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Resveratrol cross-linked chitosan loaded with phospholipid for controlled release and antioxidant activity

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ABSTRACT

Despite the therapeutic effects of resveratrol, its clinical application is restricted by its poor oral bioavailability and low water solubility. To overcome these physicochemical and pharmacokinetic limitations, encapsulation of resveratrol (RV) into nanodevices has been explored. Resveratrol cross-linked chitosan nanoparticles modified with phospholipids (RVC-lipid) were synthesized using a double emulsion technique. The surface morphology of RVC-lipid nanoparticles was evaluated with field emission scanning electron microscopy (FESEM) and transmission electron microscopy (TEM). Particle size was measured using dynamic light scattering technique (DLS), X-ray diffraction (XRD) was performed to identify the crystallographic nature and Fourier transform infrared spectroscopy (FTIR) was used to measure changes in the chemical structures of the resveratrol and RVC-lipid nanoparticles. Results showed RVC-lipid nanoparticle had a characteristic amorphous structure, a mean particle sizes of 570 nm in DI water and 950 nm in ethanol, and an encapsulation efficiency of 63.82% in aqueous medium and 85.59% in ethanol medium. *In-vitro* release studies demonstrated a slow and sustained release of resveratrol governed by diffusion. Based on assays of antioxidant activity the scavenging activity of RVC-lipid nanoparticles was inferior to that of resveratrol due to its prolonged release. We concluded that phospholipids are the potential carriers for resveratrol.

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1. Introduction

Resveratrol (RV) (*trans*-3,4,5-trihydroxystilbene), classified as a polyphenol, which is stilbene-based structure with two phenolic rings linked by a styrene double bond, and is found in various plants, especially the skin of grapes, blueberries, mulberries, and red wine [1,2]. RV possesses potent antioxidant capacity with strong anti-inflammatory, anti-tumor, and antiproliferative properties [3,4], and has been reported to be a powerful antioxidant for treatment of Alzheimer's disease (AD) [5]. Reactive oxygen species (ROS) are normal byproducts of cellular physiology and are continuously removed by enzymatic and non-enzymatic antioxidants that scavenge the radicals, preventing them from attacking biological targets. Chronic exposure of the skin to UV radiation generates high levels of ROS, which overwhelm skin cells and react with DNA, proteins, and fatty acids, altering cell structure and leading to inflammation, skin aging, and cancer [6].

In recent years, several studies have focused on novel approaches to protect human skin from UV radiation and to reduce the occurrence of cutaneous malignancies through dietary antioxidants such as resveratrol [6,7]. Early studies have focused on RV showed that it reduced the incidence of cardiovascular disease in certain groups with high-fat diet and consuming a moderate amount of red wine. This phenomenon is known as the French paradox [8]. *Trans*-resveratrol also affects many metabolic processes and has been suggested to modulate cardiovascular disease, inflammation, cancer, obesity, and diabetes [9,10]. Resveratrol's low bioavailability, stemming from its low solubility in water (<0.001 mol/l), isomerization from the *trans* to *cis* form in solution, and rapid clearance from circulation, makes it difficult to maintain

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bio-efficacious concentrations of resveratrol in the blood and target tissues of humans [11].

To overcome these physicochemical and pharmacokinetic limitations, encapsulation of RV into nanodevices has been explored, and nanotechnology represents a powerful strategy [12,13], where nanoparticles made from natural or synthetic polymer materials as drug carriers. In these systems, the drug molecules covalently couple to nanoparticles by chemical methods or are wrapped and adsorbed by physical methods. Nanoparticles allow the drug to penetrate easily through biological membranes and pass through the cell gap and blood–brain barrier to reach diseased tissue [14]. This system also uses carrier materials that are biodegradable and non-toxic. Encapsulation can also potentially be used to stabilize resveratrol against degradation and to control its release following oral administration [15]. A large number of recent studies have sought to design novel formulations to stabilize and protect RV. It was reported that the lipid-core nanocapsules increase RV concentration in brain tissue [16]. Bu et al. [17] proved that the trans-resveratrol incorporated chitosan nanoparticles (CS-NPs), biotin- chitosan nanoparticles (B-CS-NPs), and avidin biotin-chitosan nanoparticles (A-B-CS-NPs) dramatically improve drug bioavailability and liver targeting index, whereas, Gokce et al. [18] concluded that the RV-loaded nanostructured lipid carriers (NLC) appeared to be superior than simple RV for dermal applications. Zu et al. [14] have reported that RV-loaded CMCS nanoparticles (RV-CMCSNPs) improve the solubility of RV, thereby greatly improving the antioxidant activity and bioavailability of the drug.

A large number of delivery systems are suitable for encapsulation and protection of RV, including micro-emulsion based system [19], liposome/niosomes-based systems [20,21], emulsion-based systems [22], biopolymer-based systems [23,24], and molecular inclusion complexes system [25]. Among these, the emulsion-based system with phospholipids has attracted increasing attention as an efficient and nontoxic alternative lipophilic colloidal drug carrier. They can also enhance the chemical stability of compounds sensitive to light, oxidation, and hydrolysis [26,27]. Phospholipids also can be utilized in the entrapment, delivery, and release of poorly water soluble compounds, such as resveratrol, and are also convenient for water-soluble, lipid-soluble, and amphiphilic compounds.

For the present study, the anti-cancer compound trans-resveratrol was selected as a model drug and prepared resveratrol-chitosan nanoparticles (RVC-NPs). Then, we introduced a phospholipid membrane onto the surfaces of the nanoparticles (NPs). The efficiency and performance of *in-vitro* controlled release of RVC-lipid nanoparticles were also explored. We found that the RVC-lipid nanoparticle delivery system significantly improved the stability of RV, and the controlled release behavior of the RVC-lipid nanoparticles was satisfactory. The encapsulation efficiency (EE) of RVC-lipid nanoparticles was 85.59%, whereas the antioxidant activity was lower than RV.

2. Materials and methods

2.1. Materials

Chitosan derived from shrimp shells (mol.Wt. 190000–375000 Da, deacetylation degree ≥75%) supplied by sigma-aldrich was used. Acetic acid, ascorbic acid, methanol, chloroform diethylene glycol, sodium hydroxide, 1,1-diphenyl-2-picryhydrazyl, and sodium citrate tribasic dihydrate were purchased from Sigma Chemical Co. Ltd. (USA). Resveratrol was purchased from Tokyo Chemical Industry Co. Ltd., Japan. Ethylalcohol, acetic acid, monopotassium phosphate, Na_2CO_3, nitric acid, sodium chloride and phosphotungstic acid were purchased from Samchun Pure Chemical Co. Ltd., Korea. Ultra-pure water, filtered using the EYELA Still Ace SA-2100E1 (Tokyo Rikakikai Co., Japan), was used throughout the experiments.

2.2. Preparation of RVC and RVC-lipid nanoparticles

In a typical procedure for the synthesis of RVC, 0.05 g of chitosan was mixed with 1% aqueous solution of acetic acid (25 mL) and stirred for about 2 h. Further 60 mM ascorbic acid (10 mL) was added to the mixture and stirred continually again for 20 min followed by the addition of 10 mL of 30 mM resveratrol (prepared in DI water or ethanol). The solution was then ultrasonicated (150 W, 40 kHz, Fisher Scientific, Mexico) for about 5 min, further heated at 4 °C in a water bath for one day. The RVC particles obtained was then dried in a freeze dryer and kept in a desiccator for further analysis. For the synthesis of RVC-lipid particles, Phosphatidylcoline (7 g) and cholesterol (3 g) was accurately weight and dissolved in methanol: chloroform (1: 1 v/v) mixture to prepare a phospholipid solution. Above prepared RVC particles were suspended in water, and then mixed with phospholipid solution and ultra-sonicated for 3 min. Finally, the product was ultra-water sonicated (295W, 28 kHz, Shin Han, Korea) for about 60 min and then freeze-dried for about four days.

2.3. Preparation of red and white grape fermentation

In a typical procedure, fresh grapes were squeezed, freeze-dried, and stored. Sugar (21 brix) was then added to obtain higher degree of fermentation. The fermentation of red wine was accomplished by placing the sample in an incubator at 30 °C for about 30 days. To prepare white wine fermentation, grape skins were removed, and the pulp inside of the fruit was then prepared as describe above.

2.4. Characterization

Powder X-ray diffraction (XRD) analysis was performed using a X'PERT-MRD (PaNalytical LTD, Netherlands). The spectra were recorded at room temperature in the 2θ range of 10–80° at a scan rate of 2° min^{-1}, a voltage of 40 kV, and a current of 30 mA. The surface morphology of the synthesized material was probed *via* field emission scanning electron microscopy (FE-SEM) with a SUPRA40VP (Carl Zeiss, Germany) installed in the Center for University-Wide Research Facilities (CURF) at Chonbuk National University and TEM analysis with JEM 2100F (JEOL Ltd., Japan) at the Jeonju Center of the Korea Basic Science Institute. The sizes of nanoparticles were measured using dynamic light scattering (DLS, Photal, DLS-8000, Japan).

2.5. Polyphenol content

Total polyphenol content was measured by using the Folin – Danis Method. 100 μL of sample was placed in an EP tube, and 1 mL of 2% Na_2CO_3 was added and kept at room temperature for 2 min. Further 100 μL of 50% Folin-Ciocalteu's phenol reagent was added, mixed in a vortex mixer, and kept at room temperature for 30 min. Finally, the sample was analyzed by a UV–VIS spectrophotometer at 750 nm.

2.6. Antioxidant activity

2.6.1. DPPH radical scavenging activity

Measurement of free-radical scavenging by DPPH was performed by modified Blois method [28]. DPPH (500 mM) was dissolved in methanol, and 0.1 M Trizma base-HCl buffer (Triz buffer) at pH 7.4, was added. Butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) were used as standards to carry

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