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REVIEW

Therapeutic applications of resveratrol nanoformulations

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Abstract Resveratrol, or 3, 5, 4-trihydroxy-trans-stilbene, is a naturally occurring polyphenol present in several dietary sources such as grapes, soybeans, berries, pomegranate and peanuts. Resveratrol has received recent attention due to its diverse pharmacological activities. However, resveratrol clinical efficacy is limited due to its poor systemic bioavailability, of less than 1%, which is due to its low aqueous solubility, extensive first-pass metabolism and existence of enterohepatic recirculation. Therefore, in order to overcome these limitations, various nanocarriers including polymeric nanoparticles, solid lipid nanoparticles, liposomes, micelles and conjugates have been developed. These nanocarriers are able to enhance the bioavailability of resveratrol by modulating the P-glycoprotein, cytochrome P-450 enzymes and bypassing the hepatic first-pass effect. Here we review resveratrol nanoformulations for enhancing the efficacy of native resveratrol.

Keywords Resveratrol · Bioavailability · Nanoformulation · Targeting · Anticancer

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Introduction

Resveratrol (3,5,4′- trihydroxy-trans-stilbene; $C_{14}H_{12}O_3$; Mw 228.25 Da) is a lipophilic (log $P_{o/w}$ 3.1) polyphenol present in various plants and plant products, such as grapes, wine, berries, soybeans, pistachio and peanuts (Neves et al. 2012; Singh and Pai 2014c; Summerlin et al. 2015; Varoni et al. 2016). It was first isolated from the roots of white hellebore (*Veratrum grandiflorum* O. Loes) in 1940s (Takaoka 1940), and later, in 1963, from the roots of Japanese plant *Polygonum cuspidatum*, where it is produced in response to environmental stress factors such as injury, fungal infections, ozone exposure and UV irradiation (Langcake and Pryce 1976; Nonomura et al. 1963). It exists in nature as both cis and trans isomers, although trans form is pharmacologically active and most abundant in nature. However, due to its photosensitive nature, nearly 80–90% of the trans form undergoes isomerization to cis form when exposed to sunlight or high-intensity white light or ultraviolet (UV) light at 360 and 254 nm (Montsko et al. 2008; Trela and Waterhouse 1996; Vian et al. 2005).

The interest of scientific community in last few years has increased considerably toward this molecule due to its pleiotropic effects, i.e., they have the ability to downregulate multiple signaling pathways. It has demonstrated several pharmacological activities such as anticancer (Rai et al. 2016; Yang et al. 2015), antioxidant (Albuquerque et al. 2015), anti-inflammatory (Liu et al. 2015), neuroprotective (Rege et al. 2014), cardioprotective (Cheserek et al. 2016), anti-diabetic (Yazgan et al. 2015) (Fig. 1). In fact, it has been found to be responsible for "French Paradox," which demonstrates that the consumption of red wine decreases the incidence of cardiovascular diseases despite intake of a high fat diet (Criqui and Ringel 1994; Renaud and de Lorgeril 1992). The anticancer effects of resveratrol may be due to free radicals scavenging,

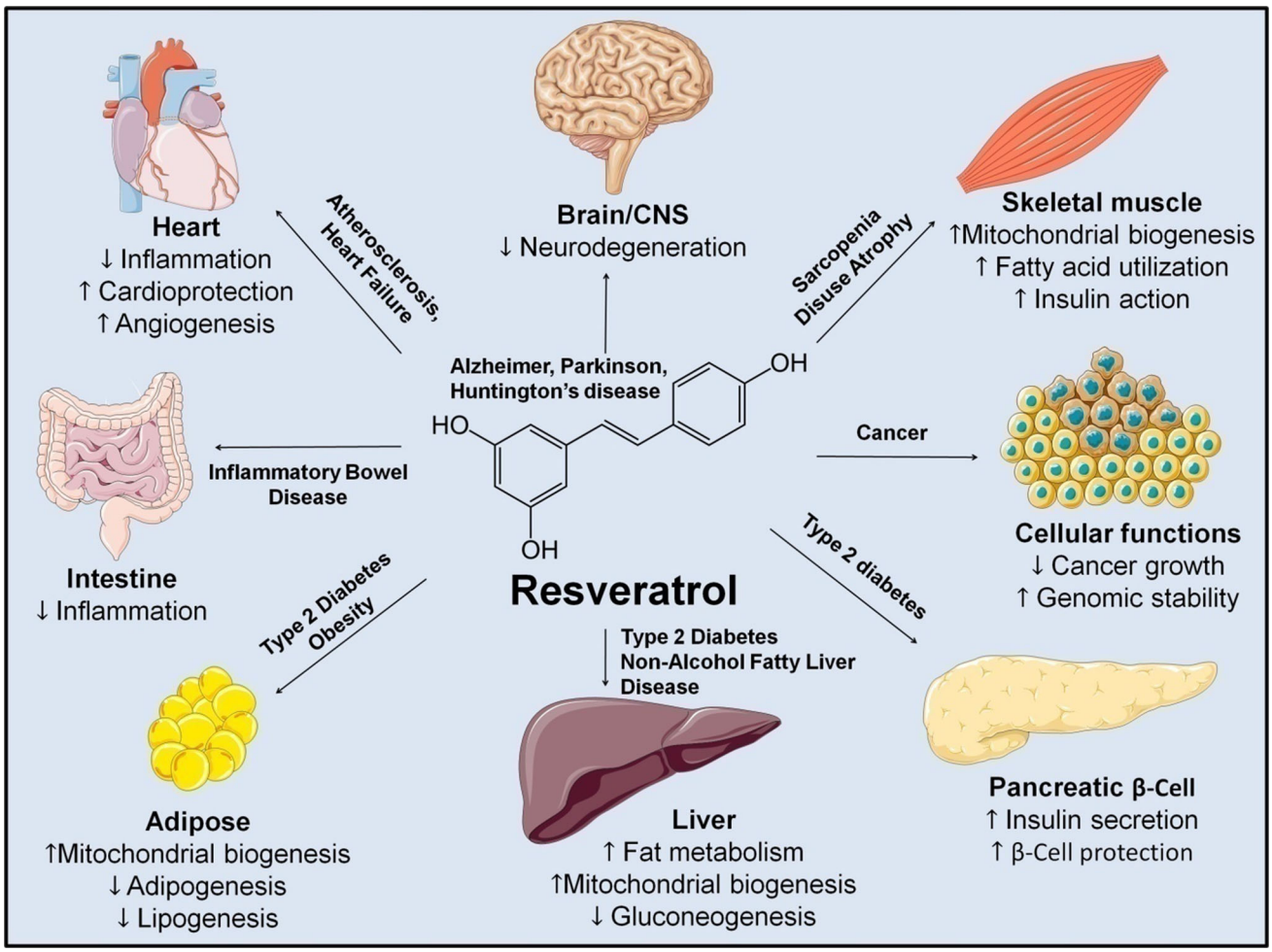

Fig. 1 Therapeutic applications of resveratrol for treatment for various diseases. *CNS* central nervous system. Modified from Lavu et al. (2008) Drawing was performed using website http://www.servier.com

suppression of cyclooxygenase activity, inhibition of enzymes such as ribonucleotide reductase, DNA polymerases and protein kinase C (Sirerol et al. 2015; Varoni et al. 2016). It has also been demonstrated to increase the activity of SIRT 1 (a member of the sirtuin family of nicotinamide adenine dinucleotide-dependent deacetylases) which ultimately results in improved cellular stress resistance and longevity (Buhrmann et al. 2016; Lavu et al. 2008). In this review, we have highlighted the implications of resveratrol nanoformulations in order to increase its therapeutic efficacy and bioavailability. This article is an abridged version of the chapter published by Arora and Jaglan (2017) in the series Sustainable Agriculture Reviews (http://www.springer.com/series/8380).

Nanocarriers for the delivery of resveratrol

Despite a lot of therapeutic activities of resveratrol, it has been associated with poor bioavailability (less than 1%) due to its poor aqueous solubility (0.03 g/L) and its extensive metabolism in the intestine and liver called enterohepatic recirculation (Mattarei et al. 2013; Summerlin et al. 2015; Walle et al. 2004). Due to this enterohepatic recirculation, after its oral administration, a peak plasma concentration is observed after 1 h and a second peak is seen after 6 h (Almeida et al. 2009; Summerlin et al. 2015). It also undergoes extensive phase I (oxidation, reduction and hydrolysis) and phase II (glucuronic acid and sulfate conjugation) metabolism to generate the key metabolites; trans-resveratrol-3-O-glucuronide and trans-resveratrol-3-sulfate, respectively (Gescher and Steward 2003; Kaldas et al. 2003; Marier et al. 2002; Neves et al. 2012). These modifications decrease the cell permeability and resulting into excretion of resveratrol. To tackle these challenges, various nanocarriers of resveratrol such as nanoparticles, liposomes, micelles, conjugates, hydrogels have been developed and evaluated in preclinical and clinical trials (Table 1).

Table 1 Nanocarriers developed for resveratrol delivery and their major outcomes

Nanocarrier	Main excipients	Size (nm)	Outcome	References
Nanoparticles	PS 80, PLA	200	Resveratrol-loaded nanoparticles displayed significant neuroprotection against MPTP-induced behavioral and neurochemical changes in C57BL/6 mice	da Rocha Lindner et al. (2015)
Liposomes	PL 90G, phospholipid Gmbh, cholesterol	120	The co-encapsulation of resveratrol and 5-fluorouracil in liposomes improved their anticancer activity on skin cancer cells as compared to both the native drugs and the single entrapped agents	Cosco et al. (2015)
Nanoparticles	Gelatin, glutaraldehyde	294	Resveratrol-GNPs demonstrated enhanced anticancer activity in NCI-H460 cells than native resveratrol by decreasing antioxidant status and increased nuclear fragmentation levels	Karthikeyan et al. (2013, 2015)
Nanoemulsion	Vitamin E, sefsol, Tween 80, Transcutol P	102	Resveratrol nanoemulsion formulation demonstrated high scavenging efficiency using DPPH assay than ascorbic acid and resveratrol solution	Pangeni et al. (2014)
Liposomes	Chol, DPPC	131	Enhanced in vitro cytotoxicity of resveratrol encapsulated liposomes in HT-29 colon cancer cells as compared to resveratrol solution	Soo et al. (2016)
Nanoparticles	Au, Ag	8–21	Resveratrol-Au nanoparticles and Ag nanoparticles demonstrated higher antibacterial activity as compared to native resveratrol in both gram positive and gram negative bacteria	Park et al. (2016)
Nanocapsules	PCL, SMS, PS80	196	The co-encapsulation of resveratrol and curcumin into lipid nanocapsules demonstrated pronounced effects with an inhibition of 37–55% between day 16 and 22 after arthritis induction	Coradini et al. (2015)
SNEDDS	Lauroglycol FCC, Labrasol, Transcutol P	56	In vivo pharmacokinetics in Wistar rats studies demonstrated enhanced area under curve (AUC) about 4.31-fold as compared to the resveratrol solution	Singh and Pai (2015b)
Nanoparticles	Zein, lysine, sodium ascorbate	307	In vivo pharmacokinetics study demonstrated in Wistar rats demonstrated enhanced oral bioavailability of resveratrol nanoparticles up to 19.2-fold higher than for the resveratrol solution	Penalva et al. (2015)
SMEDDS	Ethyl oleate, Tween 80, and PEG-400	50	SMEDDS formulation demonstrated higher antioxidant capacity with less toxicity than native resveratrol	Chen et al. (2015)
Nanoparticles	CMCS, Tween 80	155	Resveratrol-CMCS nanoparticles demonstrated enhanced in vivo absorption, prolonged duration of action and relative bioavailability by 3.5 times in rats than that of native resveratrol	Zu et al. (2014)
S-SNEDDS	HPMC, Lauroglycol FCC, Transcutol P	212	In vivo pharmacokinetic studies in rats demonstrated S-SNEDDS formulation enhanced AUC_{0-8} by nearly 1.33-fold as compared to liquid SNEDDS, at a drug dose of 20 mg/kg	Singh and Pai (2015a)
Nanoparticles	Compritol 888 ATO, Gelucire	191	In vivo pharmacokinetic studies in rats demonstrated approximately fivefold increase in the bioavailability as compared to resveratrol suspension	Singh et al. (2016)
Nanoparticles	TPGS, tristearin, S-100	203	Resveratrol-TPGS-SLN demonstrated higher in vitro cytotoxicity and in vivo pharmacokinetics in healthy Charles Foster rats demonstrated as compared to resveratrol solution, respectively	Vijayakumar et al. (2016)
Nanocapsules	PCL, Span 60, polysorbate 80	150	Resveratrol nanocapsules reduced cell viability of B16F10 melanoma cells, decreased tumor volume, increased necrotic area and inflammatory infiltrate of melanoma tumor in mice	Carletto et al. (2016)
Nanoparticles	MCM-48	283	MCM-48-resveratrol nanoparticles demonstrated enhanced in vitro cytotoxicity in HT-29 and LS147T colon cancer cell lines as compared to native resveratrol	Summerlin et al. (2016)
Nanoparticles	PEG–PLA	233	Resveratrol nanoparticles demonstrated comparable or enhanced cytotoxicity, apoptotic cell death, ^{18}F fluorodeoxyglucose uptake and reactive oxygen species with respect to native resveratrol	Jung et al. (2015)
Nanoparticles	Eudragit RL 100	180	In vivo pharmacokinetic studies in rats demonstrated enhanced AUC_{0-24} (7.25-fold) of resveratrol nanoparticles as compared to native resveratrol	Singh and Pai (2014a)

Table 1 continued

Nanocarrier	Main excipients	Size (nm)	Outcome	References
Nanoparticles	PLGA	170	In vivo pharmacokinetic studies in rats demonstrated enhanced $AUC_{0-\infty}$ (10.6-fold) of resveratrol nanoparticles as compared to native resveratrol	Singh and Pai (2014b)
Nanoparticles	Chitosan, avidin, biotin	257–319	In vivo pharmacokinetic studies in Kunming mice demonstrated improved the drug bioavailability and liver targeting index resveratrol nanoparticles as compared to native resveratrol	Bu et al. (2013)

The developed nanocarriers have been demonstrated to have better efficacy than the native resveratrol. Moreover, most of the excipients involved in development of these nanocarriers have Generally Recognized as Safe (GRAS) status by the Federal Drug Agency (FDA)

AUC area under curve, *MPTP* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *RVT* resveratrol, *PS80* Polysorbate 80, *PLA* poly(lactide), *Chol* Cholesterol *PL 90G* Phospholipon 90G, *i.n.* intranasally, *i.v.* intravenously, *DPPC* 1,2-dipalmitoyl-sn-glycero-3-phosphocholine, *CUR* curcumin, *PCL* poly(ε-caprolactone), *GSO* grape seed oil, *SMS* sorbitan monostearate, *SNEDDS* self-nanoemulsifying drug delivery systems, *LPS* lipopolysaccharide from *Salmonella enterica* serovar, *SMEDDS* self-micro-emulsified drug delivery systems, *CMCS* carboxymethyl chitosan, *S-SNEDDS* supersaturable self-nanoemulsifying drug delivery system, *HPMC* hydroxypropyl methylcellulose, *SLN* solid lipid nanoparticles, *TPGS* D-α-tocopheryl polyethylene glycol 1000 succinate, *S-100* soyaphosphotidyl choline, *MCM-48* colloidal mesoporous silica, *PEG-PLA* polyethylene glycol polylactic acid; *FDG* fluorodeoxyglucose, *PLGA* poly (DL-lactide-co-glycolide), *CS* chitosan

Nanoparticles

The nanoparticles have several key advantages such as improving the bioavailability by increasing aqueous solubility, increasing resistance time in the body and ease of surface modification due to the presence of functional groups for targeted drug delivery systems (Arora and Jaglan 2016; Mudshinge et al. 2011; Saneja et al. 2014a, b). These nanoparticles prepared using polymers, solid lipid or inorganic carriers have demonstrated improved efficacy of resveratrol over native resveratrol. For example, recently, solid lipid-based nanoparticulate system of resveratrol demonstrated oral administration of resveratrol—solid lipid nanoparticles decreased the serum biomarker enzymes (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and alkaline phosphatase) as compared to control and marketed (SILYBON®) formulations against paracetamol-induced liver cirrhosis. Moreover, pharmacokinetic studies demonstrated enhanced bioavailability ($AUC_{0\rightarrow\infty}$=3411 ± 170.34 μg/mL/h) as compared to resveratrol suspension ($AUC_{0\rightarrow\infty}$ = 653.5 ± 30.10 μg/mL/h) (AUC area under curve) (Singh et al. 2016). Summerlin et al. (2016) developed resveratrol-loaded colloidal mesoporous silica nanoparticles and demonstrated enhanced saturated solubility of resveratrol by ~95%.

Liposomes

Liposomes are the spherical vesicles composed of cholesterol and natural non-toxic phospholipids (Allen 1997). They have also gained enormous attention for resveratrol delivery due to their biocompatibility, biodegradability and ease of surface modification with targeting ligands (Akbarzadeh et al. 2013; Arora and Jaglan 2016). Recently, combinatorial liposomes of resveratrol and paclitaxel have been developed in order to tackle multi-drug resistance of paclitaxel (PTX) (Meng et al. 2016). In vitro cytotoxicity demonstrated that composite liposome could exhibit potent cytotoxicity against the drug-resistant MCF-7/Adr cancer cells.

Micelles

Polymeric micelles are formed by the self-aggregation of amphipathic monomers, each containing a hydrophilic and hydrophobic domain (Al-Achi and Lawrence 2013). In a recent study, resveratrol micelles were developed using methoxy-poly(ethylene glycol)-b-polycaprolactone (mPEG-PCL) and d-α-tocopherol polyethylene glycol succinate (Wang et al. 2015). In vitro cytotoxicity and cellular uptake demonstrated enhanced uptake efficiency of resveratrol by doxorubicin (DOX)-resistant breast cancer MCF-7/ADR cells and demonstrated higher rates of apoptotic cell death. In another study, combinatorial Pluronic® micelles of resveratrol and curcumin were developed in order to prevent doxorubicin induced cardiotoxicity (Carlson et al. 2014). In vitro cytotoxicity in ovarian cancer (SKOV-3) and cardiomyocytes (H9C2) cells demonstrated synergistic effects in SKOV-3 cells while antagonistic in H9C2 cells.

Nanoemulsions

Nanoemulsion is an emulsion system having the nanoscale droplets size (0.1–500 nm) in which oil or water droplets are finely dispersed in the opposite phase using a suitable surfactant in order to stabilize the system (Mason et al. 2006; Solans et al. 2005). Pangeni et al. (2014) developed resveratrol nanoemulsion using vitamin E/sefsol (1:1) as the oil phase, Tween 80 as the surfactant and Transcutol P as the co-surfactant in order to improve its efficacy. Their

study demonstrated higher scavenging efficiency using DPPH assay and higher concentration of the drug in the brain after intranasal administration of nanoemulsion. Lu et al. (2015) developed resveratrol self-nanoemulsifying drug delivery system (SNEDDS) using pomegranate seed oil (PSO) as an oil phase in order to exert synergistic effects with resveratrol with it. In vitro anticancer study against MCF-7 cell line demonstrated enhanced inhibitory rate of resveratrol SNEDDS about 2.03- and 1.24-fold than that of SNEDDS prepared using isopropyl palmitate at a concentration of 12.5 and 25 μg/mL, respectively.

Conjugates

Polymer drug conjugates are a new form of nanomedicines in which drugs are covalently attached through the polymer via cleavable bonds that cleaves at specific tumor-specific sites but stable in systemic circulation (Arora and Jaglan 2016; Pang et al. 2014). In a recent study, resveratrol–mPEG and mPEG–polylactic acid conjugates demonstrated improved pharmacokinetic profiles with significantly higher plasma area under curve, slower clearance and smaller volume of distribution as compared to native resveratrol (Siddalingappa et al. 2015). In an another study, polymeric methoxy-poly(ethylene glycol)-block-poly(ε-caprolactone) resveratrol conjugates were developed and demonstrated the conjugate improved solubility and stability of resveratrol as compared to resveratrol alone (Ng et al. 2015).

Hydrogels

Hydrogels (also called an aquagel) are three-dimensional (3-D), polymeric networks consisting of crosslinked hydrophilic components and have the ability to provide local, sustained delivery of resveratrol. Recently, hyaluronic acid–resveratrol hydrogel conjugates were prepared using chemical crosslinking of oxidized (Oxi) hyaluronic acid with resveratrol solution (Sheu et al. 2013). In vitro cytotoxicity studies demonstrated that the hydrogels were biocompatible and upregulated expression of type II collagen, aggrecan and Sox-9 genes while downregulating IL-1β, MMP-1, MMP-3, MMP-13 gene expression. Further, these hydrogels have ability to reduce LPS-induced inflammation and chondrocyte damage.

Conclusion

Resveratrol has emerged as one of the promising nutraceuticals with a wide array of pharmacological activities such as cancer preventive, cardioprotective, antioxidant anti-inflammatory and neuroprotective. However, its clinical efficacy is hindered due to its poor systemic bioavailability. A wide array of nanocarriers have been developed in order to overcome its pharmacokinetic limitations and demonstrated superior outcomes. The success of the nanocarriers can be witnessed by approval of certain nanoformulations of clinical drugs which are in the market such as Abraxane (paclitaxel), Lipusu (paclitaxel), Doxil (doxorubicin), DepoCyt (cytarabine), Onco-TCS (vincristine). Moreover, these nanocarriers have been fabricated using Generally Recognized as Safe (GRAS) excipients by FDA. However, in order to realize the full potential of resveratrol nanoformulations, more comprehensive preclinical and clinical evaluations are desired.

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