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Review

Resveratrol encapsulation: Designing delivery systems to overcome solubility, stability and bioavailability issues

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Resveratrol is a polyphenol from the stilbens family that has been reported to have various benefits for human health, including antioxidant, anti-inflammatory, anti-carcinogenic, anti-obesity, and heart/brain protective effects. However, the utilization of resveratrol as a nutraceutical in the food industry is currently limited due to its poor water solubility, high chemical instability, and low oral bioavailability. Encapsulation of resveratrol can be used to improve its water-dispersibility, chemical stability, and bioavailability. This paper reviews delivery systems available to encapsulate, protect and release resveratrol, and highlights their potential applications within the food industry.

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Introduction

Resveratrol (trans-resveratrol; trans-3,5,4′-trihydroxy-stilbene) is a polyphenolic compound from the stilbens family (Fig. 1), which is mainly found in grape skins, peanuts, and the roots of *Polygonum cuspidatum* (Walle, Hsieh, DeLegge, Oatis, & Walle, 2004). *In vitro* and *in vivo* studies suggest that resveratrol has a number of potential health benefits, including anti-carcinogenic, anti-inflammatory, anti-obesity, and heart/brain protective effects. For this reason, there has been considerable interest in utilizing resveratrol as a bioactive agent in foods and pharmaceuticals.

Resveratrol may help combat coronary heart diseases by inhibiting myocardial infarction, arrhythmias, hypertension, hypertrophy, fibrosis, atherosclerosis, and thrombosis (Brown *et al.*, 2009). Numerous biochemical mechanisms have been proposed to account for this ability, including antioxidant activity, modulation of nitric oxide biosynthesis and activity, alteration of cell-to-cell interactions, and inhibition of platelet COX-1 (Gresele *et al.*, 2011). The ability of resveratrol to combat certain brain diseases has been attributed to its antioxidant activity, interference with signaling pathways, and ability to elevate sirtuin production in the brain (Villaflores, Chen, Chen, Yeh, & Wu, 2012). Resveratrol has also been shown to inhibit certain types of cancer, which has been attributed to its ability to induce apoptosis, activate caspase, modulate signaling pathways, decrease cell proliferation, arrest cell cycles, and decrease metastasis (Murtaza *et al.*, 2013). Resveratrol have proven useful in the management of obesity through its ability to decrease lipid synthesis, increase lipolysis, and reduce lipid accumulation (Alves, 2012; Fischer-Posovszky *et al.*, 2010; Picard *et al.*, 2004). In primates, resveratrol was found to reduce body weight gain by increasing satiety and resting metabolic rate, as well as inhibiting torpor expression (Dal-Pan, Blanc, & Aujard, 2010). In mice fed with a high-fat diet, resveratrol decreased food intake and down-regulated adipogenic and inflammatory processes (Kim, Jin, Choi, & Park, 2011). Resveratrol supplementation was demonstrated to induce metabolic changes in obese humans, that mimics the effects of a calorie restricted diet (Timmers *et al.*, 2011). Finally, resveratrol has been shown to have anti-inflammatory effects, which is partly attributed to its ability to decrease COX-2 expression (Catalgol, Batirel, Taga, & Ozer, 2012).

Despite the potential health benefits of resveratrol, its utilization as a nutraceutical ingredient within the food

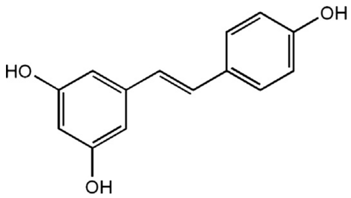

Fig. 1. *Trans*-resveratrol chemical structure.

industry is currently limited due to its poor water solubility, low bioavailability, and chemical instability. Resveratrol is highly soluble in ethanol (50 mg/ml) and dimethyl sulfoxide (16 mg/ml) (Aldrich, 1997), moderately soluble in triacylglycerol oils (0.18 mg/ml) (Hung, Chen, Liao, Lo, & Fang, 2006), but only slightly soluble in water (0.021–0.030 mg/ml) (Aldrich, 1997; SciFinder, 2013). Consequently, it is difficult to incorporate relatively high levels of resveratrol into aqueous-based food products. In addition, resveratrol is sensitive to chemical degradation within food products. Resveratrol may be chemically degraded when exposed to elevated temperatures (Lyons *et al*., 2003; Schmidt, Erdman, & Lila, 2005), pH changes (Allan, Lenehan, & Ellis, 2009), ultraviolet light (Rodriguez, Lahoz, Faza, Cid, & Lopez, 2012; Trela & Waterhouse, 1996), or certain types of enzymes (Pinto, Garcia-Barrado, & Macias, 2003). Chemical degradation often involves the isomerization of resveratrol. For example, Trela and Waterhouse (1996) reported that after irradiating a *trans*-resveratrol solution for 2 h with UV-light at 366 nm, 91% of the original *trans*-resveratrol isomerized to *cis*-resveratrol. *Trans*-resveratrol has a higher radical scavenging activity (Fauconneau *et al*., 1997) and anti-inflammatory activity (Rius *et al*., 2010) than *cis*-resveratrol, and therefore one would expect a loss of bioactivity after isomerization. Another factor limiting the bioavailability and bioactivity of resveratrol is its tendency to undergo metabolism after ingestion, *e.g.*, glucuronide and sulfate conjugates are rapidly formed in the human body (Patel *et al*., 2011). It has been estimated that the current daily intake of resveratrol is around 4 mg/day (Vang *et al*., 2011). Increasing this level may lead to improvements in human health due to the mechanisms mentioned above. Toxicology studies suggest that resveratrol is safe when consumed at doses up to 5 g per day in healthy humans, but that 2.5–5 g doses can cause mild to moderate gastrointestinal symptoms (Brown *et al*., 2010).

Research is currently being undertaken to overcome the challenges of utilizing resveratrol as a bioactive agent. However, much of this research has been carried out from a pharmaceutical perspective (Amri, Chaumeil, Sfar, & Charrueau, 2012; Santos, Veiga, & Ribeiro, 2011). In food applications, there are a number of additional factors that need to be considered when designing effective encapsulation systems (McClements, Decker, Park, & Weiss, 2009). First, all the components used to assemble a delivery system should be food-grade generally recognized as safe (GRAS) ingredients. Second, the fabrication method should be economically viable and robust so that it can be used commercially for large scale production in the food industry. Third, the delivery system should not adversely impact the organoleptic properties of the food product, such as appearance, texture, or flavor. Fourth, the delivery system should remain physically stable during food processing, transport, and storage. Finally, the resveratrol should remain in a metabolically active form within the food or beverage product (Sessa, Tsao, Liu, Ferrari, & Donsi, 2011). The purpose of this review is to provide an overview of the main encapsulation methods available to overcome the challenges associated with incorporating resveratrol into functional food and beverage products.

Delivery systems for resveratrol

In this section, the different broad categories of delivery systems available for the encapsulation of resveratrol are given.

Natural sources and foods

The total amount of resveratrol consumed by humans may be increased by consuming more resveratrol-rich foods (*e.g.*, grapes, berries, peanuts) or foods derived from them (*e.g.*, wine, juices, dried fruits, jams, and spreads). Nevertheless, there are numerous reasons that may make this approach unsuitable for widespread utilization (Murtaza *et al*., 2013). First, the bioavailability of resveratrol from natural sources is often relatively low because it is trapped within specific biological structures. Second, the amount of resveratrol within a natural source may vary considerably depending on species, climate, location, time of year, *etc*. Third, it is often impractical to consume the quantity of a natural source required to have an appreciable biological effect. Fourth, the resveratrol may be primarily located within parts of the fruit that are not normally consumed, such as the skin or seeds. For these reasons, it is often desirable to isolate the resveratrol from a natural source and then incorporate it into a suitable delivery system.

Crystalline forms

Resveratrol can be isolated from natural forms by simple processing operations, such as crushing, grinding, solvent extraction (usually aqueous alcoholic mixtures) and separation and purification techniques (Romero-Perez, Lamuela-Raventos, Andres-Lacueva, & de la Torre-Boronat, 2001; Zhao, Chen, & Du, 2012). Extraction and purification usually lead to a powdered form of resveratrol that consists of white crystals. The powdered form of resveratrol can be incorporated into capsules or tablets for use as a supplement. In principle, it can also be incorporated into food products by simple mixing, but there are a number of limitations associated with this approach. In a low viscosity fluid product (such as a beverage) the crystals may be