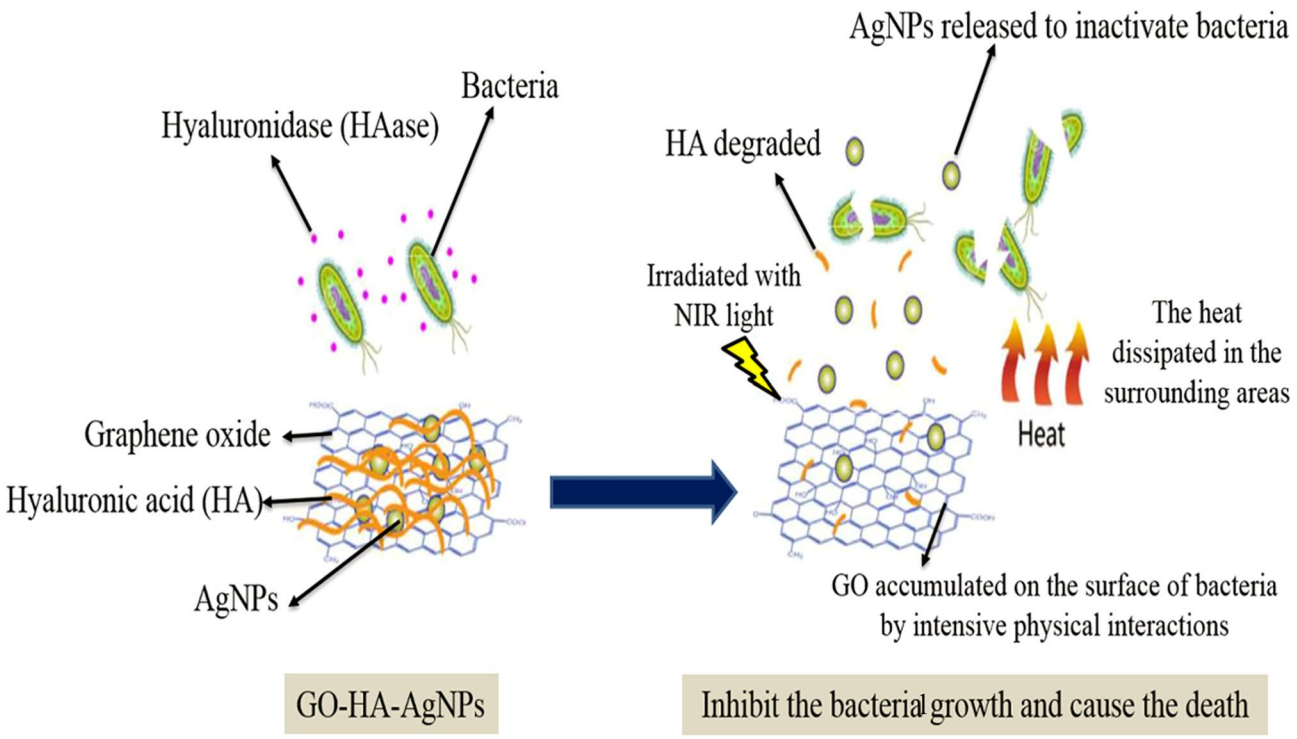

Fig. 8 HA-templated Ag nanoparticles/graphene oxide composites for synergistic antibacterial therapy (Modified from Ran et al. 2017)

Lipid nanoparticles (LNPs)

Lipid nanoparticles (LNPs) or solid lipid NPs (SLN) are considered as non-toxic, biocompatible, and easy to produce formulations. Nanoparticle lipid carrier (NLC) is a promising medium for transporting and delivering products and small drug particles (Scioli Montoto et al. 2020). SLN/NLCs, as with other nano-structures, have therefore found applications in cancer therapy (Hare et al. 2017), diseases and/or site-specific therapies of the central nervous system disorders, as antimicrobial, and for diagnostic purposes (Scioli Montoto et al. 2020). Because of their lipid hardness, SLNs can enhance drug bioavailability, reduce biological degradation and allow for controlled activation, and sustained drug release and delivery. With the advantageous physical properties and its promising combination of active compounds with their associated benefits, the SLNs are attractive for carrying colloidal drugs (Alsaad et al. 2020). Colloidal systems are dispersions of large particles or molecular aggregates of medium size, between particles in solution and particles in coarse suspension, with the acceptable sizes of 1–1000 nm (Montoto et al. 2020). SLN can be mass-produced by avoiding the use of organic solvents to reduce toxicity, and for higher stability than other nano-lipid carriers for in vivo application. However, the disadvantages include lower drug loading capacity due to its crystal structure, changes in release profiles and drug release potential after storage-induced polymeric transformation, and high water content after dispersion (Amoabediny et al. 2018). Figure 9a shows that the drugs can be incorporated into the SLNs based on drug-enriched shell-core shell, drug-enriched core-core shell or homogeneous matrix models (Mishra et al. 2018). Lipid–polymer hybrid NPs (LPHNPs) are the next-generation of core and shell nanostructures, which are derived from both lipid and polymeric NPs, where the polymer core remains surrounded by a lipid layer, and this has not been widely exploited. There has been a shift in the preparation of LPHNPs, from a two-step to a one-step strategy, including simultaneous self-assembly of polymers and lipids. In oncology, the two-in-one structure is of particular importance as an assembly platform for drug delivery. The exogenous surface can be combined with multiple routes for active targeting of anti-cancer therapy, delivery of DNA or RNA material, or as a diagnostic imaging agent (Mukherjee et al. 2019).

SLNs can be produced by solid lipid, emulsifier, and water/solvent systems using Solvent Evaporation, High-pressure homogenization, Ultrasonication/High-Speed Homogenization, Supercritical Fluid, Microemulsion/Double emulsion, Solvent Emulsification-Diffusion, and Spray Drying methods. The selection is based on the stability and solubility of the drug, type of lipid, and route of administration (Amoabediny et al. 2018). High pressure homogenization (HPH) is a potent technology used in the production of

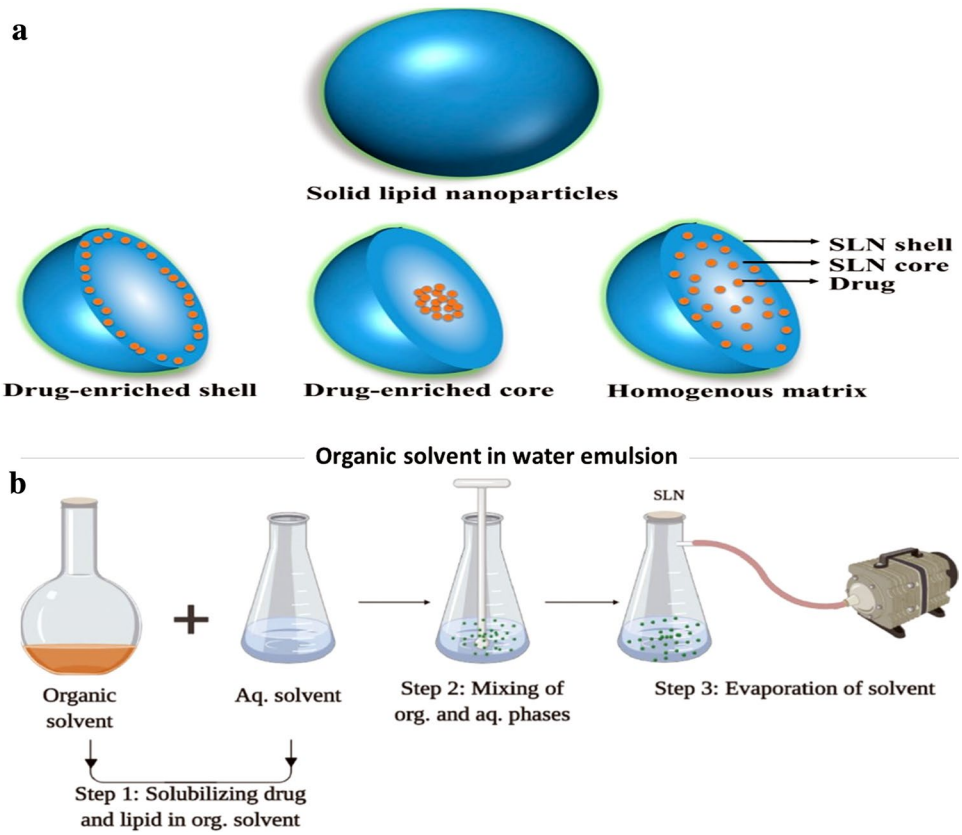

Fig. 9 **a** Models for drug incorporation into the SLN (Mishra et al. 2018); **b** Evaporation method for SLN preparation (Sastri et al. 2020) (Creative Commons Attribution License (CC BY))

SLNs which simple, reliable, and easy to scale up (Garud et al. 2012). The HPH pushes the liquid out of a narrow gap of a few micron sizes at a high speed of 100–2000 bar. The fluid comes from a short distance to a very high speed of over 1000 km/h. The particles are ruptured to the sub-micron range by the cavitation force acting on them as well as the high shear stress, but at then end only 5–10% of lipid may be used. Both hot homogenization and cold homogenization work in a similar way (Nasikkar et al. 2019). To achieve smaller molecule sizes, incorporation of ultrasonication and high-speed homogenization can be utilized to produce SLNs. The mixture of drug and molten solid lipid is added to the aqueous surfactant solution and mixed by a high-speed homogenizer (for 15 min at 8000 rpm), and the mixture solution is sonicated at 0 °C to reduce the molecule sizes. The prepared NPs are then filtered and stored at 4 °C (Amoabediny et al. 2018). In the solvent emulsification–evaporation method, hydrophobic drug and lipophilic materials are dissolved in water-immiscible organic solvents (toluene, chloroform, and cyclohexane). Using high-speed homogenization, the mixture is emulsified into an aqueous stage. The coarse emulsion is immediately allowed to flow through the microfluidizer. As shown in Fig. 9b, rotary evaporator is then used at room temperature and low-pressure to evaporate the organic solvent (Sastri et al. 2020). The main advantage is in reducing the impact of the heat stress, allowing for the combination with high-temperature drugs. The disadvantage however is the use of organic solvent that may react with the drug particles (Sastri et al. 2020).

Diffusion method is another easily scalable technique, requiring less physical pressure, and ensuring the loading of both lipophilic and hydrophilic pharmaceuticals. The synthesis of SLNs using solvent emulsification-diffusion method involves forming a solvent-in-water emulsion using water-miscible "partial" solvent containing lipids in reasonable quantities. When the oil-in-water emulsion is transferred to the water, the lipophilic substance dissolved in the organic solvent, freezes instantly due to the diffusion of the organic solvent from droplets into continuous liquid phase (Patravale and Mirani 2019). In double emulsion method, the molten drug-lipid solution is atomized by ultrasonic, centrifugal, electrostatic, pneumatic, or atomization methods, and then transferred to a spray dryer heated by hot gas. The stabilizer inhibits fractionation of the drug in the external phase during solvent evaporation of the encapsulated drug (Amoabediny et al. 2018; Nasikkar et al. 2019). Spray drying is the cheaper alternative method to lyophilization where rapid evaporation of solvents results in the formation of dry SLNs. The resulting NPs can be separated by cyclone (electrostatic precipitator or filter). This method is preferred for lipids with a melting point more than 70 °C (Amoabediny et al. 2018). The NPs can also be produced by gas/supercritical anti-solvent

(GAS/SAS), aerosol-solvent/extraction-solvent (ASES), and supercritical fluid extraction of emulsions (SFEE). In the SFEE method, the use of organic solvents is avoided, and the dry powder NPs may be obtained under mild pressure and temperature. Supercritical fluid is considered as an eco-friendly, alternative method for the formation of SLNs. The dissolving power of the fluids may be different under ambient and supercritical conditions. Drugs and lipids are dissolved in a supercritical fluid and mixed at the critical point of pressure and temperature in a homogenizer. The mixture is then passed through an atomizer in an expansion vessel. The fluid is allowed to evaporate and the SLNs are formed. Of the many candidate gases such as CO_2, ammonia, ethane, propane and methane, CO_2 is the best as supercritical fluid as it is generally more economical, environmentally-acceptable, non-toxic and safe; and has an easily accessible critical point (Amoabediny et al. 2018).

Liposomes

The SLNs are actually colloidal carriers or fat emulsions with a sub-micron size, where the liquid fat (oil) is now replaced by the solid fat, developed as an alternative system to the emulsions, liposomes, and polymeric NPs (Alsaad et al. 2020; Mukherjee et al. 2009). Liposomes and their derivatives (transferosomes, niosomes, pharmacosomes, and ethosomes), on the other hand, are Vesicular drug delivery systems (VDDS). These are lipid-based vesicles that have found applications in biology, immunology, genetic engineering, diagnostic and therapeutic application of pharmaceutical compounds for the treatment of a range of localized disorders. These are considered as a safe and effective way to improve the delivery of hydrophilic and lipophilic drugs (Witika et al. 2021). Liposomes are the first nano-DDSs that have been successfully translated into real-time clinical applications. The bilayer phospholipid vesicles have undergone major developments since their first introduction in 1965. The delivery of liposomes alters their distribution profile, strengthening the therapeutic index of different drugs (Fig. 10). Liposome-based products have been developed as DDSs in diverse areas including for anti-fungal, anti-inflammatory, therapeutic genes, and anti-cancer treatments (Fig. 11). The well-known clinical product of liposomes include Doxil®, DepoDur ™, and Ambisome® (Bulbake et al. 2017). Table 3 summarizes the advantages and properties of liposomes and drug/drugs-loaded and antibody-loadedliposomes.

There are generally four types of liposomal delivery systems—conventional liposomes, sterically-stabilized liposomes, ligand-targeted liposomes, and a combination of the above. The conventional liposomes are the first production of liposomes, consisting of a lipid bilayer with anionic, cationic, or neutral (phospho) lipids, and cholesterol, restricting the aqueous volume. For nanoparticle preparation, drugs can be dissolved in supercritical CO_2 fluid, followed by sudden expansion, supersaturation and nano/microdrug deposition (Byrappa et al. 2008). Other methods include the use of Aerosol Flow Reactor involving dissolution of drug in volatile organic solvents, and spraying with inert gas at 40–400 °C (Eerikainen et al. 2004); nanodrugs formation under high-pressure homogenizer (Krause and Muller 2001); continuous precipitation where drug is dissolved in water-soluble solvent system with stabilizer addition (Douroumis and Fahr 2006); and milling for size reduction of soluble and insoluble drugs in water or buffer media (Castrillo et al. 2007). The nanoparticle sizes can be controlled and modified based on the preparation methods and factors such as the pressure and shear stresses (Krause and Muller 2001); temperature and storage conditions (Lujan et al. 2019) and biological and irradiation methods (Shanab et al. 2021). Nanoliposomes and microliposomes have been synthesized for miRNA delivery to breast cancer cells and the mechanism is suggested through internalization

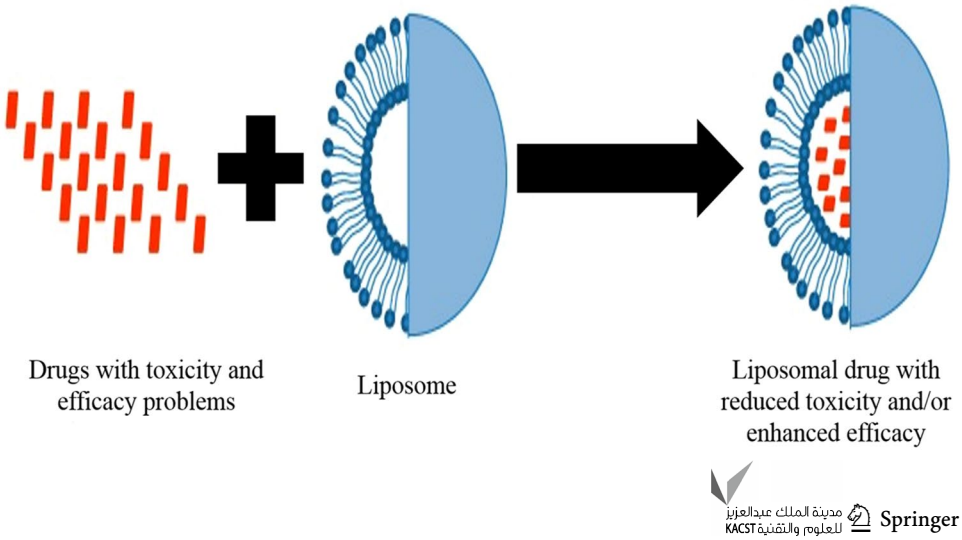

Fig. 10 The advantages of formulating drugs in liposomes (Bulbake et al. 2017) with permission from MDPI (Creative Commons Attribution (CC BY) license)

Fig. 11 Liposome-based products as drug delivery systems in diverse areas (Bulbake et al. 2017) with permission from MDPI (Creative Commons Attribution (CC BY) license)

via endocytic pathway (Lujan et al. 2019). The production of liposomal suspensions involves the use of Didodecyldimethylammonium bromide, ovine cholesterol, and tocopherol PEG 1000 succinate which are suspended in 100% ethanol, before synthetic miRNA being added and incubated at room temperature (Lujan et al. 2019).

The liposomal delivery has been proven useful to enhance the therapeutic indicator of encapsulated drugs such as amphotericin and doxorubicin (Hua and Wu 2013). The conventional liposomal formulations decrease the toxicity of compounds in vivo, by modifying the pharmacokinetics and bio-distribution to improve drug delivery to the diseased tissue, as compared to the free drug (Sercombe et al. 2015). To enhance stability and improve circulation times in blood, sterically-stabilized liposome—the hydrophilic polymer (polyethylene glycol (PEG)), is an optimal choice. The production of a steric barrier enhances the activity of encapsulated agents by decreasing the in vivo opsonization with serum composition, and fast recognition and uptake by the reticuloendothelial system (RES). This reduces the removal of drugs and elongate blood circulation and provides aggregation at the pathological sites, whilst reducing the side effects (Ishida et al. 2001). Ligand-targeted liposomes show major potential for site-specificity to deliver drugs to the cell types or organs in vivo, with selective expression of specific ligands (such as the cell adhesion molecules or receptors) at the site of disease (Hua and Wu 2013). The different types of ligands include antibodies, carbohydrates, and peptides/proteins. The coupling of antibodies (monoclonal antibodies) to produce immunoliposomes is an example of the more versatile ligands that could be attached to the liposome surfaces. These monoclonal antibodies confer stability and higher binding capacity because of the presence of two binding sites on the molecule (Bendas 2001). New type of liposome utilizes the combination of different platforms to further enhance liposomal targeting and targeted-drug delivery. Combining target-specific binding of immuno-liposomes with steric stabilization of PEG, to create a long-circulating immuno-liposomes, could significantly enhance the pharmacokinetics of immuno-liposome (Fig. 12) (Maruyama 2002; Sercombe et al. 2015).

Table 4 summarizes the liposomes formulations, which are used as the anticancer drugs against different cell lines in vivo and in vitro. The success or failure of micro/nanoDDS hinges upon the encapsulating efficiency (EE), the attainment of slow release and targeted delivery, and the stability of the API (Lujan et al. 2019). Liposome can be loaded with two or more drugs simultaneously for improved therapeutic effects on the cancer cells. The strategy aims to bind two or more compounds to reduce effective doses and their associated side effects (Fig. 13). The liposomal multi-drug carrier (MDC) could deliver both water-soluble (in the aqueous pulp) and lipophilic (reserved in the bilayers) drugs or multiple-drugs with the same solubility (hydrophilic/hydrophobic) without any interactions between the two compounds (Banerjee et al. 2015). Chemotherapeutic agents encapsulated with liposomal structures can limit normal tissue uptake of the

Table 3 The advantages and properties of liposomes and drug/drugs-loaded and antibody-loaded liposome (Daraee et al. 2014; Banerjee et al. 2015; Bulbake et al. 2017; Sharma et al. 2018)

Liposomal advantages	Properties of liposomes	Advantages of drug-loaded liposome	Drugs-loaded liposome	Antibody-mediated liposomes Ligand
Stability increased if liposome is produced by encapsulation	Liposomes are synthesized from cholesterol and nontoxic phospholipids	Biocompatibility, enhanced solubility of lipophilic, and amphiphilic drugs	Amphotericin B, Minoxidil, porphyrins, peptides, and anthracyclines; hydrophilic drugs, such as anticancer agent (doxorubicin or acyclovir)	Anti-CD74 antibody
Liposomes enhance efficacy and therapeutic effect of drug Low solubility (actinomycin-D)	Liposomes are composed of one (unilamellar) or multiple (multilamellar) lipid bilayers surrounding an aqueous layer	Sustained release system of systemically or locally administered liposomes	Doxorubicin, cortisones, cytosine arabinoside, biological proteins or peptides (vasopressin)	Monoclonal nucleosome–specific 2C5 antibody (mAb 2C5)
Liposomes decrease the toxicity of the encapsulated agent (amphotericin B, Taxol)	Positively-charged membranes, which are impermeable to Cations, and negatively charged ones are relatively permeable to anions	Passive targeting to the immune system cells, especially mononuclear phagocytic system	Porphyrins, antimonials, amphotericin B, vaccines, immune-modulators	F(ab')2 fragment of human monoclonal antibody GAH
Liposomes decrease the exposure of sensitive tissues to the toxic drugs	Liposomes size from 30 nm to several micrometers, and the size differences influences circulation times and RES uptake rates	Site-avoidance mechanism and the targeted delivery can be functionalized with ligands to deliver therapeutic agents to cellular components or cells	Doxorubicin andamphotericin B	Fab' fragments of a humanized anti-p185HER2 monoclonal antibody (rhuMAbHER2)
Site avoidance effect	Permeable to water	Site-specific targeting. The drug is prevented from reaching the healthy cells	Anti-inflammatory drugs, anticancer, anti-infection	Anti-transferrin receptor single-chain antibody fragment (TfRscFv)
Liposomes are non-toxic, flexible, biocompatible, and completely biodegradable	Osmotically sensitive	Enhanced penetration into tissues	Corticosteroids, anesthetics, and insulin	34A antibody
Flexibility to pair with site specific ligands to reach target site		Enhanced transfer of hydrophilic, charged molecules, and Size or lipid composition differences help to regulate bio-distribution of liposomes	Antibiotics, chelators, plasmids, and genes	

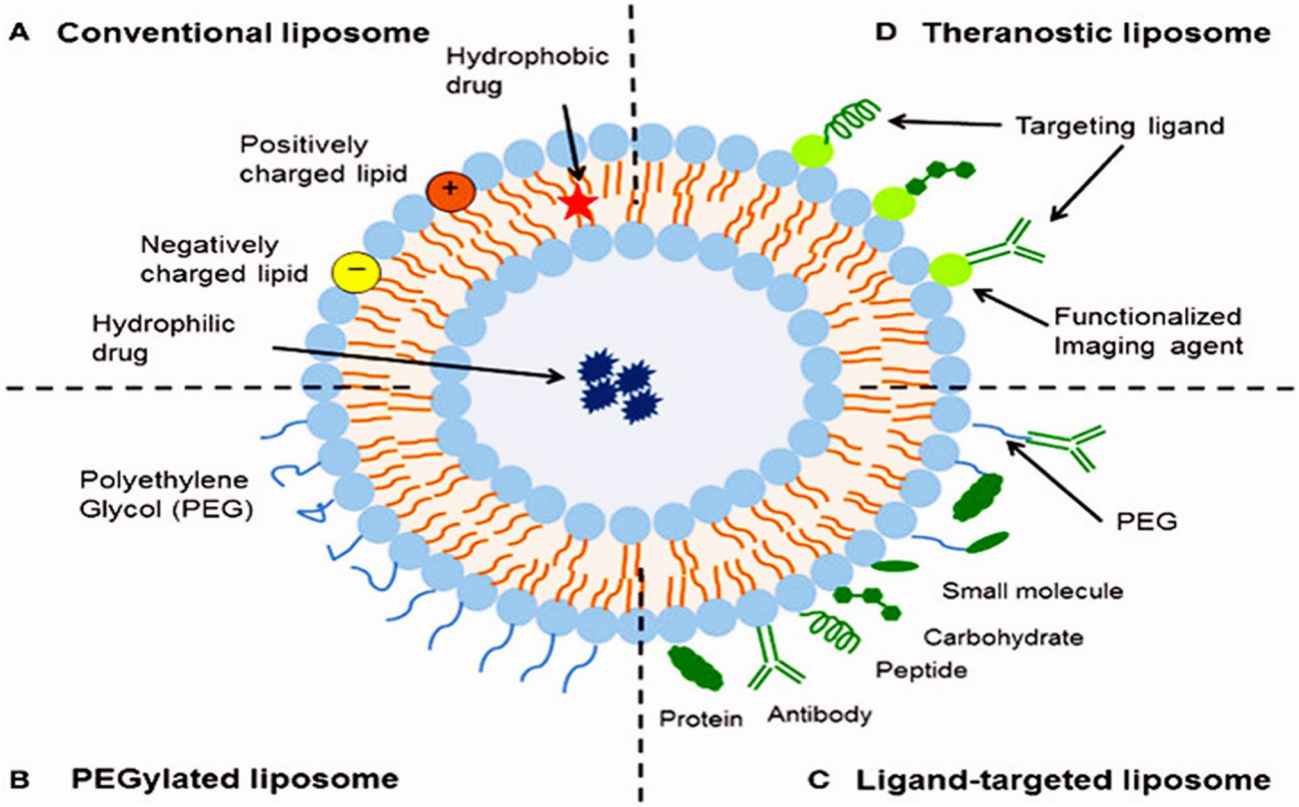

Fig. 12 Different types of liposomal drug delivery systems (Sercombe et al. 2015) with permission from Frontiers Media S.A. (Creative Commons Attribution License (CC BY))

treatment and thus enhance its therapeutic effect. By passive targeting, liposomes can preferentially target tumor cells (usually more than 24–48 h) by improving retention effect and permeability of the vasculature, where the leaky tumor vessels are combined in the absence of lymph drainage (Maeda 2001; Olusanya et al. 2018). The immunoliposomes (ILP) utilize antibody-dependent pathway with antibodies on the liposomal surface to target cancer cells or endothelial cells of the tumor vasculature (Olusanya et al. 2018). The pendant type of ILP (34A-PEG-ILP) consists of circulating polyethylene glycol (PEG)-ILP linked to the antibodies (34A antibody) at the end of the PEG chain. These ILPs exhibit higher targetability to the site of lung endothelial cells and tumor cells, than the ordinary liposomes alone. The free PEG successfully helps to avoid the RES uptake of the ILPs (Maruyama et al. 1999; Olusanya et al. 2018). The HA-decorated liposomes (HA-LIP) loaded with an anti-proliferative drug, could target the CD44 receptors on the Bronchiolitis Obliterans Syndrome (BOS) patient-derived mesenchymal cells (MCs). The HA-LIP are more effective in entering the primary BOS-MCs and do not stimulate activation of the macrophage, and therefore are promising biocompatible nano-vectors for local targeted drug delivery (Meloni et al. 2019).

The strengths and properties of HAs and liposomes are shown in Tables 1, 2, 3 and 4. The major limitations of the DDS in general are the high cost and the inability to achieve the intended dosage at the diseased sites. The application of the AgNP as DDS may need further in depth research due to the concern on its toxicity to the normal cells. For the HAs to be effective as a DDS, the major challenge will be in ensuring targeted delivery at the correct dosage on the CD44 receptors of the cancer sites. HAs are ubiquitous in human body and there are also CD44 cell surface receptors on the healthy tissues which may cause the losses of the payload delivery during circulation. There is a great need to understand the role of standard and variant isoforms of the CD44, and the importance of the HA ligand sizes which determine its biological functions (Louderbough and Schroeder 2011; Senbanjo and Chellaiah 2017). The synergistic applications of drugs with algal-based natural products and lipid nanoparticles are more promising for effective therapeutic effects with minimal or no side effects as these are Generally-Regarded As Safe (GRAS) applications, requiring simpler preparation. However, the application of liposomes as DDS has made major impacts in many biomedical applications. The Critical Quality Attributes (CQAs) required for liposomal formulations include narrow size distirbutions, high EE

Table 4 The liposome formulations used as anticancer drugs

Liposome nanocarrier type	Structure	Drugs	Cancer cells	Results	References
HSPC/DSPE/cholesterol (12.5:1:8.25 molar ratio)	Doxil®	Doxorubicin	Colorectal (in vitro)	The synergistic effects of combination of DOX and magnetic liposomes increase the ability to kill colorectal cancer cells (CT-26 cells)	Hardiansyah et al. (2014)
HSPC:Cholesterol: PEG 2000-DSPE (56:39:5 molar ratio)			Ovarian, breast cancer (in vivo)	Doxil® exhibits a much lower volume of distribution (4 L) as compared to the free drug (254 L) and reduces the side effect of free DOX treatment	Bulbake et al. (2017)
EPC:Cholesterol (55:45 molar ratio)	Myocet® (TLC D-99)	Doxorubicin	Metastatic breast cancer (in vivo)	Myocet® produces less cardiotoxicity as compared to doxorubicin, while shown comparable antitumor activity	Harris et al. (2002) and Bulbake et al. (2017)
Cholesterol, DSPC, DSPE and DSPE-PEG2000 (10 µmol total phospholipid)	DOXIL™	Doxorubicin	Prostate cancer (in vivo and in vitro	The doxorubicin encapsulated with liposomes reduce tumor growth and inhibit prostate cancer growth in vitro and in vivo	Mock et al. (2013)
DOTAP, cholesterol and ATRA (molar ratio 70:20:10) HSPC:	ATRA	All-trans retinoic acid (DOTAP lipo-ATRA)	Lung cancer (in vivo, animal)	DOTAP lipo-ATRA is the suitable carrier for ATRA in lung cancer treatment, showing higher bioavailability in blood and lung even after 24 h	Berlin Grace and Viswanathan (2017)
HSPC: DSPE-PEG2000: cholesterol: anacardic acid (molar ratio 0.55:0.05:0.35:0.05)	MXT	Mitoxantrone	Melanoma cell lines (A375 and Hs294T) and normal human dermal fibroblast line (in vitro)	The mitoxantrone loaded into liposomal-carriers with encapsulated anacardic acid show significantly increased cytotoxicity of the drug towards melanoma and protect the normal cells from damage caused by the drug	Legut et al. (2014)

Table 4 (continued)

Liposome nanocarrier type	Structure	Drugs	Cancer cells	Results	References
Egg phosphatidylcholine: cholesterol: TPGS1000-TPP (molar ratio 88:3.5:8.5)	PCX	Paclitaxel	Lung cancer cell lines (in-vivo & in-vitro)	Paclitaxel-liposomes show the highest anticancer activity in vitro and in the drug-resistant A549/cDDP xenografted tumor model by enhancing the cellular uptake, which is selectively accumulated in the mitochondria, and causing release of cytochrome C, and also enhance the cascade of caspase 9 and 3, activated pro-apoptotic Bid and Bax and suppress the anti-apoptotic (Bcl-2)	Zhou et al. (2013)
Phosphatidylcholine, cholesterol and cardiolipin	Taxol®	Paclitaxel LEP-ETU	Ovarian, breast, non-small cell lung cancer and AIDS-related Kaposi's Sarcoma (In vitro)	Less than 6% of confined paclitaxel was released after 120 h, suggesting that the drug is very stable in the entrapped form	Zhang et al. (2005)
A cationic liposome-PEG-PEI complex (LPPC)	LPPC/TAM	Tamoxifen	ER-positive breast cancer cells (MCF-7) (in vivo)	The LPPC/TAM via transdermal inhibit about 86% of tumor growth in mice, that hold BT474 tumors. This treatment of LPPC/TAM do not affect the skin or any organs	Lin et al. (2016)
Phospholipid to cholesterol (2.1:1)	TMX-DOX-liposomes	Tamoxifen and Doxorubicin	Breast cancer cells (MCF-7) (in vitro and in vivo)	The TMX-DOX-liposomes are more cytotoxic to MCF-7 cells as compared to DOX-liposomes, free DOX and TMX-DOX only. TMX-DOX liposomes show increased inhibition of MCF-7 cell-based tumor growth in nude mice in comparison to other treatment	Jain et al. (2014)

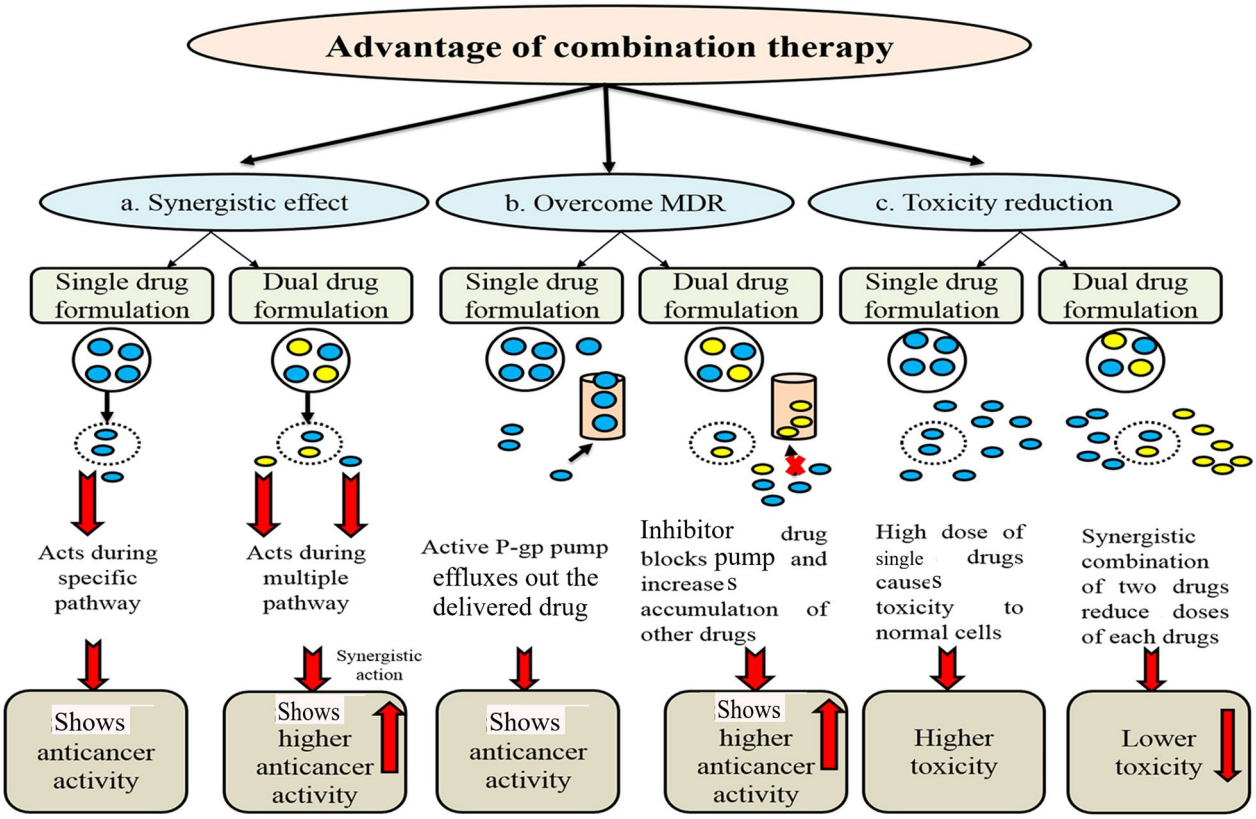

Fig. 13 Several advantages of combination therapy for cancer therapy. **a** Single drug works through a certain pathway, while multiple drugs can show improved anticancer activity by working via several pathways; **b** In single drug treatment, liposomal multidrug resistance (MDR) proteins like P-gp releases drug out of the cell, while for dual drugs formulations, the P-gp inhibitor inhibits the role of MDR proteins and raises the intracellular concentration of other co-administered drugs leading to higher activity; **c** The high dose is required to treat single drug, leading to toxicity to the normal cells, while treatment with combinations of different drugs result in synergistic action, which can decrease the dose of each single drug and decrease the toxicity (Modified from Parhi et al. 2012).

of API, stability in circulation and storage, targeted release based on prescribed administration, and low or no toxicity. Other attributes include ease and flexibility of preparation method to tolerate the wide range of APIs, sterilizability without significant losses of yield, and cost-effectiveness for scaling-up (Lujan et al. 2019). Understanding the advances in liposomal technology, and the challenges to overcome, will address the issues on existing translational and regulatory limitations. The future of DDS application in cancer treatment is promising especially with regards to achieving stability and strength of encapsulating materials for longer retention and sustained release of drugs; in the characterization and functionalization of encapsulating material surface; in the identification of receptors and ligands on the cancer sites for targeted delivery; and in achieving high killing rate of the cancer cells with no toxic effects on the surrounding healthy and normal tissues. To achieve translational success, collaboration between all stages of pharmaceutical development including manufacturing and pharmaceutical design, cellular interactions and toxicology, as well as preclinical and clinical evaluation, must be established (Sercombe et al. 2015).

Conclusion

Drugs with low solubility have biopharmaceutical delivery problems including limited bio-accessibility after oral intake, less ability to spread to the outer membrane, requirement for higher quantity for intravenous intake, and undesirable effects from the vaccination process. All of these limitations can be overcome by applying nanotechnology to the drug delivery mechanism. AgNPs could be used as multi-functional drug carriers possessing great potential for targeted drug delivery, reducing side effects, and enhancing therapeutic efficacy. HA has good biodegradability, non-immunogenicity, biocompatibility and ability to recognize specific receptors such as CD44 that are highly expressed on the surface of cancer cells, for the drugs to target and kill the tumor cells. The HA ligand allows coating of the

AgNPs for lower cytotoxicity and increased stability. The chemotherapeutic agents encapsulated with liposomal structures can limit the normal tissue uptake of the treatment and enhance the therapeutic effect. A better understanding of AgNPs, HA, and liposomal drug interaction with the biological system will facilitate the emergence of a novel class of anticancer therapeutics with enhanced activities and safety, and reduced side-effects. The AgNPs could serve as a nanoplatform including for therapeutics and theranostic applications. The large group of HA and liposome-based drugs are in preclinical/clinical trials and the formulations provide a new model in nano-therapeutics with a focus on diagnosis, treatment, and prevention. New developments have been made involving new materials such as natural products and in the preparation of responsive polymers to temperature or pH conditions, with a specific macro/microstructure and chemical profile. The design of co-application of NPs with HA or Liposomes or bioactive compounds as nanocarriers, could pave the way for a more effective and tailored DDS intended for customized medical solutions.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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