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Recent progress in nanotechnology-based drug carriers for resveratrol delivery

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ABSTRACT

Resveratrol is a polyphenol with diverse pharmacological activities, but its clinical efficacy is limited due to low solubility/permeability, light-induced isomerization, auto-oxidation, and rapid metabolism. Nanodelivery systems, such as liposomes, polymeric nanoparticles, lipid nanocarriers, micelles, nanocrystals, inorganic nanoparticles, nanoemulsions, protein-based nanoparticles, exosomes, macrophages, and red blood cells (RBCs) have shown great potential for improving the solubility, biocompatibility, and therapeutic efficacy of resveratrol. This review comprehensively summarizes the recent advances in resveratrol nanoencapsulation and describes potential strategies to improve the pharmacokinetics of existing nanoformulations, enhance targeting, reduce toxicity, and increase drug release and encapsulation efficiency. The article also suggests that in order to avoid potential safety issues, resveratrol nanoformulations must be tested *in vivo* in a wide range of diseases.

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1. Introduction

1.1. Pharmacological effects of RES

Resveratrol (RES) (Figure 1) is a natural polyphenolic antitoxin secreted by at least 100 different plants after fungal infection or pathogen attack (Nam, 2006; Vestergaard & Ingmer, 2019; Ahmed et al., 2017; Huang & Mazza, 2011; Tome-Carneiro et al., 2013). RES has been used for the treatment of various diseases (Bhullar & Hubbard, 2015), as it can effectively scavenge free radicals (Prysyazhna et al., 2019), regulate the expression and activity of antioxidant enzymes (Gal et al., 2021), as well as exert anti-inflammatory (Nunes et al., 2018), anti-aging (Grilc et al., 2021), antidiabetic (Rocha et al., 2021), and cardioprotective effects (Gal et al., 2021). RES also exhibits significant neuroprotective effects in central nervous system diseases, such as Alzheimer's disease (Huang et al., 2021), by inhibiting microglial activation and modulating neuroinflammation (Moradi et al., 2020). It can protect against cancers of the breast (Vargas et al., 2020), prostate (Khusbu et al., 2020), lung (Yousef et al., 2017), colon (Yuan et al., 2019), liver (Zhao et al., 2021), gastrointestinal tract (Xu et al., 2017), pancreas (Srivani et al., 2020), ovary (Guo et al., 2015), and skin (Iqubal et al., 2021).

1.2. Pharmacokinetics issues with RES

RES must overcome many pharmacokinetic hurdles before it can be considered clinically useful in chemotherapy. To comprehensively investigate the bioavailability of RES, ^{14}C-labeled RES was administered orally and intravenously 5–6 and five healthy subjects with doses of 25 and 0.2 mg, respectively (Walle et al., 2004). Despite the fact that it is well absorbed when taken orally, with a bioavailability of around 70%, the bioavailability of RES itself is close to zero due to extensive metabolism in the liver and intestines, including glucuronidation and sulfation, which produces metabolites with lower biological activity than RES. After ingestion of RES, two maximum peaks in RES plasmatic levels are obtained: one is found 30–60 min following ingestion, and a second peak is found after 6 h. These findings suggest that an enteric recirculation of RES metabolites takes place. In addition, peak plasma levels of RES and metabolites of 491 ± 90 ng/mL (about 2 microM) and a plasma half-life of 9.2 ± 0.6 h. RES can be rapidly absorbed, yielding peak plasma concentration (C_{max}) between 0.83 and 1.5 h post-dose. However, only trace amounts of unchanged RES (<5 ng/mL) could be detected in plasma (Cottart et al., 2010). Investigations of RES metabolism in vivo in rodent models showed that the liver is a major accumulation site for RES and its metabolites (Yu et al., 2002). Systemic in vivo distribution in rodents is characterized by a peak concentration at 30 min (Soleas et al., 2001), with metabolites becoming detectable 3 h post-administration (Sale et al., 2004). Compounding more to the problem is RES low water solubility, which is around 0.03 mg/mL, hence affecting the compound's absorption

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and bioavailability (Summerlin et al., 2015). Moreover, it exerts certain therapeutic effects only at low concentrations, implying that even a modest increase in RES bioavailability may have strong therapeutic effect (Calabrese et al., 2010; Calabrese et al., 2010).

To improve the solubility, stability and bioavailability of RES, enhance its permeability and therapeutic efficacy, and reduce its toxicity, the drug has been loaded into several natural, semi-synthetic, and synthetic nanodelivery systems (Fang & Bhandari, 2010; Ghalandarlaki et al., 2014), including liposomes (Abu Lila & Ishida, 2017), polymer nanoparticles (George et al., 2019), micelles (Lu et al., 2018), lipid nanocarriers (Garces et al., 2018), nanocrystals (Jermain et al., 2018), inorganic nanoparticles (Yang et al., 2019), dendrimers (Fischer & Vogtle, 1999), nanoemulsions (Gupta et al., 2016), and bionic drug delivery systems (Chen et al., 2016) (Figure 2). The RES bioavailability effects after RES loading with distinct types of nanotechnology-based carriers administered orally, intravenously, which are discussed next, are summarized in Table 1.

In this review, we summarize recent advances in RES nanoencapsulation and the resulting benefits, and we discuss current limitations affecting the *in vivo* behavior and therapeutic efficacy of RES-loaded nanocarriers.

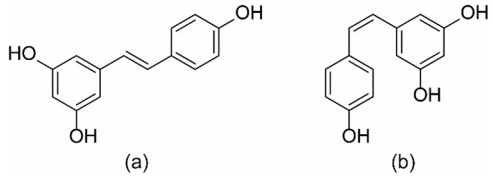

Figure 1. Configuration of (a) *trans*- and (b) *cis*-RES.

2. Nanocarriers used for RES delivery

2.1. Exogenous nanoparticles

2.1.1. Liposomes

Liposomes are stable spherical vesicles made up of cholesterol and nontoxic phospholipids. Due to their amphiphilic nature, biocompatibility, biodegradability and easy surface modification, liposomes have been extensively used as carriers for hydrophilic drugs and lipophilic molecules (Table 2) (Li et al., 2019). For example, the encapsulation of free RES into liposomes (Lip-RES) at 37 °C under light conditions improved its chemical stability and bioavailability, while also increasing RES uptake by white adipocytes by 25% (Zu et al., 2018). Lip-RES showed superior effectiveness relative to free RES in against DXR-induced renal toxicity in rats (Alhusaini et al., 2022). In addition, Lip-RES increased the uptake of RES by cardiomyocytes and thus significantly activated the maximum cellular respiratory capacity (Tsujioka et al., 2022).

Engineering liposomes to release their cargo only under specific conditions can prevent premature leakage of drugs into the circulation (Abri Aghdam et al., 2019). For example, a previous study prepared RES-loaded liposomes using 1,2-bis-myristyloxyamidopropyl ornithine and sucrose laurate L126 to achieve controlled drug release. The carbamate bond in the lipid structure was stable under neutral conditions, but acidic conditions triggered RES release, indicating that this nanoplatform can enhance RES accumulation in the acidic tumor microenvironment and improve its antitumor efficacy (Zhao et al., 2020). However, conventional liposomes are unstable during storage (Caddeo et al., 2018) and have low targeting ability (Laginha et al., 2005). Therefore, RES-loaded liposomes were modified with poly(ethylene glycol) (PEG), resulting in a nanoplatform (PEG-lip-RES) with better stability and biocompatibility; low toxicity against murine macrophage cells

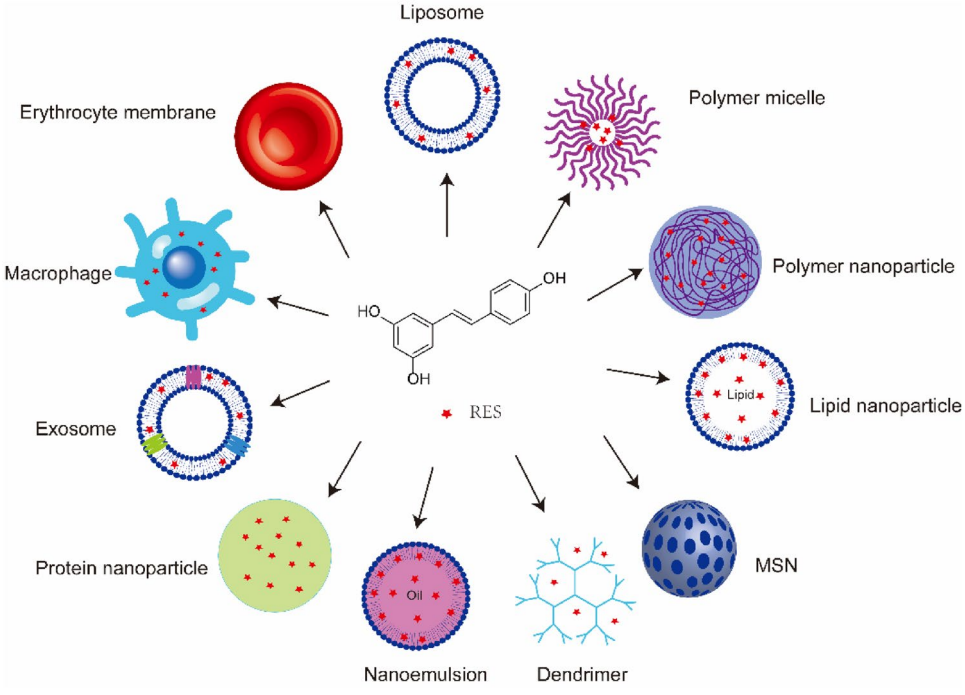

Figure 2. RES-loaded nanoformulations. MSN, mesoporous silica nanoparticles.

Table 1. List of the most relevant *in vivo* studies concerning RES bioavailability upon oral, i.v. administration of different RES-loaded nanotechnology-based carriers.

Nanocarriers	*In vivo* model	Via	RES dose	Outcomes (comparatively to free RES)	Ref
liposomes	Charles Foster rats	i.v.	2 mg/kg dose.	AUC: 30-fold increased; $t_{1/2}$: 29.7-fold increased; CL: 33-fold decreased; MRT: 29.5-fold decreased	Vijayakumar et al. (2016)
Polymeric nanoparticles (PLGA)	Wistar rats	Oral	20.0 mg/kg	$AUC_{0\rightarrow\infty}$: 10.6-fold increased; C_{max}: 1.2-fold increased; T_{max}: 28.0-fold increased; Absorption rate: Ka was 7.2-fold increased);	Singh & Pai (2014)
Lipid nanocarrier	Wistar rats	i.v.	2 mg/kg	$AUC_{0\rightarrow\infty}$:8.7-fold increased; Cmax: 1.4-fold increased; CL: 13.4-fold decreased; $t_{1/2}$: 15-fold increased.	Poonia et al. (2020)
Micelles (TPGS)	Sprague-Dawley rats	Oral	20.0 mg/kg	$AUC_{0\rightarrow\infty}$: 3.5-fold increased; Cmax: 2.2-fold increased; MRT: 1.2-fold increased.	Singh et al. (2017)
Nanocrystals	Wistar rats	Oral	40 mg/kg	AUC: 6.3-fold increased; T_{max}: 2-fold decreased; C_{max}: 3-fold increased; MRT: 3-fold increased.	Argenziano et al. (2022)
Nanoemulsions	Wistar rats	Oral	120 mg/kg	$AUC_{0\rightarrow\infty}$: 1.3-fold increased; C_{max}: 3.4-fold increased; CL: 1.2-fold decreased; MRT: 1.1-fold decreased; Vd: 1.5-fold decreased.	Hao et al. (2015)
Protein-based nanoparticles	Kunming mice	i.v.	1.5 mg/kg	Targeting efficiency increased; RES accumulation in the liver, kidney, heart, and ovaries;	Guo et al. (2010)

AUC: area under the concentration-time curve (plasma exposure); $t_{1/2:}$ plasma half life; CL: clearance; MRT: mean residence time; $AUC_{0\rightarrow\infty}$: area under the concentration time-curve from time zero to infinity; C_{max}: peak plasma concentration; i.v.: intravenous; Ka: absorption rate constant; PLGA: Poly (lactic-co-glycolic acid); RES: Resveratrol; t_{max}: time to achieve the maximum concentration; TPGS: D-α-tocopherol polyethylene glycol 400 succinate

Table 2. RES-loaded liposomes used for the treatment of various diseases.

Composition	Targeting moiety	Preparation method	Physicochemical characteristics	Cell line/animal model	Disease	Major outcome	Ref.
Soy PC; cholesterol	None	Film dispersion	PS, ~110 nm; PI, 0.140; ZP, ~-28 mV; DL, 25.3%; EE, 96%	Murine 3T3-L1 fibroblasts	Obesity	Increased water solubility and stability; enhanced browning of white fat cells	Zu et al. (2018)
1,2-Bis-myristyloxyamidopropyl ornithine; sucrose laurate L126	Tumor microenvironment	Thin-film hydration	PS, ~140 nm; ZP, ~40 mV; EE, >90%	Human breast cancer MCF-7 and MCR-5 cells; male BALB/c nude mice	Breast cancer	Enhanced bioavailability and anti-tumor activity	Zhao et al. (2020)
Pluronic® L64; tocopherol-PEG-succinate; phospholipon 90 G	None	Ice-bath sonication	PS, ~85 nm; PI, ~0.2; ZP, −20 mV; DL, 5.3%; EE, 94.9%	Erythrocyte cells	Oxidative stress	Extension of half-life in the blood circulation	Caddeo et al. (2018)
PT-98T; cholesterol; $DSPE\text{-}PEG_{2000}$	None	Thin-film hydration	PS, ~136 nm; ZP, −11 mV; DL, 3.9%; EE, 81.3%	Mouse macrophages; L929 mouse fibroblasts; human umbilical vein endothelial cells; BALB/c female mice (7–8 weeks old)	Periodontitis	High anti-inflammatory activity	Shi et al. (2021)
Chitosan; Au; SPC	Tumor microenvironment	None	PS, ~140 nm; ZP, ~7 mV	HeLa cells	Cervical cancer	Improved drug cellular uptake; synergistic antitumor effect	Wang et al. (2017)
1-Palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; cholesterol; PEG-PE; TPP-DSPE-PEG	Mitochondria	Thin-film hydration	PS, ~115 nm; PI, 0.22; ZP, ~10.46 mV	B16F-10 cells	Melanoma	Increased antitumor activity	Kang & Ko (2019)

DL: drug loading efficiency; DSPE: 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine; EE: entrapment efficiency; PC: phosphatidylcholine; PE: phosphatidyleth-anolamine; PEG: poly(ethylene glycol); PI: polydispersity index; PS: particle size; SPC: soybean phosphatidylcholine; TPP, 4-carboxybutyl triphenylphosphonium bromide; ZP: zeta potential

(RAW264.7), mouse fibroblast cells (L929), and human vascular endothelial cells (HUVEC); prolonged half-life; and good anti-oxidant effects (Shi et al., 2021). In another study, the surface of liposomes was modified with chitosan and then coated with gold nanoshells to construct multifunctional liposomes responsive to pH and near-infrared light that released

Table 3. RES-loaded polymer nanoparticles used for the treatment of various diseases.

Composition	Targeting moiety	Preparation method	Physicochemical characteristics	Cell line/animal model	Disease	Major outcome	Ref.
PLGA	None	Solvent displacement	PS, ~ 202.8 nm; PI, ~0.17; EE, 89.32 ± 3.51%	Prostate cancer LNCaP cells	Prostate cancer	Increased cytotoxicity in LNCaP cells	Nassir et al. (2018)
PLGA; polyvinyl alcohol	None	None	PS, ~ 257.9 nm; PI, ~0.26; ZP, 27.99 mV; EE, 20%	Rats	Isoproterenol-induced myocardial infarction	Improved bioactivity	Sun etal. (2020)
PLGA; *N*-oleoyl-*d*-galactosamine Tween 80	None	Solvent diffusion	PS, ~108.4 nm; PI, ~0.217; ZP, −46.3 mV; EE, 97.22 ± 2.31%	RAW264.7 cells; rats	Myocardial injury	Improved oral bioavailability	Siu et al. (2018)
Folic acid-conjugated PLGA; CTAB	Enterocytes	None	PS, 131 ± 9 nm; PI, 0.181; ZP, −10.7 mV; EE, 59.1 ± 3.3%	Caco-2 cells; rats with intestinal inflammation	Colonic inflammation	Protection under acidic conditions; inflammation suppression	Naserifar et al. (2020)
PLGA; chitosan; alginate	None	O/W emulsion technology	PS, ~255 nm; PI, 0.097 ± 0.095; ZP, ~13.5 mV; EE, 87.26%	DSS-induced ulcerative colitis mice	Colonic inflammation	Enhanced colon-targeting ability; improved inflammation indicators	Jin et al. (2021)
PLGA; polyvinyl alcohol; lactoferrin	Brain capillaries	Emulsion solvent evaporation	PS, 148.2 ± 4.2 nm; PI, 0.12 ± 0.18; ZP, −23.1 ± 3.0 mV; DL, 6.1 ± 0.3%; EE, 75.2 ± 4.1%	SH-SY5Y cells; mice with Parkinson's disease	Colonic inflammation	Increased blood-brain barrier permeability; enhanced neuroprotective effect	Katila et al. (2022)
Sulfobutylether-β-cyclodextrin (4% w/v); polyvinyl alcohol; polyethyleneimine	None	Solvent evaporation	PS, 264.2 ± 0.03 nm; PI, 0.16 ± 0.03; ZP, −1.46 ± 1.47 mV; DL, 0.72 ± 0.09%; EE, 29.1 ± 2.0%	A549, H157, H460, H4006, H358, HEK-293 cells	Non-small cell lung cancer	Increased water solubility; enhanced cytotoxicity	Wang et al. (2020)
$mPEG_{750}$-PLA_{1000}	None	None	PS, 162.2 ± 2.9 nm; PI, 0.062 ± 0.024; ZP, −11.0 ± 0.4 mV; DL, 8.7%; EE, 95.1 ± 0.1%	B16-F10 cells; C57BL/6J mouse model	Melanoma	Reduced degradation and metabolism; increased antitumor activity	Yee et al. (2022)

CTAB: cetyltrimethylammonium bromide; DL: drug loading efficiency; DSS: dextran sodium sulfate; EE: entrapment efficiency; mPEG: methoxy poly (ethylene glycol); PI: polydispersity index; PLGA: poly(lactic-*co*-glycolic acid); PS: particle size; ZP: zeta potential

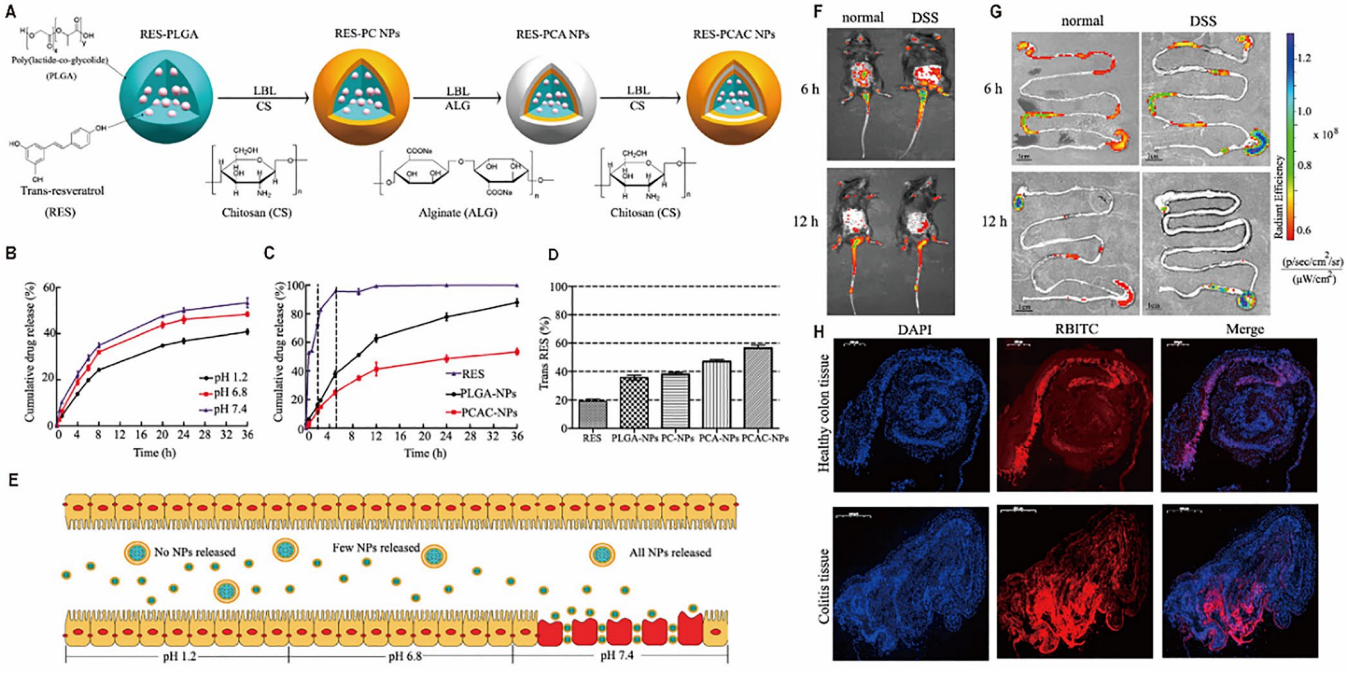

Figure 3. (A) Preparation of resveratrol (RES)-loaded PLGA nanoparticles (NPs) modified with chitosan and alginate (PCAC-NPs) by the layer-by-layer (LBL) assembly method. (**B**) Release curves of PCAC-NPs at pH 1.2, 6.8, and 7.4. (**C**) Release curves of RES, PLGA-NPs, and PCAC-NPs in simulated digestive fluid. (D) Retention of different formulations exposed to ultraviolet light for 120 min. (E) Schematic illustration of the path of PCAC-NPs after entering simulated gastric fluid. (F) Fluorescence distribution in mice at 6 and 12 h after oral administration of RES-PCAC-NPs. (G) Near-infrared fluorescence images showing the accumulation of NPs in the colon at 6 and 12 h post-administration. (H) Uptake of NPs by colon tissues after 6 h of co-incubation. Reprinted from (Shahnaz et al., 2017) with permission. DAPI: 4′ ,6-diamidino-2-phenylindole; DSS: dextran sodium sulfate; PLA: polylactic acid; PLGA: poly(lactic-*co*-glycolic acid); RBITC: rhodamine B isothiocyanate.

RES in a controlled manner, leading to synergistic antitumor effects against HeLa cells (Wang et al., 2017). RES induces cell death through the mitochondrial apoptotic pathway, where mitochondria play a central role in the release of pro-apoptotic factors. The surface of RES-loaded liposomes was modified with cationically charged compounds such as 4-carboxybutyltri phenylphosphine bromide and dequinoline, which cross the mitochondrial membrane to promote drug accumulation in mitochondria of tumor cells, leading to greater cytotoxicity against tumor cells (Maherani et al., 2011; Kang & Ko, 2019).

2.1.2. Polymer nanoparticles

Polymer nanoparticles are submicron-sized colloidal particles made from natural or synthetic polymers (Zu et al., 2021), including polylactic acid, poly(lactic-*co*-glycolic acid) (PLGA), polycaprolactone, gelatin, and polysaccharides (Lu & Park, 2013) (Table 3). Polymer nanoparticles can adsorb, wrap, or chemically bind to target compounds (Masood, 2016), enhancing the stability of drugs, especially protein drugs, prolonging their circulation *in vivo*, and releasing them in a controlled manner (Langer, 2000). Changing the composition and structure of polymer nanoparticles can also tune their behavior under different conditions (Masood, 2016; Zhang et al., 2021).

PLGA is the polymer most commonly used for the synthesis of nanocarriers. For example, loading RES into PLGA nanoparticles (15.6 μM) improved its IC_{50} value from 29.7 to 15.6 μM and induced apoptosis in LNCaP prostate cancer cells, without adverse effects on normal macrophages (Nassir et al., 2018). In another study, RES-loaded PLGA nanoparticles showed better anti-inflammatory, anti-oxidant, and cardioprotective effects than free RES in the treatment of myocardial injury *in vivo* (Sun et al., 2020). However, polymer nanoparticles do not enhance the efficiency of passive targeting (Zhang et al., 2014; Shahnaz et al., 2017). Therefore, their surface has been modified with ligands or macromolecules to enhance their ability to target disease sites. For example, modifying RES-loaded PLGA nanoparticles with the monosaccharide galactose improved intestinal uptake, antitumor effects, and oral bioavailability of RES in rats (Siu et al., 2018). In another study, modifying RES-loaded PLGA nanoparticles with folic acid enhanced their ability to enter colon cells and suppress colon inflammation (Naserifar et al., 2020).

The kinetics of cargo release from PLGA nanoparticles, especially the initial burst, is difficult to control (Reinhold & Schwendeman, 2013). To address this drawback, the surface of RES-loaded PLGA nanoparticles was modified with chitosan and alginate to form a polymer membrane (PCAC nanoparticles) (Figure 3) (Jin et al., 2021). Following oral administration to mice, the electrostatic interactions between chitosan and alginate were enhanced under acidic conditions in the stomach, reducing pore size and slowing drug release, while alkaline pH similar to that in the intestines enlarged the pores and accelerated drug release. Thus, PCAC nanoparticles not only protected the drug from degradation but also released it selectively in the simulated intestinal fluid. By labeling PCAC nanoparticles with rhodamine B isothiocyanate, investigators showed that the nanoplatform penetrated deep into the mucosa through the enhanced permeability and retention effect, targeting inflammatory cells and enhancing the therapeutic effects of RES. In another study, RES-loaded PLGA nanoparticles were modified with lactoferrin, a natural iron-binding cationic glycoprotein that targets brain capillaries, helping them cross the blood–brain barrier (Katila et al., 2022). In addition, the modification of PLGA nanoparticles with sulfobutylether-β-cyclodextrin significantly increased the water solubility of RES and enhanced its antitumor activity against non-small cell lung cancer (Wang et al., 2020). Similarly, methoxy poly (ethylene glycol)-poly(lactide) nanoparticles improved the liver accumulation and plasma stability of free RES, leading to good therapeutic effects in a mouse model of melanoma (Yee et al., 2022).

2.1.3. Nanomicelles

Nanomicelles are macromolecules with a hydrophobic core and a hydrophilic shell that form from block or graft copolymers in aqueous solution when the micelle concentration exceeds the critical micelle concentration (Table 4) (Xu et al., 2020; Feng et al., 2020). Nanomicelles can encapsulate hydrophobic drugs through covalent binding or physical trapping (Lu & Park, 2013), protecting them from the external environment, improving their pharmacokinetic properties, and reducing toxicity (Kataoka et al., 2001). The hydrophilic shell also enables them to escape clearance by the reticuloendothelial system (Sawant & Torchilin, 2010).

Pluronic F68 is widely used for the preparation of nanomicelles due to its low cost and good biocompatibility, but its high critical micelle concentration significantly reduces drug encapsulation efficiency (Chaudhari & Patil, 2014; Kim et al., 2021). Therefore, a recent study conjugated the two ends of Pluronic F68 with stearic acid and inulin, respectively, to increase the hydrophobic segment, reduce the critical micelle concentration, and protect the drug-loaded nanocapsules from the gastric environment while improving the oral bioavailability of RES and achieving controlled drug release for colon cancer treatment (Jangid et al., 2020). In another study, a mixed micellar system prepared using poloxamers 188 and 407 was loaded with RES and coated with bioresorbable polylactic acid to form hybrid nanomicelles with better biocompatibility and anti-arthritic effects than free RES (Kamel et al., 2019).

2.1.4. Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are nanosized materials that can be loaded with hydrophilic and lipophilic drugs and easily modified with ligands due to their functional surface groups (Garces et al., 2018). SLNs are considered effective carriers, as they can encapsulate or disperse

Table 4. RES-loaded nanoparticles used for the treatment of various diseases.

Classification	Composition	Preparation method	Physicochemical characteristics	Cell line/animal model	Disease	Major outcome	Ref.
Polymer micelles	Stearic acid; inulin; Pluronic F68	Solvent evaporation	PS, 172 nm; PI, 0.237; ZP, −18 mV; EE, 56.03 ± 1.0%	Human colorectal cancer cells (HCT116); Sprague-Dawley rats	Colon cancer	pH-sensitive release; enhanced cytotoxicity in HCT116 cells; improved pharmacokinetics	Jangid et al. (2020)
	Pluronic F68; Pluronic F127; Polylactic acid	Thin-film hydration	PS, ~52.97 nm; PI, ~0.684; ZP, −32.5 ± 4.10 mV; DL, 2.56 ± 0.25%; EE, 76.20 ± 4.51%	Adult male Wistar rats (150 ± 20 g)	Arthritis	Improved cartilage lesions and synovial inflammation	Kamel et al. (2019)
Solid lipid nanoparticles	Soy PC; Kolliphor® HS15; (+)-Alpha (α)-tocopherol acetate	Solvent evaporation	PS, ~140 nm; PI, 0.084; ZP, −19 mV; DL, 96.5%; EE, 28.5%	Murine 3T3-L2 fibroblasts	Obesity	Increased water solubility and stability; enhanced browning of white fat cells	Zu et al. (2018)
	Egg yolk lecithin; molten glycerol monostearate; poloxamer 188	Emulsification/ diffusion; sonication	PS, 271.13 nm; ZP, −25.8 ± 0.33 mV; EE, 23.98%	Sprague-Dawley rats	Doxorubicin-induced cardiotoxicity	Alleviation of doxorubicin-induced cardiotoxicity	Zhang et al. (2019)
	D-α-Tocopheryl polyethylene glycol 1000 succinate; stearic acid; lecithin; Tween80	Emulsification and low-temperature solidification	PS, 271.13 nm; ZP, −25.6 ± 1.3 mV; EE, 32.4 ± 2.6%	SKBR3/PR cells; SKBR3/PR tumor-bearing mice	Breast cancer	Increased cellular uptake; improved antitumor effects	Wang et al. (2021)
	Capmul MCMC10; CTAB; Tween 80	Hot high-pressure homogenization	PS, 139 nm; PI, 0.271; ZP, 50.25 mV; DL, 24.3%; EE, 83.8%	HepG2 cells; rats with hepatocellular carcinoma	Hepatocellular carcinoma	Improved antitumor activity	Rahman et al. (2020)
Nanostructured lipid carriers	Poly(ε-caprolactone); capric/caprylic triglyceride; sorbitan monostearate; polysorbate 80	None	PS, 250 ± 10 nm; PI, 0.15 ± 0.04; ZP, −15.8 ± 3.0 mV; DL, 0.964 ± 0.037%; EE, 99.89 ± 1.3%	A/J mice	Acute lung injury	Improved anti-acute lung injury activity	de Oliveira et al. (2019)
	Sodium cholate; Tween-80; trimyristin; triolein; phosphatidylcholines; span-80	Hot melt emulsification	PS, 55.78 nm; PI, 0.244; ZP, −25.6 mV	Human coronary artery endothelial cells	Hypertension	Restored vasodilator responses	Astley et al. (2021)
	Glyceryl monostearate; 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; polysorbate 80	Thin-film hydration/ ultrasonic dispersion	PS, 123.7 nm; PI, 0.082; ZP, −19.4 mV; EE, 94.4%	Pulmonary artery smooth muscle cells; male Sprague–Dawley rats	Pulmonary arterial hypertension	Improved drug delivery to the lungs	Li et al. (2020)
	Oleic acid; stearic acid; phospholipon; poloxamer; folic acid	Solvent injection	PS, 82.44 ± 2.78 nm; PI, 0.375 ± 0.124; ZP, −42.15 ± 3.76 mV; DL, 8.05 ± 0.75%; EE, 86.34 ± 1.98%	MCF-7 cells	Breast cancer	Enhanced anticancer activity; higher accumulation	Poonia et al. (2019)
	Capric triglyceride; shea butter; olivem 1000 and 800; vitamin E; red myrrh; allantoin; EDTA-2Na; sodium hyaluronate; CMC-Na; methylisothiazolinone; glycerol	Ultrasonic emulsification	PS, 175.6 ± 11.2 nm; PI, 0.179 ± 0.007; ZP, −54.3 ± 3.0 mV; EE, 97.76%	HaCaT cells; rabbits		Improved anti-ultraviolet radiation and antioxidant activity *in vivo*	Miao et al. (2021)
Nanocrystals	Pluronic F127	Wet media milling	PS, 270 ± 7.2 nm; PI, 0.310 ± 0.005	Ehrlich ascites tumor cells; Swiss albino inbred mice	Ehrlich ascites carcinoma	Reduced tumor cell proliferation	Xiong et al. (2020)
	Polyvinylpyrrolidone K90	Anti-solvent precipitation	PS, 222.54 ± 1.66 nm; PI, 0.125 ± 0.035; ZP, −9.41 ± 0.37 mV; EE, 21.74%	Madin–Darby canine kidney cells; SH-SY5Y cells; zebrafish embryos at 6 h post-fertilization; Sprague-Dawley rats	Parkinson's disease	Improved oral bioavailability and brain accumulation	Ancic et al. (2022)

(*Continued*)

Table 4. Continued.

Classification	Composition	Preparation method	Physicochemical characteristics	Cell line/animal model	Disease	Major outcome	Ref.
Gold nanoparticles	$NaAuCl_4$; gum arabic	None	PS, 16.7 ± 4.6 nm	MDAMB-231, PANC-1, PC-3 cells	Breast, pancreatic, prostate cancer	Synergistic anti-tumor effects	Thipe et al. (2019)
Dendrimers	Glycosylated maize dendrimer dextran	None	ZP, −9.5 mV; DL, 1.4%	Caco-2 cells; HaCaT cells		Enhanced drug solubility	Shi et al. (2020)
Nanoemulsions	Coconut oil; Pluronic P107; Cremophor EL	Simple vortexing	PS, 110.37 ± 2.16 nm; PI, 0.194 ± 0.003; ZP, −21.13 ± 1.628 mV	Wistar rats	Alzheimer's disease	Improved brain-targeting efficacy	Kotta et al. (2021)
	Tween 20; Neem seed oil; HEPES buffer	Simple vortexing	PS, 137.8 ± 0.5 nm; PI, 0.22 ± 0.1; ZP, −23.0 ± 0.7 mV	Human T24 bladder cancer cells	Bladder cancer	High loading capacity; enhanced solubility	Rinaldi et al. (2021)
	Miglyol 812; polysorbate 80; ethanol	None	PS, 24 ± 7 nm; PI, 0.291 ± 0.062; ZP, −15.8 ± 2.6 mV	Human immortalized T/C28a2 chondrocytes	Osteoarthritis	Improved protection against oxidative stress-mediated T/C28a2 cell death	Le Clanche et al. (2018)
	Isopropyl myristate; polysorbate 80; ethanol	None	PS, 103 ± 14 nm; PI, 0.389 ± 0.051; ZP, −14.7 ± 2.0 mV	Human immortalized T/C28a2 chondrocytes	Osteoarthritis	Improved protection against oxidative stress-mediated death in T/C28a2 cells	Le Clanche et al. (2018)

CTAB: cetyltrimethylammonium bromide; DL: drug loading efficiency; EE: entrapment efficiency; PC: phosphatidylcholine; PI: polydispersity index; PS: particle size; ZP: zeta potential

drugs in natural or synthetic solid lipids, giving rise to solid colloidal structures that can store lipophilic molecules (Table 4). For example, loading RES onto SLNs significantly increased the plasma concentration and area under the curve of the drug, reduced the time needed to reach the maximum plasma concentration, and promoted oral absorption, thereby improving the ability of RES to protect against doxorubicin-induced cardiac toxicity in mice (Zhang et al., 2019). SLNs have also been identified as a promising delivery platform for therapeutic agents against tumor drug resistance (Majidinia et al., 2020). For instance, in comparison with free resveratrol, RES-loaded SLNs promoted the absorption of drugs by down-regulating the expression of overexpression of drug efflux transporters P-gp and breast cancer drug resistance protein (Wang et al., 2021). Another study reported that cationic RES-loaded SLNs showed significantly stronger anti-hepatocellular carcinoma activity *in vitro* and *in vivo* than conventional RES-loaded SLNs because of their stronger affinity for negatively charged tumor cell membranes (Rahman et al., 2020). Nevertheless, single solid lipids may form a perfect lattice structure during the preparation of SLNs; in this case, the lattice squeezes out the drug during storage, leading to low drug loading efficiency and leakage (Chen et al., 2010; Das et al., 2012).

2.1.5. Nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) are a new generation of lipid nanoparticles developed to overcome the limitations of SLNs (Khosa et al., 2018). To prepare NLCs, a certain proportion of liquid lipids is introduced into solid lipid carriers, disrupting the perfect lattice structure of SLNs; this reduces drug leakage during storage, stabilizes the nanoparticles (Tapeinos et al., 2017), and increases their capacity for hydrophobic drugs, which are highly soluble in liquid lipids (Table 4) (Alam et al., 2015). Recent studies have shown that RES-loaded NLCs prepared by interfacial polymer deposition can improve acute lung injury (de Oliveira et al., 2019), protect blood vessels, and enhance the antihypertensive effects of RES (Astley et al., 2021; Li et al., 2021). Lecithin is naturally present in plant and animal tissue, with a combination of glycerophospholipids. A nanoplatform based on the lipid structure of lecithin to encapsulate RES was designed. This nanoparticle is stable at ambient temperature as well as at 4 °C for up to 12 months, with inherent anti-oxidant and anti-cancer properties; indicating the feasibility of using this system as an cost-effective, and low side-effect anti-cancer therapeutic (Liang et al., 2022). To improve the tumor targeting ability of such nanoparticles, RES-loaded NLCs were modified with folic acid, improving cytotoxicity in MCF-7 cells overexpressing folate receptor (Poonia et al., 2019). NLCs have also shown the ability to protect skin by delivering RES to the stratum corneum and epidermis, but their fluidity limited their stability on the skin surface. To improve the stability and accumulation of RES on the epidermis, NLCs were modified with a hydrogel with good viscosity and ductility, resulting in a

nanoplatform with promising protective effects against ultraviolet radiation and oxidants (Miao et al., 2021).

2.1.6. Nanocrystals

Drug nanocrystals are usually formed as nanosuspensions in the presence of surfactants, polymers, or their mixture as stabilizers (Lu et al., 2019; Li et al., 2021). Nanocrystals can improve the dissolution and absorption of insoluble drugs by increasing the specific surface area and saturation solubility, showing higher drug loading capacity than other nanoformulations (Fontana et al., 2018) (Table 4). The use of nanocrystals also reduces the potential toxicity of excipients and promotes drug accumulation at target sites (Lu et al., 2017). However, their interactions with biologically tissues should be investigated in detail, as they can persist for a long time in biological environments. To enhance the solubility and bioavailability of RES, another study developed RES-loaded nanocrystals by the spontaneous conjugation of RES with hydroxypropyl methyl cellulose through van der Waals forces. The prepared nano-system entered cells through lattice-protein-mediated endocytosis, significantly enhancing the cellular uptake of RES, and protecting neurons from chemically induced cytotoxicity. Moreover, they showed negligible toxicity toward zebrafish embryos and larvae and exhibited more favorable pharmacokinetics and oral bioavailability in rats. Similar results were observed in mice with Parkinson's disease, suggesting that nanocrystals may be a promising formulation for both oral and systemic delivery of RES (Xiong et al., 2020). Loading RES into nanocrystals significantly strengthened the drug's ability to inhibit the proliferation of peritoneal tumor cells in Ehrlich ascites tumor (EAT)-bearing mice. RES-loaded nanocrystals ameliorated free RES-induced hepatocyte necrosis and apoptosis and liver fibrosis; however, as with free RES, RES-loaded nanocrystals resulted in inflammation of proximal tubular necrosis and glomerular swelling, as well as a slight elevation of several biochemical parameters that did not prolong the life span of EAT bearing mice (Ancic et al., 2022). In order to increase the beneficial effects and reduce risks associated with resveratrol nanocrystals, additional factors such as dose, genetics, health status, and the nature of the target cells should also be considered.

2.1.7. Inorganic nanoparticles

Inorganic nanoparticles (Fan et al., 2020), such as mesoporous silica nanoparticles (MSNs), gold nanoparticles (GNPs), silver nanoparticles (AgNPs), and quantum dots (QDs), have been used as delivery carriers for therapeutic cargos (Sperling & Parak, 2010; Pearce & O'Reilly, 2019) due to their unique magnetic and optical properties, which distinguish them from their organic and polymeric counterparts (Huang et al., 2011) (Table 4).

GNPs exhibit good stability, high thermal, optical, and electrical activity, high surface area, and multifunctionality (Amina and Guo, 2020), RES was biocoupled with GNPs *via* the cross-linking agent polyvinylpyrrolidone (RES@PVP-GNPs) to enhance the delivery performance and anti-tumor efficacy of RES (Lee et al., 2022). However, GNPs are usually synthesized by physical or chemical methods that may be toxic to humans. In contrast, synthesizing GNPs with plant-derived secondary metabolites such as RES is environmentally friendlier and may be safer for subsequent *in vivo* use (Bharadwaj et al., 2021; Akintelu et al., 2021). For example, RES-loaded GNPs were synthesized at room temperature through the RES-mediated reduction of Au^{3+} into Au^{0}, and the nanoparticle surface was then wrapped with highly branched gum Arabic to improve drug loading efficiency and overall stability. The modified GNPs had optimal cellular uptake at 24 h post-incubation and exhibited good synergistic antitumor effects (Thipe et al., 2019). The same method was used to prepare AgNPs (Kup et al., 2020).

MSNs are also widely used in drug delivery and biomedicine due to their large surface area and pore volume. It has been reported that encapsulating RES in colloidal MSNs with high loading capacity (20% w/w) and excellent encapsulation efficiency (100%) can enhance its solubility by 95% and improve *in vitro* release kinetics, leading to stronger anti-inflammatory and anti-tumor activities than free RES (Summerlin et al., 2016).

2.1.8. Dendrimers

Dendrimers are highly branched, star-shaped macromolecules with nanometer-scale dimensions (Svenson, 2009). Unlike conventional polymers, the molecular weight and chemical composition of dendrimers can be controlled by modulating their synthesis, resulting in higher loading capacity (Menjoge et al., 2010) and improved biocompatibility, pharmacokinetics (Lee et al., 2005), and polydispersity (Boas & Heegaard, 2004). In a recent study, RES was conjugated to the amino terminus of glycosylated maize dendrimer dextran, affording a nano-delivery system with higher solubility and anti-oxidant activity that improved the cellular uptake of RES and protected against oxidative cell damage in Caco-2 cells (Shi et al., 2020) (Table 4).

2.1.9. Nanoemulsions

Nanoemulsions are a biphasic dispersion of two immiscible liquids, one in the dispersed phase and the other in the continuous phase, which are generally stabilized using surfactants and co-surfactants as emulsifiers (Bonferoni et al., 2019). Nanoemulsions are usually formed using high pressure homogenizers, high shear stirring, or ultrasound generators as external forces to promote the release and absorption of the drug after digestion (Choradiya & Patil, 2021), while enhancing targeted drug delivery and minimizing adverse and toxic reactions (Jaiswal et al., 2015) (Table 4). For example, a RES-loaded nanoemulsion was prepared using coconut oil as the oil phase and Pluronic-107 and Cremophor EL as surfactants (Kotta et al., 2021). The optimized preparation showed better drug release properties than an RES suspension in 0.5% (w/v) sodium carboxymethyl cellulose and exhibited a good brain-targeting effect after intranasal administration in rats. The nanoemulsion was also stable at room temperature for 3 months (Kotta et al., 2021).

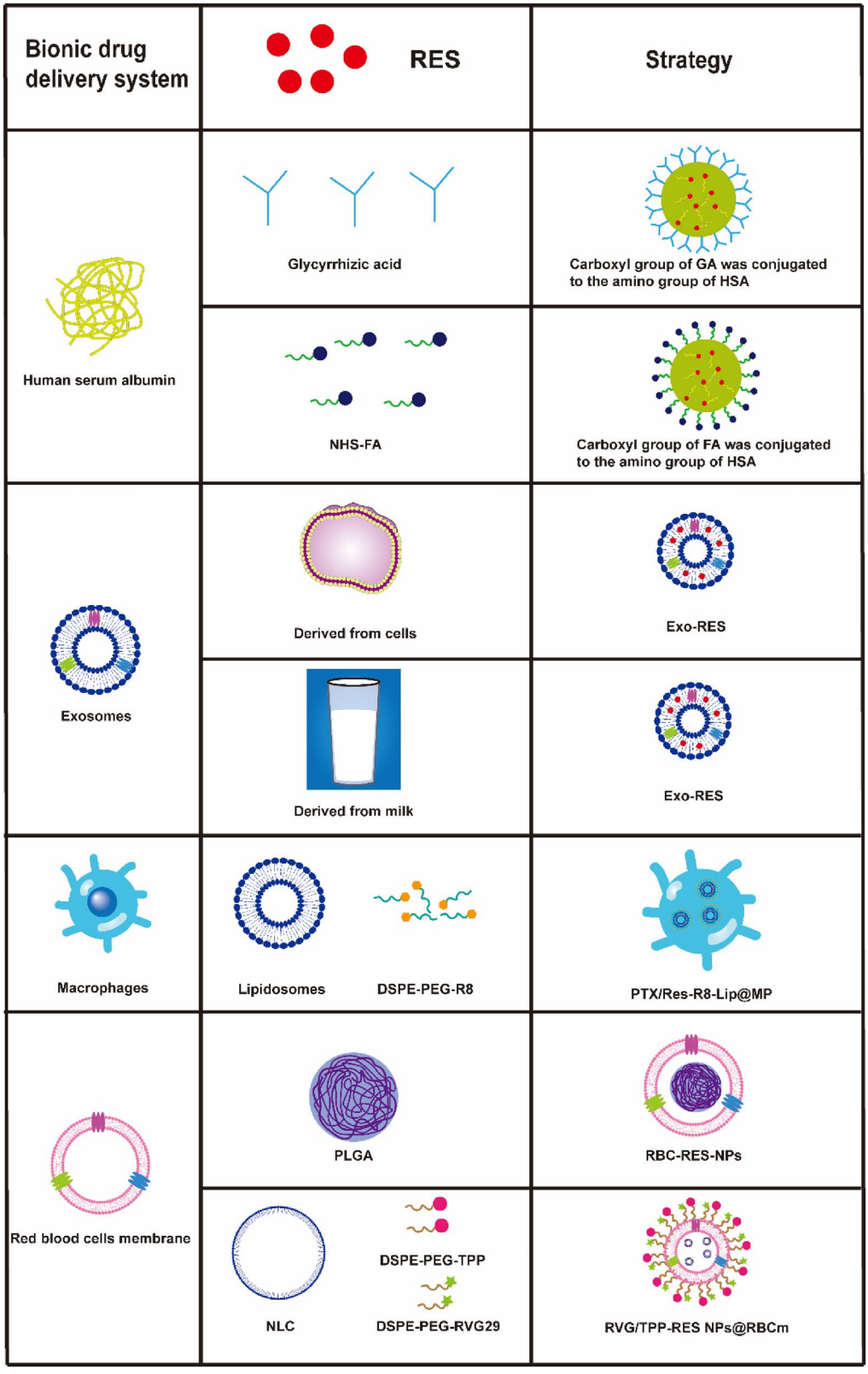

Figure 4. Bionic drug delivery systems loaded with resveratrol (RES). DSPE: 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine; Exo: exosomes; FA: folic acid; GA: glycyrrhizic acid; HSA: human serum albumin; MP: macrophage; NHS: *N*-hydroxysuccinimide; NLC: nanostructured lipid carrier; PEG: poly(ethylene glycol); PTX: paclitaxel; R8: octaarginine; PLGA: poly (lactic acid)-glycolic acid; RBCm: red blood cell membrane; RVG: rabies virus glycoprotein; TPP: 4-carboxybutyl triphenylphosphonium bromide.

Among such nanomaterials, oil-in-water (O/W) nanoemulsions are considered ideal for encapsulating RES, as they can be easily prepared through high-energy processes using natural ingredients and low emulsifier concentrations. For example, an RES-based O/W nanoemulsion significantly reduced cell viability in bladder T24 cancer cells and enhanced

the cytotoxic activity of RES through fast intracellular drug uptake (Rinaldi et al., 2021), suggesting that O/W nanoemulsions can effectively improve RES bioavailability. In another study, two RES self-emulsifying systems increased the tolerance of human immortalized chondrocytes toward RES, reduced its cytotoxicity at high concentrations, promoted drug uptake by membranes and cells, and improved the anti-oxidant activity of the free drug (Le Clanche et al., 2018).

2.2. Bionic drug delivery systems

Synthetic nanocarriers protect drugs from degradation and improve their oral bioavailability and therapeutic effects, but they suffer from weak targeting, toxicity, and easy elimination by the immune system (Torchilin, 2005). To avoid these problems, bionic drug delivery systems resemble natural particles such as cells (Chen et al., 2022), pathogens (Yin et al., 2022), and endogenous proteins (Wu et al., 2020), mimicking their *in vivo* activity and selectively delivering drugs to target sites. The result is lower immunogenicity, fewer side effects, and stronger therapeutic effects than with conventional nanoparticles (Li et al., 2021) (Figure 4).

2.2.1. Protein-based nanoparticles

Albumin, the most abundant plasma protein, plays a key role in the metabolism, transfer, and distribution of nutrients in cells. Albumin has been used extensively in nanotechnology as carrier due to its good drug binding ability, high stability, biodegradability, low toxicity, non-immunogenicity, and biocompatibility (Iqbal et al., 2021). Hydrophobic drugs such as RES can be easily encapsulated into albumin nanoparticles, while carboxyl and amino groups on the surface of albumin facilitate surface functionalization of its nanoparticles (Zhu et al., 2017). For example, encapsulating RES into glycyrrhizin acid-conjugated human serum albumin nanoparticles significantly improved its pharmacokinetic properties, bioavailability, and targeting of the liver (Wu et al., 2020). In another study, folate-modified RES-loaded human serum albumin nanoparticles selectively delivered RES to tumor sites and induced apoptosis in HepG2 cells more effectively than free RES (Lian et al., 2019).

2.2.2. Exosomes

Exosomes are cell-derived vesicles with a particle size of 40–160 nm that can transfer chemical or genomic contents from parental to daughter cells (Yan & Jiang, 2020). Their membrane also contains several integrin-interacting proteins and antigens, allowing exosomes to overcome various biological barriers and achieve specific recognition and long circulation in blood as well as escape clearance by the immune system (Wang et al., 2019; Wang et al., 2022). Thus, exosomes have been extensively used as drug carriers to improve therapeutic outcomes. For example, loading RES into exosomes derived from primary microglia allowed the drug to penetrate the blood–brain barrier and stabilized it, prolonging its therapeutic efficacy. In addition, the exosomes activated neuronal autophagy *via* PI3K signaling, significantly promoting neuronal repair after central nervous system injury (Fan et al., 2020).

However, the extraction of exosomes from biological fluids and cell culture media is inefficient (Haney et al., 2015). In contrast, milk has been identified as a cost-efficient source of large amounts of exosomes that show cross-species biocompatibility, lack toxicity, encapsulate hydrophilic and lipophilic macromolecules, and efficiently cross the blood–brain barrier (Munagala et al., 2016). RES was loaded passively into milk-derived exosomes, which then delivered the drug selectively to rat mammary tissue, inhibiting the proliferation of MCF-7 and MDA-MB-231 breast cancer cells more strongly than free RES (Gonzalez-Sarrias et al., 2022).

2.2.3. Macrophages

Macrophages enter the tumor microenvironment after surgical resection by recruiting monocyte chemoattractant protein-1 (CCL-2) and pro-inflammatory factors, suggesting that macrophage-derived carriers may enhance drug delivery and accumulation in scattered tumor cells that escape resection. In one approach, liposomes were modified with octa-arginine, a cell-penetrating peptide, and loaded simultaneously with RES and paclitaxel. The obtained liposomes were then internalized by macrophages, affording a cell-mediated carrier with high drug-loading capacity as well as the ability to target sites of inflammation and tumors. The liposomes entered tumor cells, inhibiting their growth and postoperative recurrence in a 4T1 orthotopic mouse model (Qiu et al., 2021).

2.2.4. Red blood cells

Red blood cells (RBCs) are responsible for the transport of oxygen to tissues or organs and have a lifespan of about 115 d in the human body, as some of their membrane glycoproteins protect them from immune system clearance (Dupire et al., 2012; Franco, 2012). For example, the transmembrane protein CD47 on the RBC membrane prevents their uptake by macrophages by selectively binding to the signal regulatory protein-α on macrophages, which acts as a 'don't eat me' marker (Muzykantov, 2010). Due to their high drug-loading capacity and easy collection, RBCs are considered ideal drug carriers for prolonged circulation with good biocompatibility and low immunogenicity (Gutierrez Millan et al., 2012). For example, coating RES-loaded PLGA nanoparticles with RBC membrane prolonged the circulation of RES and released the drug in a sustained manner after systemic injection in rats, leading to a half-life significantly longer than that of free RES or uncoated nanoparticles (Li et al., 2019). However, in the treatment of brain diseases such as Alzheimer's disease, the use of toxic organic reagents in the preparation of PLGA nanoparticles and the acidic by-products of PLGA during degradation may make it unsuitable for long-term use in the brain (Yang, 2010; Fuhrmann et al., 2015). NLCs based on natural lipids with better biocompatibility may be more suitable for brain formulations than PLGA nanoparticles (Fu et al., 2019). To enhance the efficacy of anti-Alzheimer's disease treatment, RBC

membrane-encapsulated nanostructured lipid particles (NPs@RBCm) were prepared and rabies virus glycoprotein (RVG29) targeting the brain and triphenylphosphine cation (TPP) targeting the mitochondria were introduced using a green lipid insertion method to the RBC membrane surface (RVG/TPP NPs@RBCm), allowing RES delivery across the blood-brain barrier and subsequent targeting of neuronal mitochondria (Han et al., 2020). The experimental nanoformulations did not cause significant damage to normal cells or organs in experimental mice, and the erythrocyte membranes were able to persist a long time in circulation. In addition, co-culture models and *in vivo* imaging showed that RVG/TPP NPs@RBCm penetrated the blood–brain barrier better than NPs@RBCm, and it targeted neuronal cells, where it localized to mitochondria. These results suggest that polymer-based bionic drug delivery systems camouflaged with RBC membranes can effectively prolong the efficacy of RES.

3. Discussion and future perspectives

RES has a wide range of pharmaceutical activities and promising applications in natural medicine, but its unstable pharmacokinetics undermine its therapeutic efficacy and hinder clinical application. To overcome these drawbacks, RES has been encapsulated into specific nanocarriers, including liposomes, polymeric nanoparticles, SLNs, protein-based nanoparticles, and inorganic nanoparticles, which can modulate drug release to reach significant therapeutic concentrations in plasma and improve bioavailability. Among these nanocarriers, polymer nanoparticles are most widely used due to their high encapsulation efficiency, which significantly reduces the amount of nanocarriers required to achieve the desired bioactivity and to reduce potential toxic and side effects (Santos et al., 2014). The behavior of polymer nanoparticles under different conditions or in response to specific stimuli can easily be tuned by changing their composition and structure, while their surface can be functionalized with ligands that bind to specific cell receptors for targeted RES delivery. Despite their advantages, synthetic nanoparticles such as inorganic nanoparticles and nano-emulsions have low encapsulation capacity and present several toxicity and safety issues that limit their therapeutic efficacy (Rezaei et al., 2019; Roy et al., 2019).

Compared to synthetic nano-systems, biologically derived carriers can greatly improve the biological distribution, cellular uptake, and controlled release of encapsulated drugs, while showing higher biocompatibility and lower toxicity (Bu et al., 2019). Bionic drug delivery systems have strong affinity for cells and can easily escape phagocytosis by endothelial reticulocytes, stabilizing drugs in the circulation. However, proteins, exosomes, and other bionic nanocarriers cannot easily be obtained on a large scale, highlighting the need to discover novel delivery systems for naturally derived drugs like RES that show low water solubility, weak ability to penetrate cells, and poor bioavailability. Additional studies are also needed to extend our knowledge on the pharmacokinetics, biodistribution, toxicity, and biocompatibility of RES-loaded nano-formulations and validate their performance *in vivo*.

4. Conclusion

Our review illustrates how the encapsulation of RES into synthetic or natural nanocarriers can improve its physicochemical properties and targeted delivery, offering an effective approach for custom-made treatments. However, the therapeutic efficacy of RES-loaded nanoparticles should be further investigated with *in vivo* studies and clinical trials to ensure their suitability for the clinic.

Ethical approval statement

NA.

Author contributions

Chunhong Li and Zhen Wang contributed equally. All authors have given approval to the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors

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