RESEARCH ARTICLE

THE CHEMICAL STABILITY, ANTICANCER ACTIVITY, METABOLISM, AND DELIVERY SYSTEMS OF RESVERATROL: A REVIEW

*Sutriyo, Dara A. Putri

Faculty of Pharmacy, University of Indonesia

ABSTRACT

**Background:** Resveratrol is a non-flavonoid polyphenolic compound in many plants. The usage of resveratrol is due to its various health benefits, including chemo-preventive agent, antioxidant, antiplatelet, anti-fungi, neuroprotective agent, cardioprotective agent, and anti-inflammatory action. However, poor water solubility, chemical instability, metabolism, poor biodistribution, and poor bioavailability limit its clinical applications, especially as anti-cancer agent. Formulations of delivery systems can improve its solubility, stability, biodistribution, bioavailability, efficacy, and safety. **Scope and approach:** In this review, the chemical stability, anticancer activity, metabolism, and types of delivered systems of resveratrol were discussed. **Key findings and conclusion:** Resveratrol is poor soluble in water, chemically instable, metabolized into inactive metabolites in intestines and liver, poorly distributed, and has poor bioavailability. Formulation and modification of delivery systems including polymeric nanoparticles, lipid-based nanocarriers, cyclodextrins, and gold nanoparticles are potential to improve the solubility, stability, biodistribution, and bioavailability of resveratrol, and thus potential to enhance efficacy and safety of resveratrol. Each delivery system has its own advantages and challenges, which could be selected depending on application needs. The combination of passive and active targeting technique might be required for targeted therapy in the future.

**Key words:** Resveratrol, Chemical Stability, Anticancer Activity, Delivery systems.

**Copyright © 2019, Sutriyo, Dara A. Putri. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**

**Citation:** Sutriyo, Dara A. Putri “The Chemical Stability, Anticancer Activity, Metabolism, And Delivery Systems of Resveratrol: A Review, 2019” International Journal of Current Research in Life Sciences, 8, (04), 3056-3061.

INTRODUCTION

Resveratrol (trans-3,5,4′-trihydroxystilbene) is a non-flavonoid polyphenolic compound derived from red grape (Vitis vinifera), olives, blackberries, pines, and peanuts (Langcake, 1976; Lachenmeier, 2014; Robinson, 2015; Cheng, 2018). Resveratrol was initially identified as active ingredient from dried roots of Polygonum cuspidatum, which widely used as Chinese and Japanese traditional medicine to treat fungal infection, skin inflammation, hepatotoxicity, and cardiovascular disease (Arichi, 1982; Vastano, 2000). Resveratrol is secondary metabolite produced by plants as response to physical damage, UV radiation, and fungal infection (Huang, 2017). In plants, resveratrol is in a bound form with sugars. There are two isomeric forms of resveratrol, trans-resveratrol and cis-resveratrol (Fig 1). **Trans**-resveratrol is more widely developed because it’s biologically more active than cis-resveratrol due to its non-planar conformation. **Trans**-resveratrol has attracted increasing development due to its pharmacological actions, including as chemo-preventive agent, antioxidant, antiplatelet, anti-fungi, neuroprotective agent, cardioprotective agent, and anti-inflammatory action (Lachenmeier, 2014; Singh, 2014; Venuti, 2014).

However, resveratrol has poor solubility, chemical instability with light exposure, poor absorption, and poor bioavailability (Bonechi, 2012). With intravenous administration, resveratrol is also rapidly metabolized into inactive metabolites and widely distributed to various tissues, limiting its clinical applications, especially as anti-cancer agent (Vitrac, 2003; Walle, 2004; El-Mohsen, 2006). Delivery systems are designed to improve its water solubility, chemical stability, bioavailability, and delivery to targeted tissues including polymeric nanoparticles (Lee, 2012; Sanna, 2013; Musazzi, 2014; Penalva, 2015; Kim, 2016; Nassir, 2018), lipid based nanocarriers (Bonechi, 2012; Carlotti, 2012; Gokce, 2012; Jose, 2014; Pandita, 2014; Park, 2014; Balanč, 2015; Meng, 2016; Neves, 2016; Ramalingam, 2016; Vijayakumar, 2016; Montenegro, 2017; Jhaveri, 2018), cyclodextrins (Lu, 2009; Venuti, 2014; Duarte, 2015; Cheng, 2018), and gold nanoparticles (Battacharya, 2007; Rahme, 2013; Kumar, 2014; Mohanty, 2014; Tomoaia, 2015). The objective of this article is to give an overview of findings regarding chemical stability, molecular activity as anti-cancer agent, and metabolism of resveratrol. Special attention is paid to drug delivery system developments to improve solubility, chemical stability, bioavailability, and biodistribution.
Chemical stability: Resveratrol consists of two phenols linked by a double bond (Fig 1). Resveratrol is lipophilic weak acid (log $P_{ow} = 3.1$) with molecular weight 228,25 g/mol. Resveratrol is soluble in ethanol and in dimethyl sulfoxide but poorly soluble in water (0.05 mg/ml). Resveratrol has shown maximum absorbance at wavelength 306 nm (Singh, 2014; Venuti, 2014). Although it’s poorly soluble in water, resveratrol has shown high permeability making it included in class II of Biopharmaceutical Classification System (BCS) (Singh, 2015).

Anticancer activity: Studies the activity of trans-resveratrol as anticancer have been reported. Study has shown that resveratrol binds to estrogen receptor-α (ERα) and disrupts phosphorylaminosilinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/AKT) pathway, inhibiting proliferation and inducing apoptosis on MCF-7 human breast cancer cells (Pozo-Guisado, 2004). Resveratrol also inhibits the activity of 6-phosphofructo-1-kinase (PFK) enzyme (Gomez, 2013). Resveratrol inhibits the activity of aromatase and telomerase enzyme on MCF-7 cells (Wang, 2006; Lanzili, 2006, Ayuningtayas 2017). Resveratrol also binds with integrin αVβ3, activating extracellular signal-regulated kinase (ERK1/2) and p53-dependent pathway and causing apoptotic effect on MCF-7 cells (Lin, 2006). Resveratrol induces apoptosis on human hepatoma HepG2 cells via p53-dependent pathway and caspase with concentration more than 10 μM (Ou, 2014). Resveratrol also enhances cancer cell sensitivity on other anticancer agents (Ma, 2015, Maesya 2017). Resveratrol can be functioned as cardioprotective agent by preventing cell apoptotic through anti-apoptotic mechanism. Resveratrol can be also functioned as chemo-preventive agent by inducing cancer cells apoptotic. The role of resveratrol as anti-apoptotic or pro-apoptotic agent depends on dose or concentration usage. Resveratrol gives chemo-preventive effect at high dose usage (10-100 μM) and cardio protective effect at lower dose (5-20 μM) (Szczo, 2000). However, study has shown that resveratrol usage could cause nephropathy on rats after high dose (3000 mg/kg) administration for 28 days (Crowel, 2004).

Resveratrol usage at high concentration (60 μM) also could induct apoptotic effect on CD34+ precursor cells, which indicates resveratrol formulation should consider to improve its biodistribution for safety purpose (Ferry-Dumazet, 2002).

Metabolism: Resveratrol is quickly absorbed and metabolized in intestines and liver through phase II biotransformation reaction by UDP-glucuronosyltransferase and sulfotransferases, resulting inactive metabolites including resveratrol’s glucuronide derivatives (resveratrol-3-) glucuronide and resveratrol-4'-O glucuronide) and sulfate derivate (resveratrol-3-O-sulfate), respectively (Penalva, 2015; Varoni, 2016). Resveratrol has short half-time in plasma (~8-14 minutes) (Das, 2011). Resveratrol bioavailability study on human has shown that less than 5 ng/ml trans-resveratrol was detected in plasma after oral administration of 25 mg trans-resveratrol. Administration via intravenous could prevent resveratrol from pre-systemic metabolism but not from systemic metabolism, which is supported by resveratrol-3-O-sulfate finding in plasma (Walle, 2004). Trans-resveratrol biodistribution study using 14C label has shown that highest amount of free resveratrol was found at liver and kidney tissue after oral administration of 5 mg/kg trans-resveratrol (Vitrac, 2003). Another study also reported that trans-resveratrol in aglycon form was found at liver, heart, lung, and brain tissue at 18 h after oral administration of 50 mg/kg trans-resveratrol (El-Mohsen, 2006). Studies have shown that resveratrol in free or metabolite form are distributed widely in various tissues. Resveratrol has poor solubility, instability, and rapid metabolism in the body, making it strongly limited for clinical applications. Researchers have developed resveratrol formulations to improve its chemical stability, bioavailability, and pharmacological effects.

Delivery systems for resveratrol: In the past decade, efforts have been done to improve chemical stability, bioavailability, and pharmacological effects of resveratrol. Currently available various types of resveratrol delivery system, including polymeric nanoparticles (Lee, 2012, Sanna, 2013; Musazzi, 2014; Penalva, 2015; Kim, 2016; Nassir, 2018), lipid based nanocarriers (Bonechi, 2012; Carlotti, 2012; Gokee, 2012; Jose, 2014, Pandita, 2014; Park, 2014; Balanč, 2015; Meng, 2016; Neves, 2016, Ramalingam, 2016; Vijayakumar, 2016; Montenegro, 2017; Jhaveri, 2018), cyclodextrins (Lu, 2009; Venuti, 2014; Duarte, 2015; Cheng, 2018), and gold nanoparticles (Battacharya, 2007; Rahme, 2013; Kumar, 2014; Mohanty, 2014; Tomoaia, 2015).

Polymeric nanoparticles: Polymeric nanoparticles can be manufactured from various types of polymers including natural polymers such as proteins, and synthetic polymers like amino methacrylate copolymer, polyvinyl alcohol (PVA), polyacrylic-c-glycolic acid (PLGA), and poly(ε-caprolactone) (PCL). PLGA is well-known for its safety and ability to control drug release. Poly(ε-caprolactone)-poly(ethylene glycol) (PCL-PEG) has amphiphilic property and stabilizes the surface of nanoparticle. The combination of both polymers could load high level of resveratrol. PLGA matrix could control release of resveratrol into physiological fluid before particle cellular uptake. However, the decrease of the cell viability in organ of Corti cells (HEI-OC1) and strivavascularis cells (SVK-1) is less intense with resveratrol-loaded nanoparticles than free resveratrol, indicating the evaluation of nanoparticles toxicity is still challenging (Musazzi, 2014). Resveratrol is successfully loaded in PCL-PLGA-PEG-COOH nanoparticles. Resveratrol
is also released from nanosystem following acidic environment, mimicking acidic tumoral environment. It also exhibits efficient cellular uptake by Pca cell lines and improves cytotoxicity effect on androgen-independent DU-145 cells and hormone-sensitive LNCAp prostate cancer cells, indicating PLC:PLGA-PEG-COOH nanosystem is potential to be used as controlled delivery of resveratrol for chemoprevention or chemotherapy (Sanna, 2013). Resveratrol nanoparticle system was prepared by solvent-evaporation technique using Eudragit E100 and PVA as excipients. This modified nanoprecipitation technique not only is simple, quick, and low cost, but also able to increase hepatoprotective effect on CCl₄-induced rats (Lee, 2012). Similar technique was applied using submicron PLGA. Resveratrol-loaded PLGA nanoparticles exhibits greater cytotoxicity on LNCAp prostate cancer cell line (Nassir, 2018). Combination of passive and active targeting system using Pluronic 127 triblock copolymer micelle nanoparticle and folic acid decreases resveratrol accumulation in heart and kidney. Folic acid as targeting moiety is able to mediate anticancer agents into targeted cells via receptor-mediated endocytosis and decrease toxicity effect on normal tissues (Hao, 2017).β-lactoglobulin, a compound of whey proteins, used as resveratrol nanocarrier due to its generally recognized as safe (GRAS) status, biodegradable property, and capability to form structure (Kim, 2016). Zein is the major storage protein in maize and corn that has amphiphilic protein with high percentage of hydrophobic amino acid, which later on could be used to control loaded compound release. Resveratrol-loaded nanoparticles based on zein matrix is released by diffusion and erosion mechanism, enhance oral bioavailability 19.2-fold higher that free resveratrol, and diminish endotoxic symptoms on lipopolysaccharide-induced mice (Penvala, 2015).

**Lipid based delivery system:** Lipid-based formulations such as liposome, nanostructure lipid carriers (NLCs), and solid lipid nanoparticle (SLN) have been applied to enhance pharmacological effect of resveratrol.

**Liposome:** Liposome are closed spherical vesicle consist of one or more phospholipid bilayers (Park, 2014). Liposome mainly consists of phosphatidylcholine and cholesterol which are biocompatible, biodegradable, and have gained FDA approval (Meng, 2016; Vijayakumar, 2016). Liposome has the ability to load hydrophilic and hydrophobic compound and enhance its delivery to targeted tissues. Liposome could be prepared by simple techniques (Balanč, 2015). But as nanocarriers of resveratrol, liposomes were mostly modified to increase its stability, prolong the circulation time, enhance accumulation in targeted tissue selectively. The optimization of liposome formulation using 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and cholesterol as resveratrol nanocarrier has shown that resveratrol is more deeply inserted in cationic liposomes than in zwitterionic liposomes. Resveratrol interacts at zwitterionic liposomes’ surface and its structures are varied upon resveratrol loading (Bonechi, 2012). Liposome coated by chitosan could enhance transdermal delivery of resveratrol. Chitosan with its positive charge property can improve the skin permeation because of the increased interaction between liposome and skin surface (Park, 2014). Liposome coated by d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) could enhance resveratrol accumulation in brain making it potential for glioma treatment. TPGS has been shown to inhibit P-glycoprotein mediated multi-drug resistance (Vijayakumar, 2016). PEGylated liposome (stealth liposome) containing resveratrol and paclitaxel was prepared using ultrasonic dispersion method has shown that stealth liposome can evade rapid clearance by the reticuloendothelial system (RES) of the body, hence, prolong the circulation time. Stealth liposome successfully encapsulate resveratrol and paclitaxel and could generate potent cytotoxicity on drug resistant MCF-7/Adtumor cells and tumour-retention of the drugs in mice (Meng, 2016). Further modification of liposome as nanocarrier for liposome involving transferrin as targeting moiety for glioblastoma treatment. Resveratrol-liposome-transferrin complex is more cytotoxic and induces higher level of apoptosis in glioblastoma cells compared to free resveratrol or resveratrol-liposome. Resveratrol-liposome-transferrin is also more effective to inhibit tumour growth and improve survival in mice with glioblastoma (Jhaveri, 2018).

**SLNs:** SLNs are first generation lipid nanoparticles consists of lipid which is solid at ambient temperature. SLNs as nanosystems have several advantages, including non-toxic and biocompatible, have high load capacity, and increase solubility and stability of loaded drug. SLNs has submicron size, easy to scale up and manufacture, and flexible to modify for controlled release (Pandita, 2014; Ramalingam, 2016). SLNs are also have minimal problems with multiple routes of administration, such as oral, intravenous, pulmonary, and transdermal administration. Recently, many SLNs formulations are developed to increase the bioavailability of resveratrol via oral. SLNs prepared by solvent diffusion-solvent evaporation technique using stearic acid as lipid core and poloxamer 188 as stabilizer is able to entrap resveratrol, release resveratrol in sustained release manner, and improve oral bioavailability by 8.035 fold compared to free resveratrol in male rats (Pandita, 2014). SLN is easily degraded under stomach acidic condition and enzymes. SLN tends to have negative charge at surface causing inaccessible drug across negative charged mucus membrane. Coating SLN with positive charged mucoadhesive polymers such chitosan and its derivatives could enhance the bioavailability of resveratrol. N-trimethyl chitosan (TMC) conjugated to SLN with palmitic acid (PA) as linker could control resveratrol release based on environmental pH. Resveratrol-SLN-PA-TMC is mainly released in intestinal condition in sustained release manner and its relative bioavailability is 3.8 fold higher than free resveratrol (Ramalingam, 2016). Another modifying technique includes cooperating tetradecyl-γ-cyclodextrin (C14CD) in SLN formulation. The complex is able to prevent trans-resveratrol from photodegradation and increase antioxidative efficacy (Carlotti, 2012). Resveratrol-loaded SLN is also used for brain delivery. Glycerol behenate-based SLN prepared by modified solvent evaporation technique increases brain concentration of resveratrol compared to free resveratrol making it potential therapeutic system to treat neoplastic diseases in brain tissue (Jose, 2014).

**NLCs:** NLCs are lipid nanoparticles consists of solid and liquid lipids. Due to structure of their lipid core, NLCs showed greater loading capacity and better stability than SLNs. NLCs are easy and low cost to prepare. NLCs can improve drug bioavailability, stability, and controlled drug release and targeting. NLCs also have occlusive property so they may be suitable for resveratrol carrier with topical administration (Montenegro, 2017). A comparison between resveratrol-loaded NLCs and SLNs formulations have shown that NLCs are more efficient in carrying resveratrol to the dermis. Resveratrol-loaded NLCs also exerts less fluorescence in normal human
dermal fibroblasts (NHDF), indicating less reactive oxygen species (ROS) production in cytofluorometric study (Göktepe, 2012). Lipid nanoparticles are also developed for oral administration of resveratrol. NLC formulation could enhance the permeability of resveratrol across Caco-2 cell monolayer compared to SLN (Neves, 2016).

**Cyclodextrins:** Cyclodextrins are macrocyclic oligosaccharides derived from starch, consists of glucopyranose units and able to form cone structure with hydrophobic cavity. This cavity is able to load various of drugs forming into inclusion complexes. This structure could protect unstable molecules from damage due to light exposure. Cyclodextrins system could be used to improve solubility, stability, and bioavailability of hydrophobic drugs. Cyclodextrins modification by substituting hydroxyl group with methyl moieties could lower toxicity (Lu, 2009; Duarte, 2015; Cheng, 2018). Hydroxypropyl-β-cyclodextrin has larger resveratrol inclusion ability and higher scavenging capacity than β-cyclodextrin, although both of them has shown little different antioxidant activity compared to free resveratrol at same concentration (Lu, 2009). Methylated-β-cyclodextrin could improve resveratrol’s aqueous dissolution by 400-fold while still maintaining its function as antibacterial and antioxidant (Duarte, 2015). Resveratrol conjugated to carboxymethyl-β-cyclodextrin exhibits less total loss compared to free resveratrol after 360 minutes of UV light exposure (Cheng, 2018). Sulfobutylether-β-cyclodextrin is non-toxic and biocompatible polyanionic cyclodextrin derivative which has greater solubility and complexing abilities compared to parent cyclodextrin. Sulfobutylether-β-cyclodextrin has high affinity to resveratrol, increases resveratrol solubility, and maintain resveratrol’s anticancer activity (Venutti, 2014).

**Gold nanoparticles:** Gold nanoparticles are the most stable metal nanoparticles. Gold nano particles are highly attractive used as delivery system because of their biocompatibility and low toxicity, the ease to prepare and obtain monodisperse nanoparticles, the ease to conjugate with functional ligand to expand circulation time and enhance selectivity and accumulation on targeted tissue, and their specific surface plasma resonance (SPR) bands to ease characterization process. Gold nanoparticle also has photophysical properties that could be used to control drug release (Battahcharya, 2007; Kumar, 2014; Mohanty, 2014). In 1951, Turkевич has developed the gold nanoparticles synthesis method by reducing Au⁺⁻ derive in HAuCl₄ form using citrate solution as reducingand capping agent. Resveratrol could stabilize the surface of gold nanoparticles and the complexation could be used as carrier to load doxorubicin (Mohanty, 2014; Tomoaia, 2015). Green synthesis has been developed to reduce gold nanoparticle without using reducing agent. The green synthesis used supernatant derived from *Delftia* sp. Strain KCM-006. The gold nanoparticle formed then conjugated to resveratrol (Kumar, 2014).

**Conclusion and future trends**

Resveratrol is a non-flavonoid polyphenolic compound derived from many types of plants. It has a lot of pharmacological effects that makes it potential to develop as pharmacological treatment, including chemo-preventive agent, antioxidant, antiplatelet, anti-fungi, neuroprotective agent, cardioprotective agent, and anti-inflammatory. However, just like any polyphenolic compounds, resveratrol has poor solubility. It’s also photochemically instable forming into less active cis form. In the body, resveratrol is rapidly metabolized in intestines and liver into inactive metabolites through phase II biotransformation reactions. Resveratrol is also distributed widely into various tissues, limiting its clinical applications due to its potential toxicity effect on normal cells, especially for diseases that urge targeted therapy. Studies of resveratrol has been developed over the years. Many types of nanocarriers (polymeric nanoparticles, lipid-based nanocarriers, cyclodextrins, and gold nanoparticles) successfully enhance solubility, stability, absorption, or/and circulation time of resveratrol. Each of formulation has its own advantages and challenges and could be selected depending on application needs. Recently, combination of passive and active targeting approach is applied to enhance solubility, stability, selective delivery, and toxicity effect on cancer tissues. This combination not only could prolong the circulation time but also enhance its cellular uptake on cancer tissues selectively, making it potentially more effective and save for cancer treatment.

**REFERENCES**


Battacharya, R. et al. 2007. Attaching folic acid on gold nanoparticles using noncovalent interaction via different polyethylene glycol backbones and targeting of cancer cells. *Nanomedicine: Nanotechnology, Biology, and Medicine,* 3, 224-238. 10.1016/j.nano.2007.07.001


human hepatoma HepG2 cells. Oncology Reports, 32, 2803-2809. DOI: https://doi.org/10.3892/or.2014.3512


Sanna, V., Siddiqui, I. A., Sechi, M., Mukhtar, H. 2013. Resveratrol-loaded nanoparticles based on poly(epsilon-caprolactone) and poly(D,L-lactic-co-glycolic acid)-poly(ethylene glycol) blend for prostate cancer treatment. Molecular Pharmaceutics, 10(10), 3871-3881. 10.1021/mp400342f


