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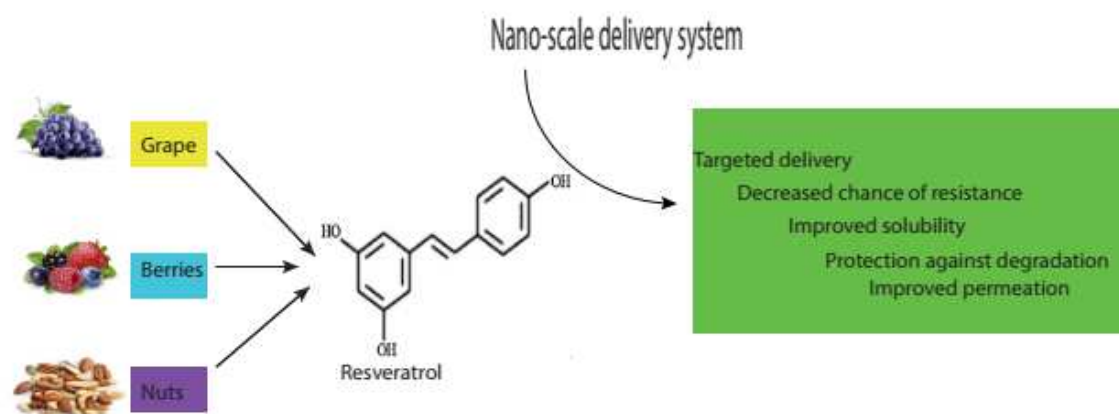
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Drug delivery systems for resveratrol, a non-flavonoid polyphenol: Emerging evidence in last decades

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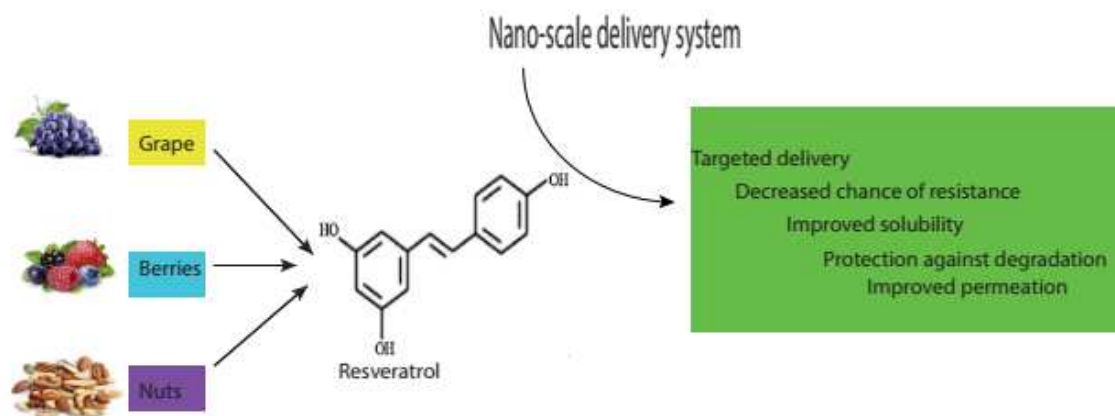
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Abstract:

Resveratrol is a naturally occurring non-flavonoid polyphenol which is found in a variety of plants, where it responds to the injury or fungal attack. This important compound has different beneficial activities such as antioxidant, antitumor, anti-inflammatory and antiaging. Also, it has anti-fibrotic and hepatoprotective effects. Besides the beneficial effects of resveratrol, limitations such as poor solubility in water, low oxidative stability and high photosensitivity have restricted its application. To prevail to these restrictions, nanotechnology is a smart strategy. This review discusses various kinds of nano delivery systems that have been applied for enclosing resveratrol.

Keywords: Resveratrol, Bioavailability, Cancer therapy, Drug delivery, Nanostructures

Graphical abstract:**Abbreviations:**

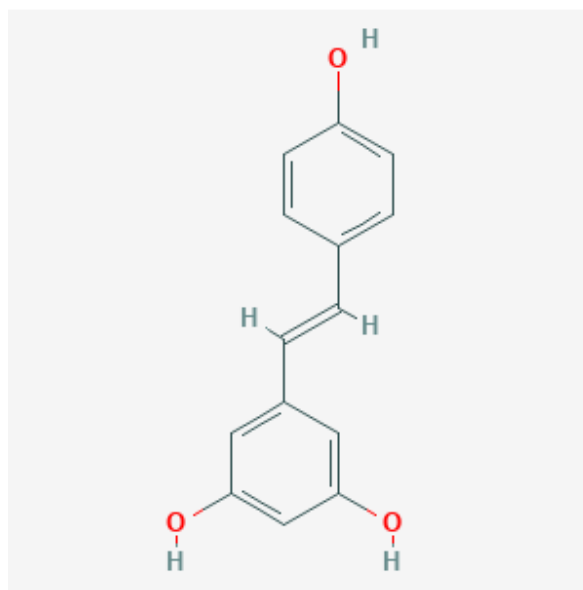
Res, resveratrol; HDF, high fat diet; SOD, superoxide dismutase; CAT, Catalase; NP, nanoparticle; EE, entrapment efficiency; ROS, reactive oxygen species; SP, silk protein; DTX, docetaxel; LPN, lipid-polymer hybrid nanoparticle; EGF, endothelial growth factor; SA, stearic acid; PEG, polyethylene glycol; PCL, poly(ϵ -caprolactone); GT, gelatin; TFE, 2,2,2-trifluoroethanol; I/R, ischemic/reperfusion; BSA, bovine serum albumin; TPP, tripolyphosphate; CS, chitosan; QUR, quercetin; IOP, intraocular pressure; PONH, polymer-oil nanohybrid; NB, nanobubble; SPI, soy protein isolate; LbL, layer by layer; NAFLD, non-alcoholic fatty liver disease; HOCl, hypochlorous; TPGS, tocopherol PEG succinate; Tf, transferrin; PTX, paclitaxel; Cur, curcumin; CMVEC, cerebromicrovascular endothelial cell; PD, parkinsonian; NIR, near-infrared; PSR, psoralen; UDL, ultraformable liposome, MLV, multilamellar lipid vesicle; 5-FU, 5-fluorouracil; PDCL, peptide cationic liposome; HUVEC, human umbilical endothelial cell; DOX, doxorubicin; LPS, lipopolysaccharide; BCCAO, bilateral common carotid artery occlusion; VE, vitamin E; EGCG, epigallocatechin gallate; SLN, solid lipid nanoparticle; MSN, mesoporous silica nanoparticle.

1. Introduction

During recent decades, herbal medicine has attracted much attention because of its safety, low side effects and valuable properties [1-10]. Resveratrol (Res) (3, 5, 4'-trihydroxy-trans-stilbene) is a naturally

occurring active biomolecule which belongs to the polyphenol family [11]. It is a non-flavonoid polyphenol and for the first time, was discovered in the roots of white hellebore (*Veratrum grandiflorum*). Also, it is mainly found in grapes, berries, red wine and nuts [12]. Interestingly, Res is synthesized in different plants exposed to damage or fungal attack [13].

This compound has a variety of beneficial activities including antioxidant [14, 15], antitumor [16-18], anti-inflammatory [19, 20], antiaging [21, 22], antidiabetic [23-26] and cardioprotective [27, 28]. Also, it is efficient for enhancing the longevity of organisms [29]. Besides, it has been shown that Res is advantageous for decreasing the level of adipose tissue [30, 31]; this study demonstrated that 6 weeks of treatment with Res at the dose of 30 mg/kg body weight/day remarkably diminishes the size of adipose tissue in various sections of body (perineal, epididymal, mesenteric, and subcutaneous) and simultaneously, does not alter food intake or body weight. Hamza and El-Shenawy investigated the ameliorative effect of Res on nicotine-induced lung alterations in male rats [32]. Their treatment period was 4 weeks and Res was administered at the dose of 20 mg/kg/b.w. Their results showed that Res exerts protective effects against nicotine toxicity in lungs, so that nicotine remarkably enhances the level of lipid peroxidation and decreases the activity of antioxidant enzymes, whereas Res reverses these adverse effects. In another study, Abdu and Al-Bogami examined the impact of Res on dimethylnitrosamine-induced liver fibrosis [14]. Their data demonstrated that Res exerts anti-fibrotic and hepatoprotective effects via enhancing antioxidant defense, reducing oxidative stress, maintaining structural integrity of cell membrane and also inhibiting steatosis and fibrosis of liver. Jimol and coworkers studied the effect of Res on high-fat diet (HFD)-induced obesity and oxidative stress in rabbits [33]. They showed that Res increases body weight and activities of superoxide dismutase (SOD) and catalase (CAT) in rabbits with HFD intake, demonstrating the potential antioxidant activity of Res. Furthermore, recently the ameliorative effects of Res on diabetes have been reported [24].



Chemical structure of resveratrol [34].

In spite of the beneficial effects of Res which have led to its extensive application in different fields, there are limitation factors that prevent its application in *in vivo* and clinical trials. These factors include limited solubility in water, low oxidative stability and high photosensitivity. Also, the applications of conventional forms of Res such as powder and tablet dosage forms have been restricted [35-38]. On the other hand, high dose consumption of a compound decreases its efficacy in next times, so that it results in drug resistance. Also, nanocarriers enable targeted delivery, so that a little dose of drug is loaded on nanoparticles (NPs) which in one hand, decreases the side effects of drug and in other hand, diminishes the chance of resistant [39, 40].

2. Drug delivery systems

To overcome the hurdle of chemotherapy, different strategies have been used to design effective drug delivery systems (DDS) [41]. These platforms transport and release an effective dosage of therapeutics to targeted cells [42]. Nanostructures possessing unique physiochemical properties including high loading capacity, cargo protection, and deep tumor penetration yielded several prerequisites for drug delivery systems [43, 44]. Notably, high safety and excellent biocompatibility are the vital features of nanoparticles that rely on the applied agents and also are affected by decomposition and excretion. During recent years, many nanoparticles including liposomes, carbon nanomaterials [45], dendrimers, quantum dots, natural nanostructures [46] and metallic nanoparticles have been developed for drug delivery applications. Some nano-formulations have been approved by the US Food and Drug Administration

(FDA), e.g., liposomal doxorubicin (Doxil®/Caelyx™) and several nanocarriers are in clinical trials for disease treatment [47].

2.1 Polymeric nanoparticles

Overall, the polymeric systems are divided into two main classes [48]: a) natural polymers such as gelatin, collagen, albumin, agarose, alginate, hyaluronic acid, carrageenan, dextran, chitosan, cyclodextrins; and b) synthetic polymers such as poly (lactic acid), poly (glycolic acid), poly lactic-co-glycolic acid (PLGA), poly (ϵ -caprolactone), polymethacrylates and polyvinyl pyrrolidone. Therapeutic agents can be adsorbed, encapsulated or conjugated either within or onto the surface of polymeric nanoparticles (PNPs). PNPs have been widely used as targeted and controlled release delivery systems based upon the rational design of polymer tailored for a particular cargo. The nanoparticles have synthesized by several methods including solvent-displacement, solvent evaporation/extraction, salting-out, and supercritical anti-solvent method [49]. In this section, we discuss the usefulness of some of these polymers in delivery of Res.

Nasir et al examined the efficacy of Res-loaded PLGA NPs on induction of programmed cell death in prostate cancer cells [50]. Res loaded PLGA NPs were synthesized using nanoprecipitation technique with the ratio of PLGA and Res 4:1, 2:1 and 1:1 (w/w) (total weight= 50 mg). The particle size and entrapment efficiency (EE%) were respectively at the range of 201.5 to 36.2 and 52.28 to 90.18. Notably, there was approximately no difference in the actual and predicted particle size and EE, so that predicted particle size and EE were respectively 206.029 and 89.549, while the actual particle size and EE were respectively 202.8 and 89.32. The *in vitro* drug release study demonstrated a maximum release of 73.87 and 34.65 for Res-PLGA and Res after 24 h, respectively. Also, MTT cytotoxicity assay, TUNEL assay, analysis of mitochondrial membrane potential, cell cycle status, caspase-3 assay and evaluation of reactive oxygen species (ROS) production showed that Res-loaded NPs stimulate apoptosis in prostate cancer cells without affecting normal cells. In another study, Res-loaded sericin NPs were designed as bionanocarriers for drug delivery [51]. Silk protein (SP)-derived NPs were prepared through desolvation. Then, Res-encapsulated SP NPs were synthesized via adding Res (dissolved in ethanol) to the pluronic F-68 solution. The quantity of Res used in the ethanol solution was different, resulting in various loading levels. Interestingly, the mean size of SP NPs was different according to the SP concentration with the larger particle sizes for higher levels of SP. *In vitro* release study showed that release of free Res occurs rapidly, reaching 100% during 8h, whereas release from SP NPs is more gradual, ranging from approximately 40-70% within the first 8h. Also, it was found that release rates are strongly associated with Res concentration, so that the release is slower in higher concentrations of Res compared to the lower concentrations. These NPs are promising nanocarriers for inhibiting the growth of cancer cells, so

that they remarkably decrease the viability and proliferation of carcinoma cell lines (Caco-2). In an effort for lung cancer therapy, docetaxel (DTX) and Res were encapsulated by lipid-polymer hybrid NPs (LPNs) [52]. First off, the conjugation of endothelial growth factor (EGF), poly-ethylene glycol (PEG) and stearic acid (SA) was performed by chemical crosslinking via a coupling agent EDC (1mM) and NHS (1mM). Then, EGF DTX/Res LPNs were synthesized through nanoprecipitation technique. The EE of DTX and Res of all samples was approximately 90%. Also, *in vitro* drug release showed the prolonged release behavior of DTX and Res from LPNs. The release of both drugs from EGF DTX/Res LPNs was slower than non EGF-modified LPNs. The flow cytometry analysis showed the good uptake of LPNs with increased uptake along with the time. It was demonstrated that EGF DTX/Res LPNs remarkably decrease the viability of tumor cells (HCC827 and NCIH2135) compared to the DTX/Res LPNs. Also, *in vivo* study on mice bearing lung cancer (intravenous administration at the dose of 50 mg/kg) showed the great ability of EGF DTX/Res LPNs in inhibition of tumor growth and also reduction in its size. Furthermore, electrospun fibers in combination with siRNA are interesting for treatment of leukemia cells [53]. In this study, poly(ϵ -caprolactone) (PCL) and gelatin (GT) electrospun fibers combining with Res were prepared in a common 2,2,2-trifluoroethanol (TFE) solvent. Loading efficiency of Res was very high ranging from 76.9 to 88.3%. In order to understand the bioactivity of Res released from the electrospun PCL-GT fibers, K562 (leukemia) cell viability was examined at 3, 5 and 8 days. Annexin V staining showed apoptosis in these cells in a time-dependent manner. Also, the viability of cells after adding siRNA in the presence of Res containing fibers was evaluated. The results exhibited significant reduction in the viability of cells after adding siRNA and this reduction was remarkably higher in presence of fibers (from 46.3 to 21.5%).

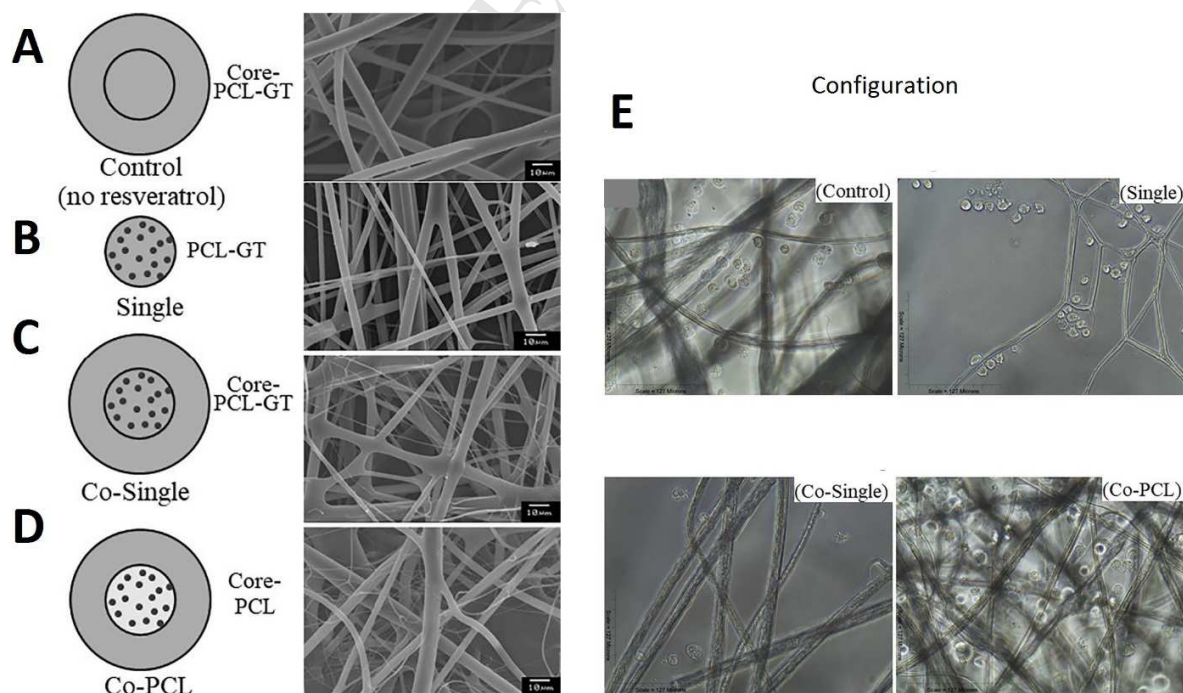


Figure 1: A) Control configuration: coaxial PCL-GT fiber with PCL-GT inner core. B) Single PCL-GT fiber with Res. C) Coaxial PCL-GT fiber with PCL-GT inner core and Res. D) Coaxial PCL-GT fiber with PCL inner core and Res. Small circles within the inner core demonstrate Res [53].

Borges and coworkers showed that Res-loaded poly (anhydride) NPs are not beneficial for intestinal damage caused by ischemia and reperfusion (I/R) [54]. It was found that loading Res on poly(anhydride) NPs significantly increases the mean size of the resulting nanocarriers (234nm for Res- NPs and 169nm for NPs), while it has partial and negligible effects on the zeta potential and poly dispersity of the resulting nanocarriers. Treatment period of mice started 5 days before induction of I/R and continued for 7 days after I/R. Mice were treated by gavage with 7 mg/kg Res (in free or nanoencapsulated form). Notably, it was demonstrated that Res results in reduction in oxidative damage caused by I/R, myenteric and glial neuronal protection, and maintenance of gastro-intestinal transit time. On the other hand, treatment with Res-loaded NPs leads to the results similar to free Res in terms of neuroprotective and antioxidant effects which demonstrate that this nanocarrier system is not suitable for the delivery of Res which maybe is due to the hepatotoxicity and myenteric neuronal loss resulted from poly(anhydride). On the other hand, chitosan NPs are efficient NPs for enhancing the delivery of Res [55]. In order to prepare stock solutions, polyphenol solution (1mM) was prepared in Tris-HCl/ethanol 50% and then diluted by serial dilution to different concentrations in Tris-HCl/ethanol. A suitable amount of chitosan was dissolved in 2% acetic acid and then the solution was adjusted to pH 5.5-6.5. Then, the conjugation of Res with chitosan-15 and chitosan-100 kDa was investigated in aqueous solution at physiological conditions, using multiple spectroscopic methods, TEM images and docking studies. Structural analysis demonstrated that binding of Res with chitosan is performed through hydrophilic, hydrophobic and H-bonding contacts and they produce stable conjugates. By enhancing the size of chitosan, the loading efficiency and stability increased. It was found that Res binding produces changes in chitosan morphology with an increase in its aggregate diameter due to Res encapsulation. These results showing that chitosan NPs can be considered as appropriate vehicles to transport and increase the bioavailability of Res. Siu and coworkers synthesized galactosylated PLGA NPs for delivery of Res [56]. Res-galactosylated NPs (Res-GNPs) were prepared using a solvent diffusion method. It was found that the amount of PLGA in the formulation remarkably affect the particle size of Res-GNPs other than EE. The formulation containing a higher level of PLGA resulted in larger NPs. Also, N-oleoyl-D-galactosamine affects the particle size and EE of Res-GNPs, so that high ratio of N-oleoyl-D-galactosamine was valuable to decrease the particle size and increase the EE. In vitro drug release showed that Res-GNPs release Res in a sustained release behavior and also, enhance the bioavailability of Res. Besides, Res-

GNPs showed good permeability through different sections of intestine, particularly duodenum and ileum which can be attributed to galactose attachment of NPs that mediates and accelerates the internalization of NPs into the enterocytes. These NPs showed rapid cellular uptake. Furthermore, the levels of TNF- α , IL-6 and NO were determined in the RAW 264.7 macrophages exposed to the LPS to assess the anti-inflammatory activity of free Res, Res-NPs and Res-GNPs and it was demonstrated that Res-GNPs have highest inhibitory effect on the secretion of these cytokines. Wan et al synthesized Res-loaded PLGA NPs for non-alcoholic fatty liver disease therapy [16]. The PLGA NPs were prepared using emulsified solvent evaporation method. The final formulation had 50 mg of PLGA, 9 mg of Res, 10 mg BSA solution and stirred for 4h. The resulting size of Res-PLGA NPs was 176.1 nm and it was found that Res does not increase the size of Res-PLGA NPs. The EE% of Res-PLGA NPs was 97.25%. The zeta potential of Res-PLGA NPs and PLGA NPs were respectively -22.6 and -20.3, showing their high colloidal stability. The release profile of Res from Res-PLGA NPs was determined through imitating conditions in gastric, intestinal and intravenous juice, respectively. At the beginning, these NPs showed an initial fast release with following prolonged release without any burst release. After 8h, at pH 7.4, the release of Res reached 29.21%, at pH 6.8 reached 12.49% and at pH 1.2, it dropped to 10.56%. Also, fluorescent staining showed the internalization of Res-PLGA NPs into HepG2 cells. The *in vitro* cytotoxicity assay showed that the drug concentration in this range is non-toxic for cells. Finally, it was demonstrated that Res-PLGA NPs remarkably alleviate lipogenesis, increase lipolysis and decrease hepatocellular proliferation compared to the free Res which are because of improved stability, water solubility and bioactivity of Res by PLGA NPs. Vijayakumar and colleagues synthesized Res-loaded PLGA NPs for brain cancer therapy [57]. Res-poly(D,L-lactide-co-glycolide)-D- α -tocopheryl polyethylene glycol 1000 succinate blend NPs (Res-PLGA-BNPs) were prepared via single-emulsion solvent evaporation technique. It was found that the PLGA:TPGS blend ratio decreases the particle size, but the ratio more than 1:1 has no effect on the particle size. The EE of Res-PLGA BNPs was at the range of 31.79 to 61.81 which is affected by the concentration of TPGS in PLGA:TPGS blend ratio, so that by increasing this ratio, the EE is reduced. Overall, Res-PLGA BNPs had spherical shape with mean particle size of 154 nm. *In vitro* drug release showed the sustained release without any burst release and it was found that the cumulative percentage of drug release after 48h is only 49.52. The cytotoxicity of Res-PLGA BNPs and Placebo-PLGA BNPs was evaluated on the C6 glioma cell line and Res-PLGA BNPs demonstrated highest cytotoxicity. Also, these NPs were significantly absorbed by C6 glioma cells with high concentration in the cytoplasm, showing their effectiveness for increasing systemic availability and improving therapeutic effect. Fonseca and colleagues synthesized bovine serum albumin (BSA)-based NPs containing Res to evaluate their antioxidant activity [58]. The Res-loaded BSA NPs were prepared using coacervation method and resulting NPs had mean particle size under 200 nm which is appropriate for drug delivery. The zeta

potential was high and also negative because of BSA end-groups on the surface, leading to its great physicochemical stability in colloidal suspension. The highest EE was 60%. *In vitro* Res release profile was biphasic, so that an initial drug release occurs during the first 8h, releasing about 14% of Res and followed by a prolonged drug release until 144h. In order to evaluate the antioxidant activity of NPs, hypochlorous acid (HOCl) scavenging assay was performed. Also, Res-NPs showed a strong antioxidant activity in a dose-dependent manner, resulting in their potential therapeutic effects in treatment or prevention of pathological conditions caused by oxidative stress such as atherosclerosis, neurodegenerative disease and cancer. Jung et al investigated the antitumor activity of Res-loaded polymeric NPs [59]. The EE of Res-loaded PEG-PLA NPs was 52.9%. The mean particle size was 120 nm and notably, mean particle size was similar in empty and Res-loaded NPs, demonstrating that Res incorporation does not remarkably affect the particle size. Also, *in vitro* release showed prolonged release of Res over 72h under physiological conditions. It was found that Res-loaded NPs have inhibitory effects on the viability and proliferation of CT26 colon cancer cells in a dose-dependent manner. Apoptotic assays showed that Res-loaded NPs are more effective in stimulating apoptosis in CT26 cancer cells compared to the free Res. Besides, the Res-loaded NPs demonstrated better inhibitory effect on the glucose uptake and ROS production. *In vivo* study was performed on the CT26 tumor-bearing mice and it was shown that Res-loaded NPs (intravenous injection) remarkably decrease the tumor growth and subsequently, increase the survival time of mice, showing the potential of PEG-PLA NPs as a suitable method to deliver Res *in vivo* for cancer therapy. Wu et al examined the biological activity of Res-loaded ionically cross-linked chitosan-sodium tripolyphosphate (TPP) NPs [21]. The NPs were synthesized using an ionic cross linking method. All NPs were well-dispersed with spherical shape. The mean particle size of Res-loaded chitosan-TPP NPs was 172-217 nm, leading to the preferentially accumulation in the tumor site. The zeta potential was more than 30mV, suggesting the stable dispersibility of Res-loaded chitosan-TPP NPs. The drug loading increased with the increasing of Res concentration and highest EE% was 11.11%. *In vitro* release study was performed at pH 7.4 and pH 6.5 to imitate the physiological and tumor tissue conditions and it was found that these NPs have a biphasic release pattern, characterized by a fast initial burst during the first 2h, followed by a slow, sustained release. To determine the antioxidant activity, scavenging capacity was evaluated and it was found that Res-loaded NPs have higher antioxidant activity compared to the free Res (10-30% increase in scavenging capacity). Also, these NPs demonstrated a high cellular uptake and viability test on human hepatocellular carcinoma cells SMMC7721 and human normal hepatocyte cells LO2 showed the high toxicity of Res-loaded NPs compared to the free Res, demonstrating the efficacy of chitosan-TPP NPs for delivery of Res. Natesan and coworkers investigated the efficacy of co-encapsulated Res and quercetin (QUR) in chitosan (CS) and PEG modified CS NPs for reducing intra ocular pressure (IOP) [60]. CS NPs were synthesized by ionic

gelation method using CS and TPP. The particle size and polydispersity index of the formulation were increased when enhancing the concentration of PEG, indicating PEG and drugs occupied in the CS-TPP complex. Besides, increased level of PEG is associated with reduction in drug loading and EE. *In vitro* release showed the sustained release of Res from CS NPs than PEG modified CS NPs. ROS scavenging test showed the higher antioxidant activity of Res and QUR loaded PEG modified CS NPs compared to the individual Res or QUR. These NPs significantly increased the corneal permeation of Res and *in vivo* IOP lowering effect in normotensive rabbits, suggesting that the QUR and Res loaded PEG modified CS NPs have higher and prolonged levels of IOP lowering effect than Res loaded modified CS NPs, demonstrating the synergistic effect of Res and QUR in decreasing IOP. Kumar et al examined the efficacy of PLGA-oil hybrid NPs for the delivery of Res [61]. Polymer-oil nanohybrids (PONHs) were synthesized using standard emulsification-solvent evaporation method. It was found that the PLGA to oil ratio of 0.25:1 to 2:1 was very critical in preparation of PONHs. The highest and lowest particle size were 20 and 233 nm. Also, zeta potential and EE% were at the range of -4.6 to -33.8 and 21.3 to 90.7, respectively. The drug release study showed a remarkable difference at the release of Res from PONHs and PLGA NPs. Approximately 48% of the drug was released from PLGA NPs at the first 4h, whereas it was just 9.7% in the case of PONHs. The decreased burst effect demonstrated the more uniform distribution of the drug inside the PONHs as compared to the standard PLGA NPs. It was demonstrated that Res-loaded PONHs have higher antioxidant activity compared to the free Res. Finally, these NPs showed an excellent biocompatibility with Vero cell lines, showing the potential of these NPs in delivery of Res. Musazzi and coworkers synthesized Res-loaded nanocarriers for delivery to cochlear cells [62]. Res-loaded polymeric NPs were prepared by adapting a solvent-diffusion technique without surfactant. The *in vitro* drug release showed the complete release of Res after 50h. The *in vitro* toxicity on cochlear cell lines (HEI-OC1 and SVK-1) showed the safety of blank NPs, native Res and Res-loaded NPs in both cell lines, demonstrating the effectiveness of Res-loaded NPs in protection of cochlear cells. Kumar et al designed a novel approach for preparing core-shell hybrid PLGA NPs for Res delivery [63]. In this study, oil as a green solvent was used to prepare polymeric NPs. The nanohybrids had core/shell structure as compared to the round structure of PLGA NPs. PLGA layer was remarkably porous in PLGA-NPs and PONHs which is due to evaporation of residual solvent while it was smooth in green-PONHs (G-PONHs). G-PONHs showed the slowest rate of drug release. The antioxidant potential of Res was maintained after incorporation in nanohybrids and also higher antioxidant activity was observed due to the protective effect of oil. The biocompatibility and cytotoxicity of NPs were assessed on Vero and MCF-7 cells, respectively. The most biocompatibility was observed in G-PONHs due to lack of toxic solvent and after incorporation of Res into nanohybrids, its cytotoxicity was increased, showing their efficacy in improving the biological activity of Res and also its delivery. Shen and coworkers synthesized

ultrasound-mediated nanobubbles (NBs) for delivery of Res [64]. The Res-loaded NBs were prepared using a double-emulsion method. These nanocarriers had great properties in terms of high Res-loading efficiency and ultrasound triggered accelerated Res release. In vitro study showed that these nanocarriers have high anti-catabolic activity. Also, in vivo study approved that the injection of Res-loaded NBs remarkably retards the degenerative process of the intervertebral disc, showing the potential of these nanocarriers in improvement of intervertebral disc degeneration. Zhang et al investigated the efficacy of alginate-shelled soy protein isolate (SPI) NPs for the encapsulation of Res [65]. The diameter and zeta potential were 204.5 nm and -36.4mV, respectively. Also, these nanocarriers showed Res EE as high as 91.9%. The encapsulation of Res did not decrease its antioxidant activity, while the encapsulation increased the resistance of Res to digestion in gastric and UV-induced isomerization. Tabibiazar et al examined the efficacy of colloidal nanodispersion of bovine serum albumin (BSA)-Res on improving the dispersibility, stability and antioxidant activity of Res [66]. The Res was stabilized using BSA at a molar ratio of 2.3:1 of Res:BSA. This complex remarkably protected Res from UV-induced isomerization. The anti-oxidant activity of Res decreased an almost 3 folds after 3 days, whereas the antioxidant activity of BSA-Res complex was not significantly changed. Also, this complex significantly enhanced the solubility and stability of Res in aqueous medium. Santos et al investigated the potential of layer by layer (LbL) nanostructures on the bioavailability of Res [67]. The LbL nano-formulations composed of 5.5 bilayers of polyallylamine hydrochloride and dextran sulfate were prepared and their pharmacokinetic was examined following oral dosing to Wistar rats (20 mg/kg). These nanocarriers significantly increased the bioavailability and chemical stability of Res. Iglesias et al synthesized chitosan-based biomaterials for delivery of Res [68]. Chitosan-NPs composites were prepared using ionically gelation of chitosan dispersion containing the Res-loaded NPs with tricarballic acid. These NPs demonstrated great features in terms of thermal stability and cumulative drug release as high as 79-81% at the simulated colon condition for 48h. Zhang et al examined the potential of zein NPs for co-encapsulation of α -tocopherol and Res [69]. Zein colloidal NPs were synthesized using desolvation method. The EE of α -tocopherol and Res was 96% and 67%, respectively. Particle size and zeta potential of NPs were 80-122nm and +27 to +60mV, respectively. These NPs showed good stability and provided a protective effect on Res and α -tocopherol. Wan et al examined the efficacy of Res-loaded PLGA NPs for non-alcoholic fatty liver disease (NAFLD) therapy [70]. The Res-loaded PLGA NPs were prepared using an oil/water emulsion technique. The average size and zeta potential were 176.1n and -22.6mV, respectively. The EE and drug loading were 97.25% and 14.9%, respectively. These NPs showed great features in terms of sustained release pattern in acidic conditions, good stability, and efficacy in alleviating lipogenesis, promoting lipolysis and reducing hepatocellular proliferation, showing the promising potential for NAFLD therapy.

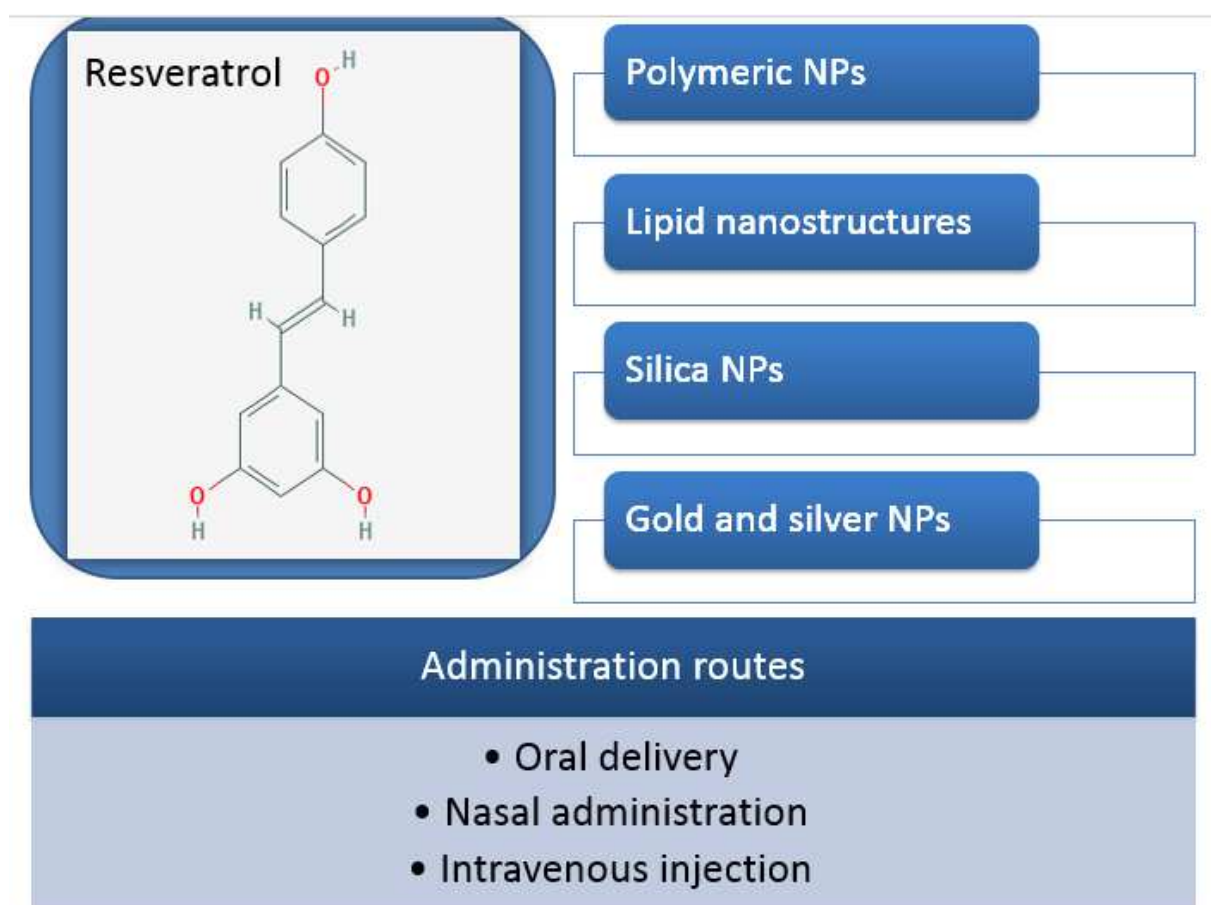


Figure 2: The different administration routes for nano-scale delivery systems.

Table 1: Studies supporting the efficacy of polymeric nanoparticles in delivery of resveratrol.

Carrier	Cell line/Animal model/Method	Major outcomes	Refs
Bovine serum albumin-based NPs	Hypochlorous acid (HOCl) scavenging assay	High antioxidant activity compared to the free Res	[58]
Polymeric NPs	CT26 mouse colon cancer cells	Dose-dependent effect and remarkable inhibitory effect on survival and growth of tumor cells	[59]
Chitosan-TPP NPs	Human SMMC7721 and LO2 cells	Excellent anti-proliferative activity against tumor cells	[21]
Chitosan and peg modified chitosan NPs	Normotensive rabbits	Improved corneal permeation and efficient reduction of intra ocular permeation	[60]
PLGA-oil hybrid NPs	DPPH free radical scavenging assay	Improved antioxidant activity	[61]
PLGA NPs	Cochlear cell lines (HEI-OC1 and SVK-1)	High cytotoxicity on HEI-OC1 and SVK-1 cells	[62]
PLGA NPs		High biocompatibility and stability as well as controlled release	[63]

2.2 Lipid-based nanocarriers

2.2.1 Liposome

Liposomes are one of the first lipid-based well-investigated drug nano-carriers (50–1000 nm in diameter) [71]. These spherical bilayered nanostructures mainly consist of phospholipids and cholesterol. The carriers can be prepared as stimuli-responsive and smart nanoplateforms to encapsulate both lipophilic and hydrophilic compounds [72]. Encapsulation of hydrophobic molecules inserted into the bilayer membrane, and hydrophilic molecules entrapped in the aqueous center protect the compounds from early inactivation, degradation and dilution in the circulation [73]. Liposomes diminish nonspecific side-effects and reduce toxicity of drugs. As a drug delivery system, liposomes offer the capacity for self-assembly [74]. Liposomes are beneficial delivery systems in terms of biocompatibility, protection of loaded drugs against degradation, delivery of low soluble drugs and ability to increase the targetability [75-77].

Caddeo et al synthesized PEG-modified liposomes containing Res [78]. In this study, liposomes were modified with PEG surfactants as a surface modification strategy to increase the stability of Res and also deliver it without affecting its antioxidant capacity. PEG-poly(propylene glycol) (PPG)-PEG, a water-soluble block polymer non-ionic surfactant and tocopherol PEG succinate (TPGS), a water-soluble non-ionic surfactant were used as surfactant modifiers. PEG-modified liposomes were synthesized using a simple method involving the sonication of the phospholipid (P90G), PEG-PPG-PEG, TPGS and Res in water. The resulting liposomes had dramatic properties, so that they showed small size (85 nm), good homogeneity and negative zeta potential (-20 mV), regardless of the presence of Res. The EE was 95% for PEG-modified liposomes and the concentration of loaded Res did not remarkably decrease during storage over the course of 2 months. Morphologically, these liposomes had fairly spherical shape with predominant unilamellar structure. The drug release study showed that PEG-modified liposomes release Res in a time-dependent manner with sustained release behavior and PEG-surfactants play a remarkable role in controlling release rate. Due to the direct contact of liposomes with blood, their possible hemolytic effect was investigated. PEG-modified liposomes demonstrated negligible hemolysis compared to the free Res and conventional liposomes, so that after 6h of incubation of human erythrocytes with the liposomal formulations, no remarkable impact was occurred and after 18h of incubation, a slight raise of hemolysis was observed. The antioxidant activity was evaluated by DPPH assay and it was found that as well as Res, PEG-modified liposomes have antioxidant activity which is maybe due to active soy phosphatidylcoline. Also, antioxidant activity of Res formulations was assessed *ex vivo* in human erythrocytes by the CAA test and Res-loaded PEG-modified liposomes showed a dose-dependent antioxidant effect, demonstrating their potential as a nanocarrier for delivery of bioactive Res. In another

study, Ethemoglu and coworkers investigated the anticonvulsant activity of Res-loaded liposomes [79]. Liposome dispersions were synthesized by thin film technique and then, other materials were added. It was found that Res at the dose of 2, 10 and 20 mg/kg has no effect on the penicillin-induced epilepsy. The particle size and zeta potential of Res-loaded liposomes were 194.55 nm and -32.6 mV, respectively. Notably, Res-loaded liposomes significantly decreased the penicillin-induced epilepsy. GST, GSH, SOD and MDA assays were performed and showed that Res-loaded liposomes have high antioxidant activity. Overall, these results demonstrate the promotion of antioxidant and antiepileptic properties of Res by liposomes. Also, transferrin (Tf)-targeted, Res-loaded liposomes are suitable choices for treatment of glioblastoma [80]. In this study, the liposomes were synthesized using the thin film hydration method. Then, to synthesize Tf-targeted liposomes, Tf moieties were attached to the distal ends of liposome-grafted PEG chains. Approximately 70-75% of initially added Res was encapsulated within liposomes, showing good drug binding efficiency. The particle size of liposomes was < 200 nm and addition of Tf increased their size by about 20-30 nm. It was demonstrated that Tf modification of liposomes increases their association with U-87 MG human glioblastoma cells and TfR-modified endocytic pathway is involved in the uptake of Tf-liposomes by cells. The zeta potential of Tf-Res-liposomes was -34.1 mV. These liposomes demonstrated higher cytotoxicity against U-87 MG cells compared to the Res-liposomes in a dose-dependent manner. *In vivo* study was performed on U-87 MG tumor xenograft-bearing mice. It was found that Tf-Res-liposomes significantly inhibit the tumor growth and increase the survival of mice compared to the free Res, showing their efficacy in treatment on glioblastoma tumor. Zu et al designed Res liposomes to increase the cytotoxicity of Res on murine 3T3-L1 fibroblasts [81]. After encapsulation of Res in lipid nanocarriers (Res-nano) and liposomes (Res-lipo), the aqueous solubility and stability of Res were improved. In this study, triglyceride was replaced by α -tocopherol acetate (α TA), consequently eliminating exogenous triglyceride and increasing the anti-oxidative capacity of nanocarriers. The particle size of nanocarriers was under 100 nm and zeta potential of Res-nano and Res-lipo was around -19 and -28 mV, respectively. The EE of Res-nano and Res-lipo was 96.5% and 96.0%, respectively and Res's loading capacity in Res-nano and Res-lipo was 28.5% and 25.3%, respectively. *In vitro* release experiment exhibited the prolonged release of Res from Res-nano and Res-lipo. It was demonstrated that these nanocarriers are biocompatible because of their non-toxicity on 3T3-L1 fibroblast cells. Also, Res-nano and -lipo remarkably increased the cellular uptake of Res which resulted in higher expression of UCP1, beige marker CD137 and other browning markers and lower expression of white marker IGFBP3, demonstrating the potential of these nanocarriers in promoting browning efficacy with minimal side effects.

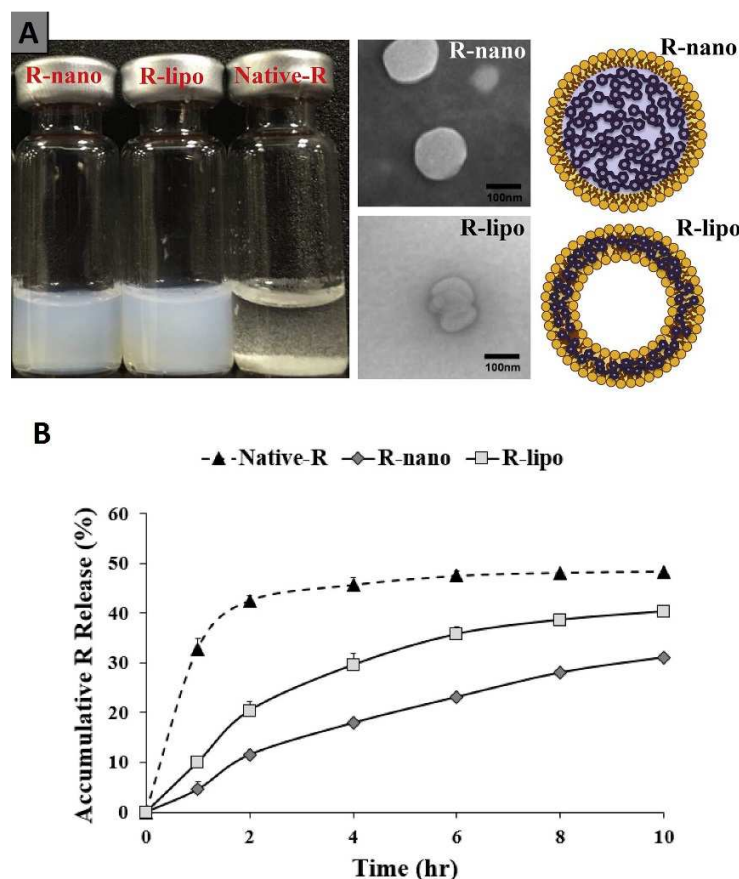


Figure 3: A) Visual observation of R-nano, R-lipo and native R and transmission electron microscope (TEM) and predicted structures of R-nano and R-lipo. B) Accumulative R release for native R, R-nano and R-lipo [81].

On the other hand, Park et al prepared chitosan-coated liposomes to increase the skin permeation of Res [82]. After the synthesis of NPs, chitosan was added to coat liposomes. The particle size of uncoated liposomes was 212.83nm and after coating with chitosan, their size was elevated and the maximum size was 558.35nm. So, the particle size dependent on chitosan concentration. The zeta potential of chitosan-coated liposomes was at the range of 26.5 to 39.2 mV. The EE of uncoated liposomes was 83.91%, but this value for chitosan-coated liposomes was at the range of 81.36 to 82.95%, showing that chitosan decreases the EE of nanocarriers, though not to a significant level. *In vitro* skin-permeation efficiency of Res showed that chitosan-coated liposomes increase the stability and skin permeation of Res, suggesting that these liposomes can be considered as appropriate transdermal delivery systems for an antioxidant defense system to delay skin aging. Bonechi et al designed liposomes as carriers for Res [83]. The liposomes were made by a saturated phosphatidyl-choline (DPPC) and cholesterol (or its positively charge derivative DC-CHOL) to optimize the loading of Res. In DPPC/CHOL liposomes, the maximum

loading of Res was 6.9×10^{-4} M with the mean diameter at the range of 240 to 380 nm and zeta potential at the range of -1 to -10mV. In DPPC/DC-CHOL liposomes, the maximum loading of Res was 5.9×10^{-4} M, mean diameter was at the range of 110 to 130nm with zeta potential at the range of +54 to +57mV. These nanocarriers were biocompatible, so that the toxicity assay showed that they are at least safe for the NIH3T3 and U3763-MG (mouse fibroblasts and astrocytes), showing the potential of these nanocarriers for using in *in vivo* experiments. Meng et al synthesized liposomes containing Res and paclitaxel (PTX) for drug resistance reversal in breast cancer cells [84]. In this study, Res was co-encapsulated with PTX in a PEGylated liposome. The PEGylated liposome was synthesized using the standard ultrasonic dispersion method. Modification of liposome surface with PEG may decrease the capture of liposome by the liver or spleen. The liposomes were moderately uniform and spherical in shape. The average liposome size was 50nm, resulting in decreased capture of liposome by macrophage in liver and spleen. The EE was more than 50%, showing that PTX or Res can be loaded together into a composite liposome. Standard viability assay was used to evaluate the antitumor efficacy of liposome-encapsulated drugs against drug-sensitive and drug-resistant breast cancer cells and it was shown that the greatest toxicity is associated with composite liposome containing PTX and a higher dose of Res. *In vivo* study was performed on nude mice with the drug-sensitive MCF-7 or the drug-resistant MCF7/Adr xenografts and it was found that composite liposomes containing PTX and Res (intravenous injection) have highest inhibitory effect on the tumor growth and also its volume, showing that the co-delivery of Res and cytotoxic agents by a nanocarrier is beneficial in treatment of drug-resistant malignancies. Narayanan et al investigated the efficacy of liposome containing curcumin (Cur) and Res in decreasing prostate cancer incidence [85]. Notably, it was found that oral administration of liposome containing Res and Cur results in higher serum concentration of Cur (252 ng/ml) compared to the lipo-Cur alone (100 ng/ml). Liposomes were administered by oral gavage in male B6C3F1/J mice and it was shown that liposomes containing Res and Cur significantly decrease the weight and growth of prostate tumors, showing the potential therapeutic effect of these liposomes in treatment of prostate cancer. Csiszar and colleagues examined the efficacy of fusogenic liposomes containing Res in activation of Nrf2 and alleviation of oxidative stress [86]. Flow cytometry and laser scanning microscopy demonstrated that these liposomes increase the uptake of Res by cerebrovascular endothelial cells (CMVECs) from aged rats. Also, Res encapsulated in fusogenic liposomes increased the transcriptional activity of Nrf2, attenuated oxidative stress and exerted anti-apoptotic effects in aged CMVECs, demonstrating the capability of these nanocarriers in prevention or control of oxidative stress-related pathophysiological conditions in aging. Lu et al investigated the effect of liposome encapsulation technique in improving anti-carcinoma effect of Res [87]. The Res liposomes were prepared by reverse-phase evaporation method. It was demonstrated that EE is increased by reduction in the level of cholesterol, but in according to the positive effect of cholesterol on stabilizing the

bilayer structure of liposome, a certain amount of cholesterol is always vital for the formation of liposome. These liposomes were spherical and addition of Res increased their particle density and particle size of Res liposomes was 120nm. *In vitro* release experiment exhibited that the release of Res from liposomes is pH-independent, but the relative lower level of drug release rate at pH 7.4 was promising to obtain the long circulating property. The toxicity of Res liposomes was performed on the HeLa and HepG2 cells and it was found that Res-liposomes exert more inhibitory effect on the tumor growth compared to the free Res. Wang et al examined the protective effect of Res derived from *Polygonum cuspidatum* and its liposomal form on nigral cells of parkinsonian (PD) rats [88]. Lecithin and cholesterol were used to synthesize liposomes. ROS levels and T-AOC were respectively increased and decreased in the nigral area of PD model rats, and Res and Res liposomes, specifically Res-liposome, remarkably decreased the levels of ROS, while remarkably increased the level of T-AOC. Also, the number of apoptotic cells was increased in PD rats by 4 folds, and Res and Res liposomes, particularly Res liposomes remarkably decreased the number of apoptotic cells, showing the more potent therapeutic effects of Res liposome due to its increased bioavailability. Wang et al investigated the anti-tumor effect of gold nanoshell coated thermos-pH dual responsive liposomes containing Res [89]. In this study, a multifunctional responsive drug carrier was prepared by loading Res in chitosan (CS) modified liposomes and coated by gold nanoshells (GNS-CS-Res-liposomes). The resultant liposomes had excellent properties in terms of broad near-infrared (NIR) absorbance, high capability, stability, high loading capacity of Res, great cellular uptake under NIR laser irradiation. MTT assay was performed to manifest the toxicity of these liposomes and it was found that these liposomes significantly decrease the viability of HeLa cells, showing a promising application of GNS-CS-Res-liposome as a biocompatible and multifunctional agent for impressible cancer treatment. Doppalapudi et al prepared psoralen (PSR) and Res co-loaded ultraformable liposomes (UDL) for the treatment of vitiligo [90]. UDL were synthesized by thin film hydration technique. The particle size and zeta potential respectively were at the range of 105.55 to 157.45nm and 38.35 to 47.95mV. These nanocarriers showed good stability. *In vitro* release profile showed that Res and PSR release in a prolonged release behavior from UDL. These nanocarriers showed remarkable cell uptake and high cytotoxicity against human melanoma cells (B16F10 cells). Also, PSR and Res co-loaded UDL demonstrated significant antioxidant activity and potential induction of melanin and tyrosinase activity, showing their potential therapeutic strategy for vitiligo treatment. Balanc et al designed new Res delivery systems based on alginate-sucrose and alginate-chitosan microbeads containing liposomes [91]. Multilamellar lipid vesicles (MLV) were synthesized by proliposome method. The average diameter of liposomes without cryoprotectant was 412nm and addition of sucrose increased their size to 471nm. The zeta potential of nanocarriers was more than 20mV and it was demonstrated that after addition of sucrose and 7 days of storage, the zeta potential decreases which

is due to desorption of sucrose from the liposomes surface, leading to the increased liposome electrophoretic mobility. The chitosan coating was performed to decrease the diameter of particles and release rate, but on the other hand, it resulted in lower drug EE and weaker particles. Also, it was found that a combination of alginate and sucrose leads to the increased barrier to Res diffusion but better rehydration properties, showing the efficacy of these nanocarriers for application in the food industry and pharmacy. Caddeo et al examined the impact of QUR and Res co-incorporated in liposomes on skin cancer-associated inflammatory/oxidative response [92]. The liposomes were prepared using dispersion method. The QUR-Res liposomes had great properties in terms of good mean size (97nm), zeta potential (-40mV) and high EE as much as 71.2% for QUR and 72.1% for Res. It was shown that liposomal formulation does not decrease the antioxidant activity of the polyphenols and also the empty vesicles exhibited antioxidant because of active soy phospholipids. Cell viability showed that QUR-Res liposomes have lower toxicity on the viability and survival of human dermal fibroblasts and these liposomes increased the intracellular uptake of QUR and Res. Also, QUR-Res liposomes remarkably decreased the levels of ROS which is in line with both greater cellular uptake and increased cell viability. *In vivo* study demonstrated that topical treatment with QUR-Res liposomes leads to the moderate attenuation of the lesion at the back of mice, and subsequently, tissue repair and wound healing, showing the potential therapeutic effect of QUR-Res liposomes for the treatment of skin conditions associated with inflammation and oxidative stress. Cadena et al investigated the effect of nano-encapsulation of QUR and Res into elastic liposomes on the subcutaneous fat [93]. These liposomes were prepared using thin lipid film method. These nanocarriers showed great properties in terms of good stability, excellent EE (at the range of 86 to 97.3%) and mean size of at the range of 106.5 to 166.7nm. *In vitro* release study showed that both Res and QUR release from liposomes, initially with a burst release and then, followed by a controlled release. These results demonstrate the efficacy of these liposomes in delivering Res and QUR, but more researches should be performed to ensure their safety and efficacy for using in injectable form in treatment of subcutaneous fat reduction. Caddeo et al synthesized succinyl chitosan-stabilized liposomes for the oral co-delivery of quercetin (QUR) and Res [94]. The succinyl-chitosan liposomes were prepared by dropwise addition of liposomes to a N-succinyl-chitosan aqueous solution under gentle stirring. Light scattering results exhibited that these liposomes are small in size (approximately 80nm) with good homogeneity and highly negative zeta potential value (-38mV). Also, the EE was about 70%. It was shown that these liposomes have good resistant to acidic conditions. The succinyl-chitosan forms a pH-sensitive shell on the liposome surface to protect liposomes against the acidic pH of stomach. *In vitro* release study showed that QUR releases from liposomes in a rapid pattern which reaches to maximum in 20 min, while Res released in a slow and steady pace. These results demonstrate that succinyl-chitosan liposomes are appropriate delivery systems for the incorporation, protection and release of QUR and Res

in oral delivery. Cosco et al synthesized ultradeformable liposomes (UDLs) for topical delivery of Res and 5-fluorouracil (5-FU) [95]. The mean diameter of UDLs was less than 120nm with a polydispersity index of 0.2, showing a non-homogenous size distribution. It was found that encapsulation of drugs increases the size of these NPs. The zeta potential was at the range of -25 to -30mV. The EE for Res and 5-FU were approximately 77% and 50%, respectively. The release profile evaluation showed the prolonged release of these drugs from UDLs. Percutaneous permeation experiments showed that encapsulation of Res and 5-FU into UDLs significantly increases their percutaneous permeation compared to free drugs. To assess the anti-tumor activity of these carriers, their toxicity on skin cancer cells (Colo-38 cells) was determined and these nanocarriers remarkably decreased the viability of skin cancer cells (about 70%). Xu et al prepared peptide cationic liposomes (PDCLs) for co-delivery of Res and p53 gene [96]. These liposomes were synthesized using thin-film and ultrasonic dispersing method. The zeta potential was at the range of 81.4 to 109.8mV, ensuring the stability of drug-loaded liposomes for at least 3 months in terms of appearance and turbidity. The particle size was from 65.9 to 220.7nm and it was found that the particle size increases by enhancing the concentration of Res. The EE was at the range of 65.13 to 94.32%. MTT assay was performed to evaluate the inhibitory effects of these nanocarriers containing Res and P53 gene on MCF-7 and HeLa cells. It was found that Res and P53 gene have synergistic effect and these nanocarriers remarkably decrease the viability of cancer cells. Also, Res-P53 gene-loaded liposomes showed high apoptosis-inducing activity, demonstrating their potential for cancer therapy. Joraholmen et al prepared Res-loaded liposomes for topical treatment of vaginal inflammation and infections [97]. The Res-loaded liposomes showed great properties in terms of vesicle size (206 to 225nm), polydispersity index (0.12 to 0.14), zeta potential (14.77mV) and EE (74 to 80%), good mucoadhesive property and prolonged release of Res as well as excellent anti-oxidant and anti-inflammatory activities. Also, these liposomes demonstrated anti-microbial property, showing their efficacy against vaginal pathogens. Vanaja et al investigated the anti-oxidant activity of Res-loaded liposomes with and without vitamin C [98]. The liposomes were synthesized using thin film method. The particle size was at the range of 10.3.3 to 134.2nm and zeta potential was more than -30mV. It was shown that these liposomes increase the radical scavenging effect of Res. Also, Res-loaded liposomes inhibited the oxidative burst reaction in buffy coats with the effect slightly increased in the presence of vitamin C. Reduction in the ROS production during incubation of human umbilical endothelial cells (HUVECs) with H₂O₂ further approved the antioxidant activity of Res-loaded liposomes, showing their potential for decreasing the intracellular accumulation of ROS.

Table 2: Studies supporting the efficacy of liposomes for delivery of resveratrol.

Carrier	Cell line/Animal model	Major outcomes	Refs
Ultradeflexible liposomes	Melanocyte cells (B16F10)	High penetration and improved antioxidant activity as well as induction of pigmentation and restoration of redox balance	[90]
Alginate-sucrose and alginate-chitosan microbeads containing liposomes		Small diameter of particles and slower release of Res	[91]
Liposome	Human dermal fibroblasts	Great anti-ROS activity and neutralizing inflammatory response, resulting in tissue repair and wound healing	[92]
Elastic liposomes		Promising for subcutaneous injection	[93]
Succinyl chitosan-stabilized liposomes		Promising for oral delivery due to protection of bioactive polyphenols	[94]
Ultradeflexible liposomes	SK-MEL-28 and Colo-38 cells	Great antitumor activity on skin cancer cells and potential treatment for squamous cell carcinoma	[95]
Peptide cationic liposomal nanocarrier	HeLa and MCF-7 cells	High tumor growth inhibition and great apoptosis-inducing activity	[96]
Liposome	Murine macrophage J714A.1 cells	Great toxicity against vaginal inflammation and infection	[97]
Liposome	Human umbilical vein endothelial cells	Excellent antioxidant activity	[98]

2.2.2 Micelle

Nano-sized polymeric micelles composed of amphiphilic polymer macromolecules can encapsulate water insoluble agents in their hydrophobic core to solubilize hydrophobic therapeutics and imaging agents [99, 100]. The hydrophilic segment forms the corona that shields the core, allows compatibility of the micelles in the aqueous environment and protects the loaded drugs from interactions with the blood components [101]. Within recent decades, much attention has been performed towards micelles because of their biocompatibility and target delivery [101].

Guo and coworkers investigated the effect of Res- and DTX-loaded polymeric micelles for improvement of drug-resistant tumors [64]. Res-DTX-loaded micelles had an average particle size of 17.1nm and polydispersity index of 0.27. Also, the loadings of Res and DTX in the micelles were 16.89% and 16.87%, respectively. *In vitro* drug release study showed the continuous and fast release in the first 12h and after that, release rate was decreased and finally, the cumulative release of both DTX and Res reached approximately 80% at 72h. The MTT assay evaluated the cytotoxicity of Res-DTX-loaded micelles on MCF-7 cells. The blank polymeric micelles showed no cytotoxicity, suggesting their biocompatibility, while Res-DTX-loaded micelles significantly decreased the viability of MCF-7 cells which is due to increased endocytosis uptake at the presence of PEG shell on the surface. *In vivo* study on rats showed that these micelles (intravenous administration) remarkably increase the exposing time of Res and DTX in the blood circulation, demonstrating the potential of these nanocarriers in treatment of drug-resistant tumors. Lu et al examined the role of Res-loaded polymeric micelles in protection of cells from A β -induced oxidative stress [102]. In this study, poly-caprolactone (PCL) was selected as the hydrophobic core of the block polymer due to its good drug encapsulation ability and polyethyleneglycol (PEG) was selected as the hydrophilic shell due to its biocompatibility and hydrophilicity. These nanocarriers had a spherical shape with smooth surface. The highest drug loading and EE were 20% and 89%, respectively. Drug release experiment demonstrated the sustained release of Res from these NPs and also these nanocarriers significantly absorbed by PC12 cells. It was found that Res-loaded NPs protect PC12 cells from A β -induced damage in a dose-dependent manner via decreasing intracellular oxidative stress and caspase-3 activity. Cote and colleagues investigated the effect of Res-QUR-loaded polymeric micelles on the doxorubicin (DOX)-induced cardiotoxicity [103]. These micelles were capable of retaining 1.1mg/ml and 1.42mg/ml of Res and QUR, respectively. The *in vitro* release study showed the first order kinetics over 48h. *In vitro* cell viability showed the synergistic effect of both drugs in decreasing viability of human ovarian cancer cells (SKOV-3) and antagonistic effect in rat cardiomyocytes (H9C2). Also, these nanocarriers exhibited high scavenging activity in H9C2 cells. *In vivo* study provided another proof for

cardioprotective effect of these nanocarriers, showing the potential of Res-QUR-loaded polymeric micelles in alleviation of acute DOX-induced cardiotoxicity. Carlson et al investigated the efficacy of Res-Cur -loaded polymeric micelles on amelioration of DOX-induced cardiotoxicity [104]. Res-Cur at a molar ratio of 5:1 in F127 micelles were synthesized using the solvent casting method. The particle size of micelles was 25.05nm with a polydispersity index of 0.059, showing a unimolar distribution. The cell viability indicated that this combination of Res and Cur are synergistic in SKOV-3 (ovarian cancer cells) and antagonistic in H9C2 cells (cardiomyocytes). Also, ROS activity was restored to the baseline in H9C2 cells. Overall, results showed that co-administration of Res and Cur by micelles decrease the DOX-induced cardiotoxicity via reduction of apoptosis and ROS, whereas these micelles improve DOX potency in ovarian cancer cells. Katherine et al examined the potential of polymeric micelles in increasing loading efficiency and efficacy of DOX and Res [105]. The enhanced loading is because of desirable interactions of DOX and Res as well as to the interaction with benzyl substituents of PEG-b-PBCL diblock copolymer micelles. Also, these micelles significantly enhanced the EE% of DOX (from 31% to 87.7%). These polymeric micelles containing DOX exhibited enhanced cytotoxicity against HeLa cells compared to DOX only loaded micelles. The micelles were synthesized using a solvent evaporation method with the average size from 44.3nm (PEG-b-PCL micelles) to 71.5nm (PEG-b-PBCL micelles). Also, these micelles were spherical with fairly narrow dispersity. The highest EE was 87.7%. Hu et al prepared paclitaxel (PTX)-Res-loaded polymeric micelles for increasing the antitumor activity [106]. The polymeric micelles were synthesized using thin film method. The particle diameter and EE were 20nm and 95%, respectively. Also, *in vitro* drug release showed the time-dependent sequential release of Res and PTX, leading to the sensitizing of cancer cells to apoptosis. Notably, *in vitro* cytotoxicity assay was performed and it was found that this combination strategy exerts synergistic effect and significant cytotoxicity on PTX-resistant human lung adenocarcinoma epithelial (A549/T) cell line and mice sarcoma 180 (S180) cells, whereas they have restricted toxicity on normal cells. This inhibitory effect on the viability of tumor cells is due to manipulation of ROS levels by redox modulation and decreasing protective autophagy. *In vivo* experiment on S180 bearing mice indicated the decreased tumor volume and growth, showing the efficacy of PTX-Res-loaded polymeric micelles in treatment of cancer. Kim et al synthesized self-assembled polymeric micelles for combined delivery of Res and heme oxygenase-1 gene (pHO-1) [107]. Cholesterol-conjugated polyamidoamine (PAM-Chol) was prepared for delivery of Res and pHO-1 into lungs by inhalation. The *in vitro* transfection assay showed the higher transfection efficiency of PAM-Chol micelles compared to the lipofectamine and polyethylenimine. Res was added into the cores of PAM-Chol micelles using the oil-in-water emulsion/solvent evaporation method. In order to approve the anti-inflammatory effects, Res-loaded PAM-Chol micelles were added to the lipopolysaccharide (LPS)-activated macrophage cells and remarkably decreased the level of pro-

inflammatory cytokines. The delivery of Res and pHO-1 by inhalation in AL1 animal model was assessed and it was demonstrated that Res delivery by PAM-Chol/Res micelles inhibits the nuclear translocation of NF- κ B and decreases pro-inflammatory cytokines in lungs, showing the potential of these nanocarriers in treatment of acute lung injury.

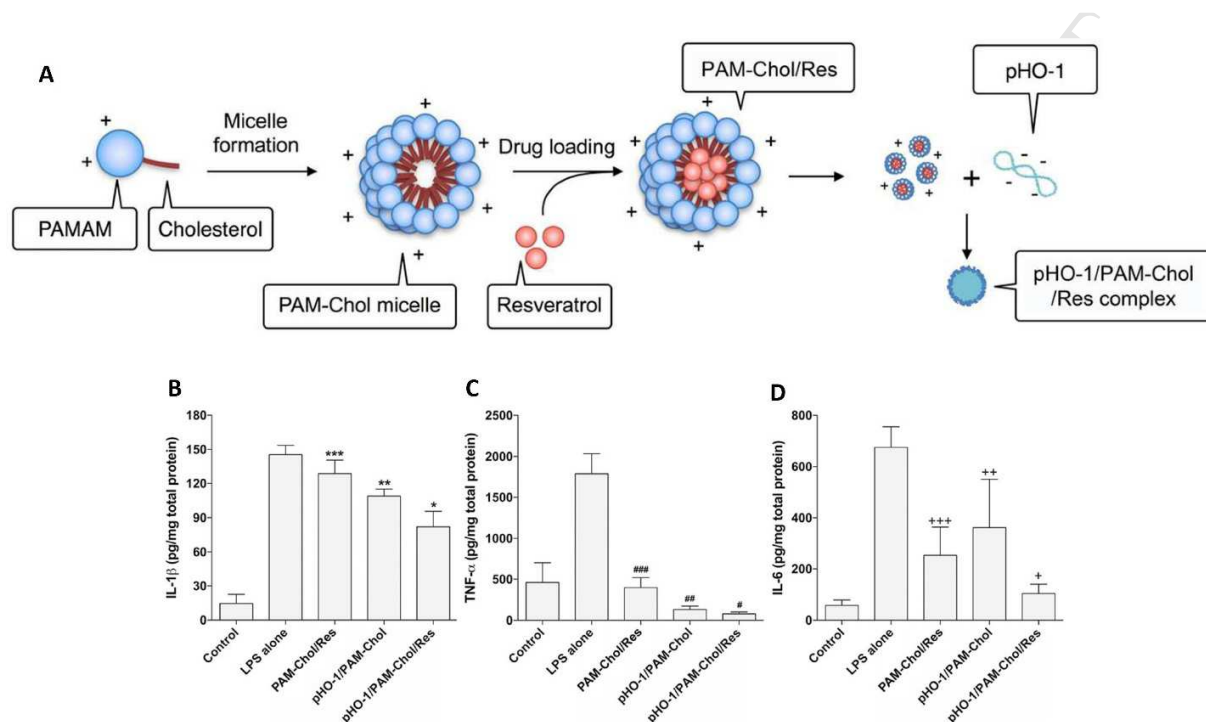


Figure 4: A) Schematic presentation of Res-loaded micelles. B, C and D) Anti-inflammation property of Res-loaded micelles [107].

2.2.3 Lipid nanoparticles

Solid lipid nanoparticles (SLN) are considered as efficient nanostructures because of their great properties such as lack of organic solvent, excellent stability with maintaining solid status at body temperature. The latter feature made them an alternative not only to organic nanoparticles but also to previous lipid based formulations (e.g. liposomes). Further studies on the formulation helped on the betterment of the SLN. The incorporation of a liquid lipid to the solid matrix of the nanoparticle was shown to enhance the number of imperfections in the core solid matrix, thus facilitating the incorporation of an enhanced amount of drug, while maintaining the physical stability of the nanostructures. The new unstructured-matrix SLN was designed as nanostructured lipid carriers (NLC) [108]. Lipid NPs are appropriate systems for delivery of lipophilic agents like Res.

Yadav et al examined the effect of Res-loaded solid lipid NPs on mitochondrial oxidative stress in vascular dementia [109]. These NPs had an average size of 286nm and EE of 91.25%. *In vitro* release study showed the sustained release behavior of Res from these NPs. Also, it was shown that Res-loaded lipid NPs had 4.5 times higher levels of Res in brain than when administered as free Res. *In vivo* experiment was performed on bilateral common carotid artery occlusion (BCCAO) rats. It was found that Res-loaded NPs remarkably decrease oxidative stress via activation of Nrf2/HO-1 pathway, showing the efficacy of these NPs in treatment of neurodegenerative disorders. Chen and coworkers prepared Res-, vitamin E (VE) and -epigallocatechin gallate (EGCG)-loaded lipid NPs for skin care applications [110]. These nanocarriers showed great properties in terms of high uniformity, good stability, protection of Res and VE against UV degradation and sustained release of Res. Skin permeation study demonstrated the improved penetration of Res through stratum corneum by these lipid NPs. Jose and colleagues evaluated the efficacy of Res-loaded solid lipid NPs for brain delivery [111]. In this study, Tween 80 or a combination of Tween 80 and polyvinyl alcohol were used as surfactants. The average particle size and zeta potential were 248.30nm and -25.49mV, respectively. Also, these NPs were spherical in shape with smooth surface and showed sustained release pattern. The *in vivo* study on Wistar rats exhibited that solid lipid NPs effectively increase the concentration of Res in brain compared to the free Res. Pandita and colleagues designed solid lipid NPs to enhance the oral bioavailability of Res [112]. These NPs were synthesized using solvent diffusion-solvent evaporation method. These NPs demonstrated excellent properties such as smooth surface, average diameter of 134nm, zeta potential of -34.3mV and EE of 88.9%. It was shown that these NPs significantly increase the oral bioavailability of Res (8.035-fold improvement) compared to the drug suspension. In another study, the potential of N-trimethyl chitosan-palmitic acid (TMC-g-PA) surface-modified solid lipid NPs for improving the oral delivery of Res was examined [113]. The particle size and polydispersity index were 258.28nm and 0.32, respectively. Zeta potential and EE were 20.79mV and 95.45%, respectively. The *in vitro* release experiment demonstrated the partial and negligible release of Res in simulated gastric and prolonged release in simulated intestinal conditions. It was shown that bioavailability of Res is significantly higher (3.8 fold) from TMC-g-PA solid lipid NPs compared to the Res suspension. Trotta et al designed chitosan-coated lipid NPs for brain delivery of Res [114]. The mean diameter of NPs was at the range of 68.5 to 84.5nm which is appropriate for nasal delivery. Zeta potential of chitosan-coated NPs was at the range of 24 to 44.6mV. It was shown that nasal delivery of Res by these NPs remarkably increase the concentration of Res in rat cerebrospinal fluid (CSF) compared to the free Res. In another study, the mediation of cell uptake of Res by solid lipid NPs was evaluated [115]. The solid lipid NPs were synthesized by the melt-emulsification mechanism. The polydispersity index was about 0.3, showing an acceptable homogeneity and zeta potential of -38mV demonstrates physical stability. Also, solid lipid NPs showed high cellular uptake and distribution. These

nanocarriers induced no alteration in cell morphology, metabolic activity or cell cycle. Besides, Res-loaded solid lipid NPs were concentrated around nuclei, releasing Res in a prolonged pattern and resulted in cytostatic impact with outstanding S-arrest of cell cycle and a large drop of G2/M phase, showing the potential of these NPs for prevention of skin cancer. In a study, Res and grape extract-loaded solid lipid NPs were used to remedy Alzheimer's disease [116]. The size of unloaded NPs was 142nm and adding grape extract increased their size by 188nm. EE was at the range of 88 to 97%. It was shown that solid lipid NPs functionalized with anti-transferrin receptor monoclonal antibody (OX26mAb) have higher cellular uptake by human-brain endothelial cells compared to the normal lipid NPs. Neves and coworkers designed Res-loaded solid lipid NPs functionalized with apolipoprotein E for targeting brain [117]. These nanocarriers had excellent features such as average size lower than 200nm, zeta potential of -13mV, high EE (90%) and great biocompatibility. Permeability assay revealed that Res-loaded solid lipid NPs functionalized with apolipoprotein E have higher penetration ability (1.8-fold higher) compared to the non-functionalized ones. Neves and colleagues synthesized novel lipid NPs to improve the oral bioavailability of Res [118]. The method which was used to synthesize lipid NPs, was a combination of high shear homogenization and ultrasound method. These NPs demonstrated good characteristics in terms of EE of 70%, average size of 150-250nm, polydispersity index of 0.2, zeta potential of -30mV and good stability. The *in vitro* release study exhibited that the Res remained mostly associated with the lipid NPs after their incubation in digestive fluids. Gokce and coworkers assessed the anti-oxidant potential of Res-loaded solid lipid NPs (Res-SLN) and nanostructured lipid NPs (NLC) [119]. NPs were synthesized using high shear homogenization. Particle size for Res-SLN and NLC was -15.3 and -13.8mV, respectively. Overall, NLC are more effective for delivering Res to the epidermis due to their lower ROS production. In another study, Montenegro et al showed that the occlusion factor is beneficial to forecast the *in vivo* skin hydration resulting from topical application of various lipid nanocarriers loading Res which has no inherent hydrating activity [120]. Shrotriya et al synthesized Res-loaded solid lipid NPs for skin targeting [121]. Res-loaded solid lipid NPs were prepared using the probe ultrasonication method utilizing Precivol ATO5 and Tween 20. These nanocarriers had mean size below than 100nm and 68-89% of EE. Also, they showed controlled drug release up to 24h. In vitro deposition experiment demonstrated that these NPs remarkably target skin without making any irritation. The *in vivo* study provided a result about the efficacy of Res-loaded solid lipid nanoparticle gel in inhibiting ear swelling. Serini et al examined the antineoplastic activity of omega-3 PUFA loaded in Res-based solid lipid NPs [122]. The average particle size and polydispersity index were at the range of 571 to 1000nm and 0.198 to 0.22, respectively. The nanocarriers were prepared using a microemulsion technique at moderate temperature according to gasco procedure [123]. It was found that encapsulation of omega-3 PUFA into Res-loaded solid lipid NPs remarkably enhance their incorporation in human HT-29 colorectal cancer cells and also their growth

inhibitory effects via decreasing cell proliferation. In another study, Wang and colleagues investigated the antitumor effects of Res-loaded solid lipid NPs [124]. The emulsification and low-temperature solidification method was used to synthesize these nanocarriers. The Res-loaded solid lipid NPs showed good properties in terms of small size, negative charge, and narrow size distribution. It was shown that Res-loaded solid lipid NPs have higher potential in inhibiting the proliferation, invasion and migration of breast cancer cells (MDA-MB-231 cells). Also, western blot analysis demonstrated that these nanocarriers are able to increase the ratio of Bax/Bcl-2, but decrease the expression of cyclinD1 and c-Myc. Rigon et al examined the efficacy of Res-loaded solid lipid NPs in treatment of skin disorders [125]. The average particle size and polydispersity index were at the range of 137.6 to 194.9nm and 0.14 to 0.23. Also, zeta potential was from -1.54 to -2.66mV. MTT assay confirmed the biocompatibility of these nanocarriers. Up to 45% of Res permeated through the skin after 24h and it was found that Res-loaded solid lipid nanocarriers remarkably inhibit tyrosinase and can be considered as potential agents in treatment of skin disorders. Neves et al examined the efficacy of solid lipid NPs (SLNs) and nanostructured lipid carriers (NLCs) in delivery of Res [126]. These nanocarriers showed great features such as mean diameter between 160 and 190nm, high negative zeta potential of -30mV and Res EE of 80%, making them appropriate for Res oral delivery. MTT assay showed the biocompatibility of these nanocarriers, so that SLNs or NLCs had no negative effect on the cell viability and integrity of Caco-2 cell monolayers. These nanocarriers remarkably increased the intestinal permeability of Res, suggesting their potential for Res oral administration.

Table 3: Studies supporting the efficiency of lipid NPs for delivery of resveratrol.

Carrier	Cell line/Animal model	Major outcomes	Refs
Solid lipid NPs	Male Wistar rats	Prolonged release of Res and improved oral bioavailability	[112]
m N -trimethyl chitosan-g -palmitic acid surface-modified solid lipid NPs	NIH/3T3 mouse embryonic fibroblast cells	Improved oral delivery of Res and prolonged release	[113]
Chitosan-coated lipid microparticles	NCM460 cell line	High biocompatibility, specific brain delivery, ease of administration and non-invasiveness	[114]
Solid lipid NPs	Human keratinocyte cell line (NCTC2544)	High cellular uptake and improved effects of Res on cellular fate	[115]

2.3 Gold and silver nanoparticles

Metallic nanostructures, particularly gold nanoparticles (Au NPs) possessing several physic-chemical and biological features widely investigated for biomedical applications including biosensing, molecular imaging, drug carriers. Biocompatible Au NPs can be easily synthesized via several physical, chemical and biological techniques in various sizes and shapes such as spherical, rod-like, and hollow structures. The unique optical properties provide them as theranostic agents. These nanomaterials can be targeted via surface functionalization by aptamers, antibodies and other targeting ligands for drugs and gene delivery [127]. Gold and silver NPs are biocompatible water soluble nanocarriers which are suitable choices for delivery of Res.

In an attempt in line with this strategy, Kamal et al investigated the anti-tumor activity of Res-loaded gold NPs [128]. NPs were synthesized by surface coating of Res on gum arabic stabilized gold NPs. Zeta potential and particle size were 8.9-11.2mV and 20-30nm, respectively. These NPs were radiolabeled with Tc-99m and labeling efficiency was more than 90%. The cytotoxicity of Res-loaded gold NPs against HT29 colon cancer cell was more than 70%. Also, colon tumor bearing rats were used to determine the efficacy of these nanocarriers *in vivo* and it was found that Res-loaded gold NPs (intravenous injection) are remarkably absorbed and low reticuloendothelial uptake and slow clearance of NPs from blood pool is associated with increased bioavailability of Res. Park et al examined the antibacterial property of Res-loaded gold and silver NPs [129]. NPs were synthesized by a green synthetic route which Res was applied as a reducing agent to chemically reduce gold and silver ions. These NPs were spherical and had a size of 8.32 to 21.84nm. Zeta potentials were at the range of -20.58 to -48.54mV. It was shown that Res-loaded gold and silver NPs have higher antibacterial activity compared to the free Res and greatest antibacterial effect was detected against *Streptococcus pneumoniae*. Also, it was found that addition of sodium dodecyl sulfate during the preparation of Res-loaded silver NPs increase the antibacterial activity. Kumar et al investigated the potential of bacterial gold NPs for delivery of Res [130]. These NPs were synthesized using the culture supernatant of *Delftia* sp. strain KCM-006. The resulting NPs had excellent properties in terms of good average size (11.3nm), photoluminescence and crystalline nature, great zeta potential (-25mV) with mono-dispersed, spherical shape. The *in vitro* release experiment showed the significant release of Res (95%) under acidic condition. Cell viability assay was performed on the human lung cancer cell line (A549) and these nanocarriers showed higher cytotoxicity (65% more effective) compared to the

free Res. Mohanty et al indicated the anti-tumor activity of Res-DOX-loaded gold NPs [131]. The average size and zeta potential of these nanostructures were 35nm and -21.2mV, respectively. These NPs demonstrated the biocompatibility and non-toxicity of these nanocarriers. The cytotoxicity study against glioma carcinoma cell line (LN229) showed the potential anti-tumor activity of Res-DOX-loaded NPs. In another study, the anti-cancer property of Res-DOX-loaded gold NPs was evaluated [132]. These NPs exhibited excellent properties such as high stability, good average diameter (20nm) and zeta potential (-20.7mV). The effects of Res-DOX-loaded gold NPs on the cell viability of HeLa and CaSKi cells were assessed and showed high cytotoxicity against human cervical carcinoma cell lines with high apoptosis-inducing activity, showing the efficacy of these nanocarriers in cancer treatment.

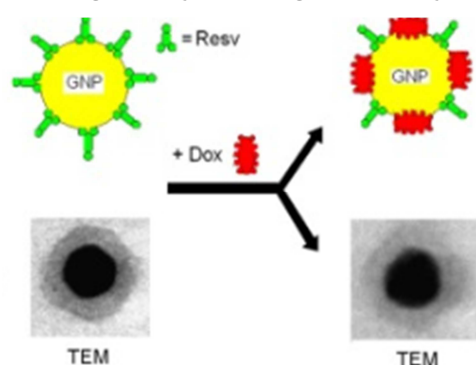


Figure 5: Res-loaded gold nanoparticles [132].

2.4 Silica NPs

Mesoporous silica NPs (MSNs), as a promising tool for innovative oncotherapy demonstrate a number of great properties compared to other inorganic nanoparticles. They are biocompatible *in vivo* and have large surface areas with pore volumes which are suitable for delivery of poorly water-soluble drugs [133-137]. The porous structure provides a great drug loading capacity and a prolonged drug release. The therapeutic agents can also be absorbed to the surface of MSN. The stimuli-responsive nano-carriers can be easily functionalized with different ligands for targeted cancer therapy [47].

Summerlin et al prepared colloidal MSNs for enhancing the biological activity of Res [138]. These nanocarriers increased the saturated solubility of Res by 95% and also enhanced its *in vitro* release kinetics than free Res. Res-loaded MSNs showed great properties in terms of high loading capacity (2% w/w) and excellent EE (100%). The MTT assay was performed on HT-29 and LS147T colon cancer cell lines and it was found that Res-loaded MSNs have higher inhibitory effect on the viability of cancer cells compared to the free Res, mediated by the PARP and ClAP1 pathways. Besides, these nanocarriers demonstrated improved anti-inflammatory activity by inhibiting lipopolysaccharide-induced NF- κ B stimulation in RAW264.7 cells. Li et al investigated the efficacy of MSNs in improving the dissolution of

Res [139]. The MSNs were prepared using fluid-bed coating technique which showed higher drug loading and more complete dissolution. The particle size and drug loading were at the range of 91.23 to 107.6nm and 14 to 33.7%. These nanocarriers appropriately inhibited the recrystallization of Res by loading Res into their pore channel and/or on the surface. Also, it was found that pore volume and pore diameter of the MSNs have more significant impacts than specific surface area on the drug loading and *in vitro* dissolution effects. Overall, it was found that the mixture of fluid bed and MSNs is a potential strategy to promote the drug loading and dissolution of Res. Juere et al examined the dissolution, permeability and anti-inflammatory properties of Res-loaded MSNs [140]. The particle size was from 90 to 300nm. It was shown that the saturated solubility relies on either on the pore size or particle size of NPs. The human colon carcinoma cell monolayer (Caco-2) was used to determine the permeability of Res and it was found that these Res-loaded MSNs remarkably increase the permeability of Res compared to the Res suspension. Also, these nanocarriers did not change the bioactivity of Res and it was found that at lower concentration (5 $\mu\text{g/ml}$), Res encapsulation provides higher anti-inflammatory activity compared to the Res solution and suspension, showing their potential for delivery and improving the properties of Res.

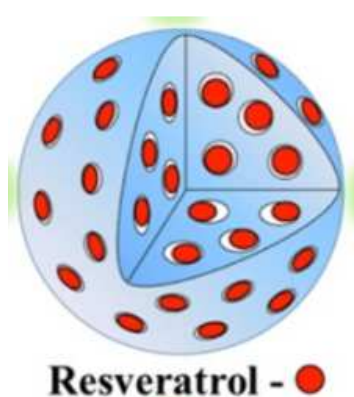


Figure 6: Res-loaded MSN [138].

3. Conclusion

Although Res has many beneficial properties, there are drawbacks including low solubility, high photosensitivity and low oxidative stability which result in its restricted use in clinical trials. This review demonstrated that nanostrategies for delivery of Res can overcome to these drawbacks. It has been shown that in most of the studies, better pharmacological impacts of Res were observed with various nano delivery systems. Improved toxicity against tumor cells was achieved via polymeric and lipid-based nanocarriers. Also, silica NPs significantly promoted the biological activity and loading capacity of Res

and gold and silver NPs improved antibacterial and antitumor activities of Res. However, more studies are needed to approve the usefulness of these nano delivery systems in clinics.

Conflict of interest:

The authors declare no conflict of interest.

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