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Characterization of Resveratrol Loaded Nanoparticles-A Review

DrakalskaSersemova Elena[1], Miceva Dijana[1], Angelovska Bistra[1], Makraduli Liljana[2]

[1]*Faculty of medical sciences ,,UniversityGoceDelchev"- Shtip, R.N. Macedonia*
[2]*Replek farm – Skopje, R.N.Macedonia*

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ABSTRACT: Resveratrol (3,5,4-trihydroxy-trans-stilbene) is natural phenol and phytoalexin, extracted from red grapes, berries and cacao beans and found also in significant concentration in red wine. This active compound exhibited potent pleiotropic, antineoplastic activity without documented toxicity to normal cells. In addition, numerous studies reported that resveratrol, as most researched stilbene, possess numerous health-benefit properties, such as cardioprotective, antidiabetic, neuroprotective and chemopreventive. Regretfully, clinical realization of resveratrol is restricted due to its poor aqueous solubility (0.05 mg/ml), degradation at physiological pH associated with extremely low systemic bioavailability. An intriguing strategy to overcome these limitations is formulation of resveratrol-loaded nanoparticles such as nanoemulsions, liposomes and solid-lipid nanoparticles as platforms for delivery to target tissues.

KEYWORDS:resveratrol, nanoemulsions, bioavailability, liposomes

I. INTRODUCTION

Resveratrol is biologically active polyphenol, isolated from skin of berries, grapes, cacao and peanuts, produced in order to protect the plant of inflammation, UV irradiation and fungal infection [1]. Resveratrol is identified as (3,5,4′-trihydroxy-trans-stilbene), classified as natural polyphenol consisting of two phenolic rings attached by methylene bridge presented on Figure 1. The presence of double bond is responsible for cis and trans isomerism of resveratrol. Many studies confirmed that trans isomer of resveratrol is more stable and biologically active isomer due to its non-planar conformation [2] [3] [4].

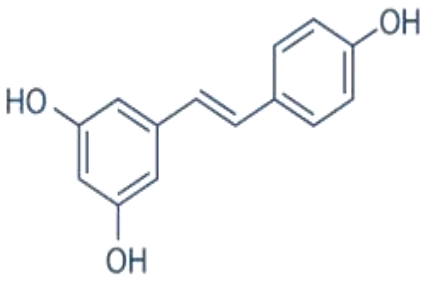

Figure 1. Structure of trans-resveratrol

Resveratrol was first isolated in 1939 by M.Takaoka from the rhizome of VeratrumGrandiflorum and is called resveratrol because it is resorcinol derivative from this species [5]. However, the interest in resveratrol has extensively increased after,, French paradox" in 1992 based on epidemiological data collected from French volunteers from 30-70 years [6]. Results revealed lower mortality rate from cardiovascular diseases in French people with moderate wine intake despite the high consumption of high saturated fat [6]. Many in vitro studies proved that cardioprotective effect of resveratrol is associated with inhibition of LDL oxidation [7], vasorelaxation [8] and upregulation of NO synthase [9]. Free radical-scavenging activity was demonstrated in animal models with induced arrhythmia [10]. Obtained results showed prevention of induced arrhythmia and lower mortality due to anti-oxidant activity and ability of resveratrol to upregulate NO synthase [10]. In addition, it is well documented that resveratrol plays an important role in platelet aggregation generally by inhibition of arachidonic acid metabolizing enzymes and production of eicosanoids from human platelets, demonstrated by 50% reduction of platelets in human plasma [11].

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Anticancer activity of resveratrol is related to modulation of activity of numerous genes and enzymes attributed with inhibition of carcinogenesis and induction of tumor cell death, such as downregulation of NF-κBsignaling pathways for example [12]. Another conducted in vitro and in vivo studies presented that resveratrol also has impact on COX2 and is responsible for downregulation of AKT and MAPK, associated with inflammation and tumorigenesis [13] [14] [15]. However, the main mechanism of anti-proliferative effect of resveratrol has not been discovered yet in vivo due to unpredicted deregulation of multiple signaling pathways in tumor tissue [16], [17]. Despite the numerous advantages, resveratrol has extremely low aqueous solubility (0.05 mg/ml) [18], rapid degradation at physiological pH [19] and significant presystemic biotransformation mainly via glucuronide and sulfate conjugation [20]. Consequently, oral bioavailability of resveratrol is extremely low, almost zero, without possibility to achieve therapeutic concentration in target cells [21,22]. In order to optimize the unfavorable characteristics, a possible approach is incorporation in nanoparticles such as solid lipid nanoparticles, nanoemulsions and liposomes as promising platforms for delivery of resveratrol.

II. LIPOSOMES AS PLATFORMS FOR DELIVERY OF RESVERATROL

Liposomes are class of most promising platforms for delivery of hydrophobic drugs, first discovered in 1961 by Bangham [23]. Membranes of liposomes are composed of natural phospholipids or lipids approved by FDA. Most common lipids used for liposome formulation are egg phosphatidylcholine, soybean phosphatidylcholine, 1,2-distearolyl-sn-glycero-3-phosphatydylcholine. Unique characteristics of liposomes are owing to the amphiphiliccharac-ter, low size and thickness of the membrane [24]. Liposomes are spherical in form, composed of phospholipid lamellas, which close central aqueous cavity suitable for encapsulation of hydrophobic and hydrophilic drugs.

A recent study reported the potential of resveratrol as anticonvulsant agent incorporated in liposomes. For the purpose, Sprague-Dawley rats with penicillin induced epileptic seizures were tested. Results showed that resveratrol loaded liposomes can cross BBB, had immediate effect on epileptic seizures and significantly increased the activity of Glutathione S Transferase, Malondialdehyde and Superoxide dismutase compared with free solution of resveratrol [25].

In another study, resveratrol was incorporated into chitosan-coated liposomes for treat-ment of vaginal infection. Resveratrol loaded liposomes showed sustained release and average size of 200 nm. Obtained results presented higher anti-inflammatory activity of resveratrol-loaded liposomes compared with free solution on LPS-induced J774A.1 cells [26].

Enhanced bioavailability of resveratrol was reported when combined with curcumin into liposomes in vivo. The concentration was tested in serum and prostate tissue and the results showed higher stability for longer period and significant anticancer effect on invasive adenocarcinoma [27].

Cytotoxicity enhancement of resveratrol was also reported. Resveratrol was incorporated in liposomes modified with transferrin in order to direct the nanoparticle to target glioblastoma cells. Obtained results presented significantly higher cytotoxicity and internalization of resveratrol into glioblastoma cells, compared with free drug and non-modified liposomes which makes them promising candidates for resveratrol delivery [28].

Bacteriostatic activity of resveratrol was evaluated using microdilution method. resveratrol loaded liposomes were prepared using thin film hydration method and the results revealed particle size of approximately 118 nm and high encapsulation efficiency. Obtained results showed that bacteriostatic activity of resveratrol loaded liposomes against Klebsiella pneumonia and methicillin-resistant Staphylococcus aureus is significantly higher with MIC from 70- 300 µg/ml compared with free solution of resveratrol. These results indicate that resveratrol loaded liposomes could be used as potential candidates for intrahospital infections [29].

Confocal microscopy, flow cytometry and HPLC were used in order to determine the amount of resveratrol accumulation in cerebrovascular endothelial cells isolated from aged F344xBN rats. Resveratrol was encapsulated into novel fusogenic liposomes, composed of combination of positively charged lipid (1,2-dioleoyl-3-trimethylammonium-propane, chloride salt DOTAP) and conventional liposomes. Obtained results reported that the main mechanism of antioxidant effect of resveratrol is based on activation of cellular Nrf2 which significantly decreased the reactive oxygen species due to rapid delivery of the active substance by fusogenic liposomes into aged endothelial cells [30].

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In order to overcome the limitations of liposomes, in a recent study resveratrol was co-encapsulated as liposomal formulation into cyclodextrine in form of inclusion complex. The obtained results showed complete drug release and high stability on room temperature for 4 days. Cytotoxicity was tested in vitro on colon cancer cell lines using MTS colorimetric assay and results showed significantly higher cytotoxicity of hybrid resveratrol nanoformulation compared with free DMSO solution of the active substance [31].

Resveratrol loaded liposomes with enhanced bioavailability and stability were prepared by Balanc et al., for testing the antioxidant activity of the active agent. Liposomes were prepared by thin film hydration and proliposome method using commercial lipids DPPC and phopsholipon, characterized with spherical form, size of app.150 nm and negative zeta potential suitable for systemic application. Results showed 95% inhibition of lipid peroxidation compared with free solution [32].

Despite the numerous advantages listed above, low entrapment efficiency is the main problem associated with liposomes owing to the membrane destabilization because resveratrol is localized as hydrophobic molecule mainly into phospholipid bilayer.

III. RESVERATROL LOADED NANOEMULSIONS

Nanoemulsions are promising candidates for encapsulation and delivery of hydrophobic drugs due to low droplet size (20-200nm), high thermodynamic stability and low toxicity. Generally, nanoemulsions are composed of natural fats as lipid phase dispersed into aqueous phase with surfactants and natural emulsifiers used as stabilizers of the emulsion. Numerous research studies reported the potential of these nanocariers for delivery of resveratrol [33], [34].

Resveratrol as a free powder encapsulated in self-nanoemulsifying delivery was tested as potential anti-fatigue agent in exhausted rats by measuring the parameters linked to this condition such as glucose, lactate and ammonia. Nanoemulsions were composed of Capryol 90, Cremophor EL, and Tween 20, and obtained nanoparticles were characterized with average size of 41 nm and negative zeta potential suitable for systemic application. Encapsulation into nanoemulsions not only showed improved oral bioavailability, but also decreased the plasma ammonia level, accelerated lactate recovery and increased the time of rats' exhaustion by swimming [35].

An intriguing approach to overcome resveratrol pre-systemic and systemic transformation is incorporation in nanoemulsions prepared by emulsification method and high-pressure homogenization for treatment of Parkinson's disease. As oil phase in nanoemulsion vitamin E and selfsol was used. Tween 80 and Transcutol P were used as surfactant and co-surfactant for stabilization of nanoemulsion. Results from this study showed size of 104 nm, negative zeta potential and high percentage of released resveratrol after 24 hours. Also, higher concentration of resveratrol in BBB was observed, associated with significantly lower concentration of MDA and higher level of GSH and SOD [36].

Nanoemulsions prepared by high-pressure homogenization method exhibited significant improvement in penetration of resveratrol in Caco 2 cells compared to free drug in DMSO solution. Soy lecithin and Tween 20 were used as components in nanoemulsion. Also, increased physicochemical stability of the formulation in this study has been reported [37].

However, the expensive formulation is one of the major disadvantages of nanoemulsions. Also, use of high concentration of surfactants and high environmental stability dependence significantly limits the application of nanoemulsions as platforms for drug delivery [38].

IV. CONCLUSION

In summary, resveratrol was successfully incorporated into different nanoparticles such as liposomes, solid lipid nanoparticles and nanoemulsions described in this review. Resveratrol loaded nanoparticles showed remarkable advantages over non-encapsulated agent. Low-solubility problems, low systemic circulation and stability were significantly improved with encapsulation of this efficacious agent into nanoparticles. However, despite the numerous ad-vantages of nanoparticles as platforms for resveratrol delivery, future in vitro and in vivo studies are required in order to achieve full utilization of therapeutic potential of resveratrol.

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