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Review

# Administration of resveratrol: What formulation solutions to bioavailability limitations?

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ABSTRACT

Resveratrol (3,5,4′-trihydroxystilbene), a naturally occurring polyphenol, has attracted considerable interest for its beneficial potentials for human health, which include anti-oxidant, anti-inflammatory, cardioprotective and anti-tumor activities. However, the in vivo biological effects of resveratrol appear strongly limited by its low bioavailability, which is a barrier to the development of therapeutic applications. In this context, an increasing number of recent studies have aimed at designing novel resveratrol formulations to overcome its poor solubility, limited stability, high metabolization and weak bioavailability. This review outlines physicochemical and pharmacokinetic limitations to resveratrol bioavailability, describes formulations tested for resveratrol administration, controlled release and targeting, and identifies future opportunities for resveratrol delivery.



**Contents**



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## 1. Introduction

Resveratrol (3,5,4′-trihydroxystilbene) is a non-flavonoid polyphenolic compound abundant in grapes, peanuts and other foods that are commonly consumed as part of human diet. The compound was first isolated from the root of *Polygonum cuspidatum,* a plant used in traditional Chinese and Japanese medicine [1]. Polyphenols accumulate in plants in response to exogenous stress factors such as injury, fungal infections or UV irradiation [2]. Humans have been exposed to dietary polyphenols for millions of years, and have developed tolerance to this group of plant defense compounds [3,4].

Starting in the 1990s and continuing to date, scientific studies have reported that resveratrol has a broad range of desirable biological actions, including cardioprotection [5,6], cancer prevention [7] and prolongation of lifespan in several species [8,9]. The biological properties of resveratrol are attributed to its ability to inhibit the oxidation of human low-density lipoprotein, while its suppression of cyclooxygenase-2 and inducible nitric oxide synthase activities also contribute to its anti-inflammatory and antioxidant effects [10,11]. Furthermore, the chemopreventive effect of resveratrol is thought to be due to inhibition of quinone reductase 2 activity, which in turn up-regulates the expression of cellular antioxidant and detoxification enzymes to improve cellular resistance to oxidative stress [12]. Resveratrol also increases the activity of SIRT (a member of the sirtuin family of nicotinamide adenine dinucleotide-dependent deacetylases), resulting in improved cellular stress resistance and longevity [8–10,13]. Resveratrol can also regulate the expression of hormone-dependent genes such as the oncosuppressor BRCA1 in breast cells, due to its structural similarity to diethylstilbestrol [14,15].

However, therapeutic application of these beneficial effects of resveratrol remains very limited due to its short biological half-life, labile properties, and rapid metabolism and elimination [10]. Results from pharmacokinetic studies indicate that the oral bioavailability of resveratrol is almost zero, which casts doubt on the physiological relevance of the high concentrations typically used for in vitro experiments [16,17].

Resveratrol has attracted great interest in the research community, with 4064 publications referenced on the U.S. National Library of Medicine's PubMed service between 1978 and 2011 [18], of which 96% were between 2000 and 2011. Analysis of recent literature reveals an increasing number of formulations under study (Fig. 1), which reflects the major interest in developing pharmaceutical forms able to improve resveratrol bioavailability as a step towards applying its therapeutic potential in vivo. The purpose of this review is to present the physicochemical properties and pharmacokinetic characteristics of resveratrol, then to cover formulation attempts designed to overcome its bioavailability limitations, and finally to close by identifying future opportunities for resveratrol delivery.

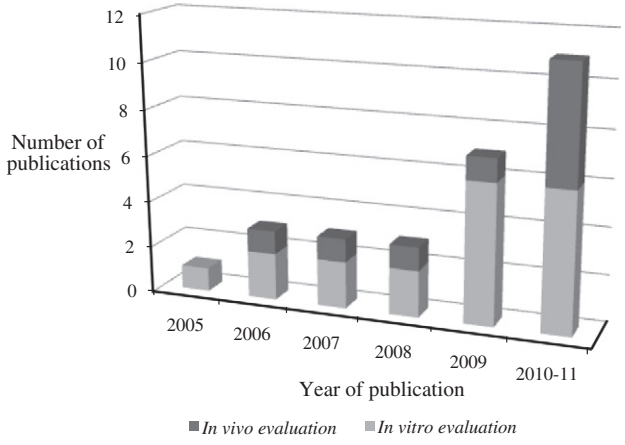


**Fig. 1.** Trends in scientific publication on resveratrol formulations over the last 7 years, with the focus on in vitro and in vivo evaluation.

## 2. Physicochemical properties of resveratrol

Resveratrol (Chemical Abstracts Service Registry Number CAS 501-36-0 [19]) is a solid off-white powder with molecular formula $C_{14}H_{12}O_3$, molecular weight of 228.25 g.mol$^{-1}$[20] and a melting point between 253 and 255 °C. Resveratrol is a fat-soluble compound that is also soluble in ethanol at ~50 mg.ml$^{-1}$ (~200 mM) and in DMSO at ~16 mg.ml$^{-1}$ (~70 mM) [21]. However, its hydrosolubility of ~3 mg.100 ml$^{-1}$ (~0.13 mM) [22–24] makes it "pratically insoluble" in water according to the European Pharmacopeia definition, and its log P is 3.1 [25]. Despite this poor water solubility, resveratrol exhibits high membrane permeability and can be considered a class-II compound in the Biopharmaceutical Classification System [26].

Resveratrol exists as two structural isomers: *cis*- (Z) and *trans*- (E) (Fig. 2). The *trans*-isomer is biologically more active than the *cis*-isomer [27,28], probably due to its nonplanar conformation [29]. *Cis*-resveratrol has been reported to be unstable and is therefore not available commercially [30,31]. In fact, when protected from light, *trans*-resveratrol is stable for at least 42 h (CV ≤1%) and for at least 28 days (CV ≤4.7%) in pH 1–7 buffers, whereas the *cis* form is only stable at neutral pH when completely shielded from light [32].

Resveratrol is an extremely photosensitive compound: Vian et al. [22] demonstrated that 80–90% of the *trans*-resveratrol in solution was converted to *cis*-resveratrol if exposed to light for 1 h. Trela and Waterhouse [32] also reported that *trans*-resveratrol was susceptible to UV-induced isomerization: when pure *trans*-resveratrol was irradiated for 120 min at 366 nm, 90.6% was converted to *cis*-resveratrol.

## 3. Pharmacokinetic characteristics of resveratrol

In order to determine the absorption, metabolism and subsequent bioavailability of resveratrol, several in vitro and in vivo studies have helped clarify the pharmacokinetic characteristics of this polyphenol. The in vivo fate of resveratrol following oral administration has been reconstituted based on miscellaneous data obtained in vitro on cell cultures, ex vivo on isolated small intestine models, and in vivo in animals and humans (Fig. 3).

### 3.1. Intestinal absorption and metabolism

In 2000, Andlauer et al. [33] studied the intestinal systemic uptake of resveratrol using an isolated rat small intestine perfusion model. In their study, the intestine was perfused with nutritionally relevant concentrations of 28, 34 and 57 mmol.l$^{-1}$. In a single-pass perfusion, 46% of the luminally administered resveratrol was extracted by the small intestine whereas 21% of administered resveratrol appeared at the vascular side and 2% was found in intestinal tissue. The majority of the absorbed resveratrol was conjugated to yield resveratrol glucuronide (16.8%), and the rate of unchanged *trans*-resveratrol was only 3.4%.

More recent studies on intestinal cells describe the absorption and transport mechanisms of resveratrol and its metabolites in the Caco-2 human intestinal cell line. Transcellular transport of resveratrol

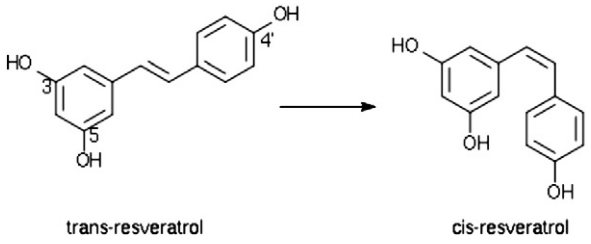


**Fig. 2.** Chemical structure of resveratrol.

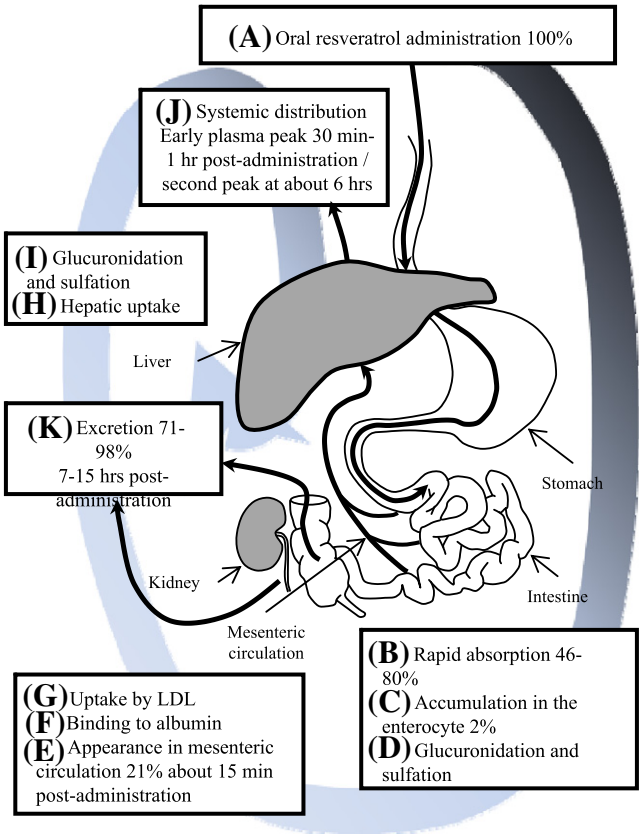


**Fig. 3.** In vivo fate of resveratrol following oral administration. Schematic illustration put together based on miscellaneous data obtained in vitro on cell cultures, ex vivo on isolated small intestine models, and in vivo in animals and humans. (A) Oral administration = 100%. (B) Intestinal absorption as a result of a rapid passive diffusion process observed on Caco-2 cells [34,35] is estimated at 46% on isolated perfused rat small intestine [33], 77–80% in vivo in rats [40], and at least 70% in humans [16,58]. (C) Accumulation in the enterocyte accounts for 2% in isolated perfused rat small intestine [33]. (D) Metabolism within the enterocyte consists in the formation of glucuroconjugates and sulfoconjugates of resveratrol which are either absorbed toward the vascular space or excreted in the lumen [33]; sulfation and glucuronidation occur on human duodenum samples [42] and in the human Caco-2 intestinal cell line [34,35]. (E) Appearance of resveratrol in mesenteric circulation represents 21% on isolated perfused rat small intestine [33]. (F) Binding to albumin [48,49]. (G) Uptake of resveratrol into human low-density lipoprotein [54]. (H) Hepatic uptake results from the contribution of a passive diffusion process and a carrier-mediated process in the human hepatoblastoma cell line HepG2 and in human hepatocytes [48]. (I) Hepatic metabolism consists in sulfation and glucuronidation in human liver samples [42,50]. (J) Systemic in vivo distribution in rodents is characterized by a peak concentration at 30 min [40,41], with metabolites becoming detectable 3 h post-administration [41,51]. In humans, free resveratrol in plasma and serum accounts for less than 2% of total resveratrol, or is even below the limit of detection [17]. The highest serum level of about 2 μM of total resveratrol (free and metabolites) is recorded at 30 min [45], or 1 h [16]; a second peak at about 1.3 μM is observed at 6 h, suggesting enteric recirculation of conjugated metabolites by reabsorbtion following intestinal hydrolysis [16]. The highest serum level of free resveratrol recorded at 30 min is cited at below 40 nM [45], or even less than 22 nM [16]. (K) Excretion of the non-absorbed fraction represents 40% of free resveratrol, 11% of glucuronide and 3% of sulfate conjugates in isolated perfused rat small intestine [33]. Renal excretion is the major route of elimination in animals and humans [16,41,44,45,55–57]. Total excretion (in urine and feces) after oral administration in humans is 71 to 98% (vs. 54–91% after i.v. dose) [16]. Renal excretion varies from 26 to 34 to 52% with doses of 1 to 0.5 to 0.03 mg/kg [55], and to 53–85% in healthy volunteers [16], while fecal excretion varies between 3.3 and 35% [16].

appeared to occur through a rapid passive direct-independent diffusion mechanism [34,35]. The metabolism of resveratrol by Caco-2 cells was also investigated. The fact that resveratrol transport has limited linearity over time suggests extensive metabolism of resveratrol by the Caco-2 cells. Studies demonstrate a concentration-dependent biotransformation of resveratrol [36]. Two metabolites, resveratrol-3-sulfate and resveratrol-3-glucuronide, were detected as phase II biotransformation products [34,35], and sulfate conjugation was the major pathway for resveratrol in Caco-2 [34].

The intestinal metabolism of resveratrol in vivo was first described in rodent models by Bertelli's team [37–39]. The authors measured resveratrol absorption in rats by administering red wine with a known resveratrol content (6.5 $mg.l^{-1}$). The resveratrol was quickly absorbed, reaching its peak concentration approximately 60 min after wine ingestion, with initial resveratrol concentrations found after 30 min. Further investigations confirmed rapid absorption with resveratrol becoming detectable as early as 15 min post-administration and reaching peak concentrations after 30 min [40,41]. The identification of resveratrol metabolites indicates that *trans*-resveratrol-3-O-glucuronide and *trans*-resveratrol-3-sulfate are the most abundant metabolites of resveratrol, while virtually no unconjugated resveratrol was detected in urine or serum samples of rodents [41]. The sulfation of resveratrol was confirmed in human duodenum samples [42].

The bioavailability of resveratrol in humans has recently been investigated [43]. In 2001, Soleas et al. [44] were the first to study resveratrol absorption in humans. They found that quantities of free resveratrol in plasma were very low, ranging from 1–5 $ng.ml^{-1}$. The absorption and bioavailability of resveratrol, catechin and quercetin were evaluated by Goldberg et al. [45] in 12 healthy male human subjects after oral ingestion. For both total resveratrol and resveratrol aglycone, the highest recorded concentrations in serum occurred 30 min after administration, and values returned to baseline within 4 h. The serum concentration of free resveratrol aglycone was a small fraction of the total resveratrol concentration, with the highest observed values being only 1.7 to 1.9%. Goldberg concluded that "the voluminous literature reporting powerful in vitro-anti-cancer and anti-inflammatory effects of the free polyphenol is irrelevant, given that they are absorbed as conjugates". In 2004, Walle et al. [16] examined the absorption, bioavailability, and metabolism of $^{14}C$-resveratrol after oral and i.v. doses in human volunteers. About 70% of the resveratrol dose

given orally was absorbed. The i.v. dose of resveratrol was converted to sulfate conjugate within 30 min. Both sulfate and glucuronide conjugates were detected after oral dosing. Total sulfate conjugates accounted for 37% of the metabolites in the urine and total glucuronide conjugates 19%, with the remainder being made up largely by unknown metabolites. Only trace amounts (below 5 ng.ml$^{-1}$–22 nM) of unchanged resveratrol could be detected in the blood after a 25 mg oral dose. When resveratrol was administered at higher doses, up to 5 g, plasma concentration of free resveratrol increased to 539 ng.ml$^{-1}$ (~2360 nM) [46]. Finally, repeated administration of 13 doses of resveratrol (150 mg each) within 2 days led to a maximum plasma concentration of over 64 ng.ml$^{-1}$ (~280 nM) [47].

### 3.2. Hepatic uptake and metabolism

The hepatic uptake of resveratrol was investigated by Lançon et al. [48] using two different cellular models: a human hepatoblastoma cell line (HepG2), which is responsive to the antiproliferative effects of resveratrol, and human hepatocytes in order to compare resveratrol transport in normal vs. tumor cells. The authors showed that resveratrol influx does not occur only by passive diffusion but also involves a carrier-mediated process. In physiological conditions, this process would allow efficient hepatic uptake of the resveratrol in circulating blood, despite binding to serum proteins, particularly with albumin [48,49].

In 2000, De Santi et al. studied in vitro sulfation and glucuronidation in human liver samples and showed that resveratrol is a good substrate for human hepatic sulfotransferase [42] and glucuronosyl transferase [50]. Investigations of resveratrol metabolism in vivo in rodent models showed that the liver is a major accumulation site for resveratrol and its metabolites, although it is not yet known if accumulation of resveratrol metabolites in the liver takes place due to resveratrol metabolism in the small intestine and its subsequent absorption, or to in situ metabolism [51].

### 3.3. Distribution and excretion

The plasma pharmacokinetics of *trans*-resveratrol after administration of wine to rats were described by Bertelli et al. as an open one- or two-compartment model with significant cardiac bioavailability and a strong affinity for the liver and kidneys [52]. The appearance of a second resveratrol plasma peak 6 h after consumption suggested enteric recirculation of conjugated metabolites by reabsorption following intestinal hydrolysis [16]. Burkon and Somoza reported that more than 90% of free resveratrol was bound to human plasma and that 50% of the plasma *trans*-resveratrol-3-sulfate, *trans*-resveratrol-disulfates and the novel *trans*-resveratrol-C/O-diglucuronides were bound to proteins [53]. This confirmed the interaction of resveratrol with albumin observed experimentally [48,49]. In a study investigating resveratrol binding to LDL, Urpi-Sardà et al. reported that resveratrol and its metabolites were recovered in the LDL fraction of healthy volunteers after consumption of 250 ml of Merlot wine [54].

Excretion of the non-absorbed fraction represents 40% of free resveratrol, 11% of glucuronide and 3% of sulfate conjugates in isolated perfused rat small intestine [33]. Renal excretion is the major route of elimination in animals and humans [40,41,44,45,54–57]. Total excretion in urine and feces after oral administration in humans was 71 to 98% (vs. 54–91% after i.v. dose) [16]. Renal excretion varied from 26 to 34 to 52% with doses of 1 to 0.5 to 0.03 mg.kg$^{-1}$[55] and from 53–85% in healthy volunteers [16], while fecal excretion ranged between 3.3 and 35% [16]. In urine, two isomeric glucuronic acid conjugates and one sulfate conjugate were identified that accounted for 22 to 44% of the dose or 31 to 63% of the metabolites in the 0 to 12-h urine [16]. More recently, the role of microbiota in the intestinal degradation of resveratrol was suggested to explain the urinary excretion of polar metabolites subsequent to bacterial degradation and further enteric absorption [58].

## 4. Formulation research to increase resveratrol bioavailability

In most experimental and clinical settings investigating its in vivo fate, resveratrol has been used in its free form, either as a solid in capsules [43,46,47] or dissolved/diluted/suspended in different vehicles (i.e. wine [37–40,44,45,52,54], grape juice [55], ethanol [16], ethanol + physiological saline [57], ethanol + corn or neobee oil [41], propylene glycol + water [56], glycerol formal [51], among others.). While the solid forms present very poor hydrosolubility, the liquid forms often use excipients known to have a recognized action or effect (i.e. ethanol and propylene glycol). Hence, administration forms of resveratrol are far from optimized.

The oral bioavailability of small molecule drugs is widely thought to be determined by the aqueous solubility, membrane permeability and metabolic stability of the given drugs [59,60]. In recent years, several studies have focused on novel formulation approaches to stabilize and protect resveratrol from degradation, increase its solubility in water in order to improve its bioavailability, to achieve a sustained release, and ultimately to target resveratrol to specific locations via multiparticulate forms and colloidal carriers. These attempted test formulations are presented in Table 1 along with their objectives and the excipients used.

### 4.1. Formulations to stabilize and protect resveratrol

Since resveratrol is an extremely photosensitive compound [22,32], Nam et al. [61] applied monodisperse functionalized porous polymeric microspheres as support material for the stabilization and preservation of resveratrol. Monodisperse porous polymer particles of about 5 μm in diameter and containing cyano groups were prepared by seeded polymerization in the presence of porogen. It was found that the wetting time during the immobilization process and existence of cyano-functional groups were important factors for stabilizing resveratrol in the porous particles. As the crosslinking density of the porous particles increased, the loading content of resveratrol decreased, due to the high hydrophobicity of the porous particles. The antioxidant activity of immobilized resveratrol was preserved in over 93% compared to raw resveratrol. In addition, the bioactivity of resveratrol immobilized in the porous particles was sustained for 5 weeks.

In 2008, Shi et al. [62] demonstrated the successful preparation of yeast-encapsulated resveratrol using *Saccharomyces cerevisiae* as encapsulating wall material. The formulation showed slower photodecomposition and stronger free radical scavenging than non-encapsulated resveratrol. In addition, the encapsulated resveratrol was more stable under wet and high-light stresses. The in vitro releasing property of yeast-encapsulated resveratrol was determined in a simulated gastric fluid without pepsin (pH 1.2); the resulting release profile showed that about 90% of resveratrol was released within 90 min. Despite the fact that no in vivo study was carried out, the authors concluded that the poor bioavailability due to rapid metabolism and elimination of resveratrol could be partially offset by yeast cell encapsulation technology.

### 4.2. Formulations to improve resveratrol aqueous solubility

To improve *trans*-resveratrol solubility, complexation with β-cyclodextrin (β-CD), hydroxypropyl-β-CD (HP-β-CD), randomly methylated-β-cyclodextrin (RM-β-CD) and maltosyl-β-cyclodextrin ($G_2$-β-CD) have all been investigated [23,63–65]. López-Nicolás et al. [23] demonstrated that resveratrol formed a 1:1 complex with β-CD. By applying the complexation of *trans*-resveratrol with β-CD and HP-β-CD, Lu et al. [64] proved that the limited water solubility of resveratrol could be overcome by the formation of inclusion

**Table 1**
Formulations tested to increase resveratrol bioavailability.

| Objective | Pharmaceutical form / size | Excipients | Reference |
|---|---|---|---|
| Stabilize and protect resveratrol | Monodisperse cyano-functionalized porous polymeric microspheres / ~5 μm | Styrene, polystyrene, acrylonitrile, ethanol, 1-chlorododecane, benzoyl peroxide, toluene, heptane, polyvinyl alcohol, divinylbenzene and sodium laurylsulfate | [61] |
| | Yeast-encapsulated resveratrol / ~6–8 μm | *S. cerevisiae*, absolute ethanol, water | [62] |
| Increase resveratrol aqueous solubility | β-cyclodextrin-resveratrol complex | β-cyclodextrin | [23] |
| | β-cyclodextrin and maltosyl β-cyclodextrin / resveratrol complexes | β-cyclodextrin and maltosyl β-cyclodextrin | [63] |
| | β-cyclodextrin and hydroxypropyl-β-cyclodextrin / resveratrol complexes | β-cyclodextrin and hydroxypropyl-β-cyclodextrin | [64] |
| | β-cyclodextrin, hydroxypropyl-β-cyclodextrin and randomly methylated-β-cyclodextrin / resveratrol complexes | β-cyclodextrin, hydroxypropyl-β-cyclodextrin and randomly methylated-β-cyclodextrin | [65][a] |
| | Nanoemulsion / ~17 nm | Poly(oxyethylene) hydrogenated castor oil, ethanol and isopropyl myristate | [66] |
| | Micellar solution | Sodium salts of cholic acid, 7-monoketocholic acid, 12-monoketocholic acid, 7,12-diketocholic acid, 3,7,12-triketocholic acid, 12-monoketodeoxycholic acid and distilled water | [67] |
| Sustain resveratrol release (SR) | Ca-pectinate beads / ~1 mm | Pectin, calcium chloride and deionized water | [68] |
| SR + deliver resveratrol specifically to the colon | Colon-targeted calcium-pectinate beads / ~1 mm | Pectin, calcium chloride, polyethyleneimine and deionized water | [69] |
| | Colon-targeted calcium-pectinate and zinc-pectinate beads / ~1 mm | Pectin, calcium chloride, zinc acetate dihydrate and distilled water | [70] |
| | Colon-targeted zinc-pectinate microparticules / ~900–950 μm | Pectin, zinc acetate dihydrate, glutaraldehyde and distilled water | [71][a] |
| | Colon-targeted calcium-pectinate microparticules / ~1 mm | Pectin, calcium chloride, glutaraldehyde and deionized water | [72][a] |
| | Colon-targeted zinc-pectin-chitosan microparticules / ~920–980 μm | Pectin, zinc acetate dihydrate, chitosan, acetic acid and deionized water | [73][a] |
| | Colon-targeted calcium-pectinate beads / ~1 mm | Pectin, calcium chloride, polyethyleneimine and deionized water | [74][a] |
| SR | Double-layered ultrafine fibers / ~134–1585 nm | Polycaprolactone (MM 80,000), chloroform and ethanol | [75] |
| SR + increase solubility, stability, cytotoxicity, and permeation of resveratrol | Cyclodextrin-based nanosponges / ~400–500 nm | β-cyclodextrin, dimethylformamide, carbonyldiimidazole, deionized water, ethanol | [76] |
| SR | Acoustically active lipospheres / ~250–350 nm | Hydrogenated soybean phosphatidylcholine, cholesterol, pluronic F68, brij 98, coconut oil, chloroform, methanol, perfluoropentane and perfluorohexane | [77] |
| Improve resveratrol bioavailability in the brain | Polymeric lipid-core nanocapsules / ~240 nm | Poly(ε-caprolactone), caprylic/capric triglyceride, polysorbate 80, sorbitan monostearate, acetone and deionized water | [78][a] |
| SR + decrease resveratrol cytotoxicity | Solid lipid nanoparticles / ~180 nm | Glyceryl behenate, hydrogenated soybean lecithin and poloxamer 188 | [79] |
| SR + improve cell-stress response | Liposomes / ~70–100 nm | Enriched soy phosphatidylcholine, dicetyl phosphate, cholesterol and Tris–HCl buffer | [80] |
| SR + improve efficacy of resveratrol on cell proliferation + photoprotection | Liposomes / ~70–100 nm | Enriched soy phosphatidylcholine, dicetyl phosphate, cholesterol and Tris–HCl buffer | [25] |
| Synergicistically increase resveratrol and curcumin bioavailability and enhance anti-cancer effect | Liposomes / size not determined | 1,2-dimyristoyl-rac-glycero-3-phosphocholine, dimethylsulfoxide and ter-butanol | [81][a] |
| Increase solubility, photostability and anti-tumor response | Liposomes / size not determined | Dipalmitoylphosphatidylcholine, poly(ethyleneglycol)-2000 distearoylphosphatidylethanolamine, cholesterol and ethanol | [82][a] |
| SR + enhance growth inhibition against glioma cells | Nanoparticles / ~90 nm | Methoxy poly(ethylene glycol)-poly(caprolactone) | [83] |
| Protect cells from Aβ-induced oxidative stress | Nanoparticles / ~90 nm | Methoxy poly(ethylene glycol)-poly(caprolactone) | [84] |
| SR + inhibit vascular intimal thickening | Emulsion-liposome blends / vesicles 114–195 nm; liposomes 43–56 nm | Coconut oil, soybean lecithin, glycerol formal, and non-ionic surfactants | [85][a] |
| SR + limit vascular intimal thickening | Aqueous micellar system / 30–100 nm | Soybean phosphatidylcholine, chloroform, methanol, glycerol formal, water, ± brij 30, brij 35, span 80, tween 80, distearolylphosphatidylethanolamine-PEG 2000 and cholesterol-PEG 200 | [86][a] |
| | Emulsion without vitamin E / 60–140 nm | Above-cited excipients + coconut oil | |
| | Emulsion with vitamin E / 100–130 nm | Above-cited excipients + coconut oil + vitamin E | |

[a] Designates in vivo investigations: the main results of these studies are summarized in Table 2 (pharmacokinetic studies in healthy rats) and Table 3 (evaluations in pathological models).

complexes. HP-β-CD exhibited stronger inclusive ability than native β-CD due to the enlargement of the cavity in relation to intramolecular hydrogen bond network loosening induced by hydroxypropyl substitutions. The antioxidant activity of the complexes, determined by scavenging of the stable radical 2,2′-diphenyl-1-picryl hydrazyl, was not significantly different from that of free-form resveratrol at the same concentration [64].

Complexation with β-CD and $G_2$-β-CD was also investigated [63]. In addition to increasing resveratrol hydrosolubility, entrapment in the internal cavity of CDs delayed resveratrol oxidation by

lipoxygenase. The authors concluded that CDs could be used as resveratrol carrier systems, since they acted as substrate reservoir in a dosage-controlled manner [63].

According to López-Nicolás et al. [23], the use of *trans*-resveratrol-β-CD complexes could slow down the rapid metabolism and elimination of *trans*-resveratrol and thereby improve its bioavailability, as has already been demonstrated for other β-CD complexes. However, this hypothesis was disproved by experimental data in healthy rats [65].

Yang et al. (cited in [66]) proposed a resveratrol nanoemulsion formulation that was optimized by drawing the ternary-phase diagrams: poly(oxyethylene)-hydrogenated castor oil was selected as surfactant, ethanol as cosurfactant and isopropyl myristate as oil phase, and resveratrol loading was $6.18 \pm 0.11$ mg.l$^{-1}$. Stability evaluation showed that the resveratrol nanoemulsion was clear and transparent, without layering or flocculation after 3-month storage. The nanoemulsion was stable at a temperature range of −4 to +60 °C. However, no indication on the pharmacokinetic behavior of this preparation was given.

The solubilization of resveratrol in micellar solutions of bile acids was also investigated [67]. Results showed that a micellar solution of 3,7,12-triketocholic acid had the highest affinity for resveratrol solubilization, and its critical micellar concentration was 2.0 mM. The authors concluded that derivatives of bile acids, which have the smallest membranolytic potential, solubilize resveratrol most efficiently.

### 4.3. Formulations to achieve targeted and/or sustained release of resveratrol

The development of formulations with sustained release characteristics that may eventually transport and deliver resveratrol to specific desired locations is a promising strategy tackled through several studies using either multiparticulate forms in the millimeter to micrometer range or colloidal carriers in the nanometer range. The following paragraphs describe these forms in decreasing order of size.

#### 4.3.1. Resveratrol-loaded Ca-pectinate beads and Zn-pectinate microparticles

To solve the problem of quick resveratrol absorption and metabolism in the upper gastro-intestinal tract, Das and Ng attempted to prepare resveratrol-loaded Ca-pectinate beads for site-specific and sustained-release drug delivery [68,69] by varying six different formulation parameters (crosslinking solution pH, crosslinking agent concentration, crosslinking time, drying conditions, pectin concentration, and pectin-to-resveratrol ratio). The beads of about 1 mm in diameter were prepared using an ionotropic gelation method. Resveratrol was highly entrapped inside the beads (up to 98%) and was stable for 6 months at +4 °C and at room temperature. The beads incubated in simulated gastric fluid showed over 97% resveratrol retention after 6 h, while in vitro release of resveratrol in the intestinal media after 10 h incubation was 80–100% [68]. This formulation was optimized to obtain a colon-specific delivery of resveratrol [69] for the treatment of colon diseases such as colorectal cancer or colonic inflammation. The calcium-pectinate beads were hardened by adding polyethyleneimine in the crosslinking solution. Amounts of 60 to 94% of resveratrol were encapsulated into beads without altering the resveratrol retention pattern in simulated gastro-intestinal conditions [69].

However, these calcium-pectinate beads primarily failed to display colon-specific resveratrol release in vivo. To achieve this goal, zinc-pectinate microparticles were formulated based on the rationale that zinc produces a stronger pectinate network than calcium [70]. The teams also used either glutaraldehyde as hardening agent [71,72] or chitosan as a cationic polysaccharide to form a polyelectrolyte complex with pectin via electrostatic and hydrogen bonds [73]. Spherical zinc-pectinate microparticles of about 950 μm in diameter and about 94 to 98% resveratrol encapsulation efficiency were obtained, and both the glutaraldehyde-modified and the chitosan-containing microparticles demonstrated colon-specific in vitro and in vivo release in rats [71–73].

As an alternative, these authors also re-evaluated polyethyleneimine as a crosslinking agent to strengthen the calcium-pectinate network of the pectin beads. They adjusted the pH of the crosslinking solution to 1.5 (vs. 10.5 without adjustment). Under these particular conditions, spherical beads of 1 mm in diameter, with about 97% resveratrol encapsulation efficiency, demonstrated colon-specific in vitro release and a pharmacokinetic profile typical of colon-specific drug delivery in rats [74].

#### 4.3.2. Double-layered ultrafine fibers

In 2006, Huang et al. [75] described an electrospinning process to produce double-layered ultrafine fibers with diameters ranging from 134 to 1585 nm. A bioabsorbable polymer, polycaprolactone (PCL), was used as the outer layer, and resveratrol was used as the inner layer. They showed that solutions of 4% to 10% resveratrol in ethanol without any fiber-forming additive could be encapsulated in the PCL ultrafine fibers, although they alone cannot be made into a fiber form. In vitro, the degradation and drug release rate of the core-shell structured composite nanofibers containing resveratrol exhibited a sustained release characteristic: a fast initial release was followed by a smooth release over 170 h.

#### 4.3.3. β-cyclodextrin nanosponges

Nanosponge-based formulations have recently been developed for resveratrol delivery [76]. β-CD nanosponges were prepared by crosslinking β-CD dissolved in dimethylformamide with carbonyldiimidazole at two ratios, 1:2 and 1:4. The nanosponges were loaded with resveratrol at weight ratios of 1:5 and 1:10. Encapsulation efficiency was between 30 and 40%, and particle size ranged from 400 to 500 nm. Encapsulating resveratrol in β-CD nanosponges improved its solubility in water by factors of 33 to 48, respectively for nanosponges 1:2 and 1:4 complexes in 1:5 weight ratios, while also improving its photostability and in vitro release. Increased cytotoxicity on HCPC-I cells was observed together with higher ex vivo accumulation of resveratrol in rabbit buccal mucosa, plus good ex vivo permeation in pig skin. The authors concluded that resveratrol-loaded nanosponges were viable for oral and topical delivery systems [76].

#### 4.3.4. Acoustically active lipospheres (AALs)

Microbubbles of perfluorocarbons stabilized by phospholipid coating and referred to as 'acoustically active lipospheres' (AALs), have been developed for site-specific delivery of resveratrol through ultrasound treatment after i.v. administration [77]. Resveratrol was solubilized in coconut oil which formed a film around the perfluoropentane or perfluorohexane microbubbles. The microbubbles were coated with soybean phosphatidylcholine and cholesterol, and formed lipospheres of 250–350 nm in diameter with high encapsulation rates of about 90%. Compared to the in vitro drug release rate from the free form, AALs slowed resveratrol delivery from 50 μg/cm$^2$/h to 10–40 μg/cm$^2$/h depending on the various AAL systems tested, thus supporting future application for sustained drug release.

#### 4.3.5. Lipid-core nanocapsules

Polymeric lipid-core nanocapsules have been loaded with *trans*-resveratrol to improve its biodistribution and decrease its intensively fast metabolism [78]. *Trans*-resveratrol was encapsulated into nanocapsules through the interfacial polymer deposition approach, which led to a 99.9% encapsulation efficiency. The nanocapsules were about 240 nm in size, 0.16 in polydispersity and −14 mV in zeta potential. The pH of the formulations was about 5.2. These characteristics remained stable after 3 months of storage at room temperature. In vivo distribution evaluation in healthy rats showed significantly higher concentrations of *trans*-resveratrol in the brain,

liver and kidney vs. free *trans*-resveratrol after i.p. and oral administration. Further, given that resveratrol is a potent cyclooxygenase-1 inhibitor, the authors also evaluated the gastrointestinal damage following daily administration of *trans*-resveratrol for 14 days. They found improved gastrointestinal safety with *trans*-resveratrol-loaded lipid-core nanocapsules. Hence, the lesional indexes in the animals treated with the nanocapsules were reduced 6 to 9-fold vs. free *trans*-resveratrol in the duodenum, jejunum and ileum following oral as well as i.p. treatment [78].

*4.3.6. Solid lipid nanoparticles (SLNs)*

To investigate cell uptake, transport and internalization of resveratrol in keratinocytes, Teskac and Kristl [79] prepared solid lipid nanoparticles (SLNs) by a melt-emulsification process with glyceryl behenate, hydrogenated soybean lecithin and poloxamer 188. Average hydrodynamic diameter and loading capacity were estimated at 180 nm and 85%, respectively. Results showed that SLNs released resveratrol in a sustained manner. The SLNs passed rapidly through keratinocyte membranes, causing no significant changes in cell morphology, metabolic activity or cell cycle. The SLNs prevented the keratinocytes against the cytotoxic effects induced by resveratrol alone.

*4.3.7. Resveratrol incorporated in liposomes*

The possibility of using liposomal incorporation to improve the efficacy of resveratrol on cell proliferation, photoprotection [80] and the cell-stress response [25] has been investigated. Empty small oligolamellar vesicles with mean diameter of 70–100 nm were prepared by sonication and extrusion before adding the resveratrol. Entrapment efficiency was above 70% [25,80]. These studies proved that inclusion in liposomes improved resveratrol stability and biological activity against UV-B-induced oxidative damage [80] and decreased the cytotoxicity of resveratrol at high concentrations, even at 100 μM, avoiding its immediate and massive intracellular distribution [25,80]. Liposomes acted as an inert carrier system allowing a sustained release of resveratrol.

More recently, Narayanan et al. [81] developed the liposomal encapsulation of a combination of curcumin and resveratrol to synergistically improve their bioavailability and enhance their anti-tumor effect against prostate cancer. In vivo, oral administration of the liposome- encapsulated curcumin–resveratrol in prostate-specific PTEN-knockout mice induced an increase in both resveratrol and curcumin levels in the serum and prostate tissue, and enhanced chemoprotective efficacy in prostate cancer [81].

Liposomal resveratrol formulations designed for i.v. administration have also shown interesting properties. Resveratrol was incorporated within the lipid bilayer to a final molar ratio ranging from 0.3 to 11 mol% total lipid. Encapsulation of resveratrol in liposomes was primarily active as solubilizer and reached about 5 $mg.\mu mol^{-1}$ of total lipid. The encapsulation process conferred protection against *trans–cis* isomerization, with 70% *trans*-resveratrol still present after 16 min of UV light exposure vs. just 10% when resveratrol was exposed in its free form. In vivo, i.v. injection of 5 $mg.kg^{-1}$ body weight of resveratrol in nude Balb/c female mice with subcutaneous head and neck squamous-cell carcinoma led to a significant roughly 70% reduction in tumor volume [82].

*4.3.8. Biodegradable nanoparticles*

Shao et al. encapsulated resveratrol into the hydrophobic core of biodegradable nanoparticles prepared by nanoprecipitation of the amphilic block copolymer methoxy poly(ethylene glycol)-poly(caprolactone) [83]. The freeze-dried resveratrol-loaded nanoparticles were about 90 nm in diameter and demonstrated over 90% encapsulation efficiency. After an initial burst of over a 50% release in 5 h, resveratrol was delivered in a sustained manner from the core-shell nanoparticles. The encapsulation process combining resveratrol and biodegradable nanoparticles efficiently demonstrated a superior ability to penetrate cell membranes and a better efficacy against glioma cells than free resveratrol. In addition, Lu et al. [84] showed that these resveratrol-loaded nanoparticles efficiently shielded cultured PC12 cells against β-amyloid peptide-induced damage by attenuating oxidative stress and affecting apoptosis without long-term cytotoxicity. The authors hypothesized that administering resveratrol via an injectable and biodegradable drug delivery system might be a potential therapeutic tool.

*4.3.9. Emulsion–liposome blends and emulsions*

Blends of emulsions and liposomes have also been developed for resveratrol delivery [85]. These blends were composed of coconut oil, soybean lecithin, glycerol formal and non-ionic surfactants, and achieved about 70% encapsulation. These systems retarded the release of resveratrol both in the presence and absence of plasma in vitro. In an experimental model of common carotid artery-induced restenosis in rats, the i.p. injection of the emulsion–liposome blends of resveratrol significantly reduced vascular intimal thickening.

The same authors also evaluated two emulsion systems, i.e. one with and one without vitamin E, and an oil free aqueous micellar system for resveratrol delivery [86]. The three types of formulation, incorporating 0.2% resveratrol, had mean droplet sizes of 100–130 nm, 60–140 nm and 30–100 nm, respectively. In vitro, they retarded resveratrol release in the order aqueous micellar system>emulsion with vitamin E>emulsion without vitamin E. In vivo, after daily i.p. injections repeated for 21 days (7 days prior to and 14 days after induction of arterial injury), they limited neointimal hyperplasia in rats, without significant difference between the three formulations. The authors concluded that oil-in-water emulsification of resveratrol could be a central approach in the search for an aqueous formulation system.

## 5. Future opportunities for resveratrol delivery

The development of the therapeutic potential of resveratrol can only be applied in vivo if the limitations tied to its bioavailability can be overcome. Research is currently exploring different means of enhancing resveratrol bioavailablility, including i) co-administration with resveratrol metabolism inhibitors in order to prolong its presence in vivo, ii) the use of resveratrol analogs possessing a better bioavailability, iii) investigation into the activity potential of resveratrol metabolites, and iv) drug delivery system design with the onus on nanotechnology [87]. Concerning the first approach, some authors have evaluated the opportunities for enhancing the pharmacokinetic parameters of resveratrol by partially inhibiting its glucuronidation via a co-administration with inhibitors, thereby slowing its elimination. Johnson et al. [88] used piperine, an alkaloid derived from black pepper, in vivo to inhibit glucuronidation, and observed a 1544% increase in the maximum serum resveratrol concentration, a 229% enhancement of the area under the concentration curve expressing the degree of exposure to resveratrol, and a two-fold increase in $T_{max}$ after single oral administration in healthy mice. There is also increasing interest in the second strategy, consisting in evaluating novel naturally-occurring and/or synthetic analogs of resveratrol possessing the same structural backbone but with chemical modifications resulting in superior efficacy [27,89]. Kapetanovic et al. [90] studied the naturally-occurring dimethylether analog of resveratrol, pterostilbene (3,5-dimethoxy-4′-hydroxy-*trans*-stilbene), and compared its absolute and relative bioavailability to that of resveratrol in healthy rats. A single i.v. administration of equimolar doses (10 $mg.kg^{-1}$ resveratrol and 11.2 $mg.kg^{-1}$ pterostilbene), as well as repeated oral administration for 14 days (50–150 $mg.kg^{-1}.d^{-1}$ resveratrol and 56–168 $mg.kg^{-1}.d^{-1}$ pterostilbene) resulted in a 3- to 4-fold higher bioavailability and total plasma levels of both the parent compound and its metabolites for pterostilbene than for resveratrol. Further studies are needed to determine whether the improved pharmacokinetics

of pterostilbene vs. resveratrol is associated with higher efficacy in vivo. There is speculation that resveratrol metabolites may retain some activity [10,16,33,45], making it necessary to lead further studies on the effects of metabolites, including a possible deconjugation to free resveratrol in the target tissues [45]. Indeed, despite being quickly metabolized, resveratrol presents undeniable activity in experimental models. Among the numerous resveratrol metabolites, piceatannol (3,5,3′,4′-tetrahydroxy-*trans*-stilbene), which results from the conversion of resveratrol by the cytochrome P450 enzyme CYP1B1, significantly decreased dextran sulfate sodium- induced inflammatory injury and upregulated iNOS expression in the same way as resveratrol did in mouse colitis [91].

Finally, the design of drug delivery systems able to enhance resveratrol bioavailability is particularly promising. While conventional forms such as tablets or capsules [43,46,47] are only mentioned in clinical studies evaluating resveratrol bioavailability in humans, research is currently focused on exploring multiparticulate forms in the millimeter to micrometer range and colloidal carriers in the nanometer range. As for route of administration, research has leaned towards oral forms as they allow easy chronic administration, but parenteral forms which escape intestinal metabolism are also envisaged for acute treatment. Alternative routes such as buccal and topical routes have attracted only marginal interest. Conventional formulations alone probably cannot bring solutions to the physicochemical and pharmacokinetic limitations governing resveratrol bioavailability. On the other hand, innovative multiparticulate formulations offer promising perspectives in terms of resveratrol protection and stabilization, along with sustained release and targeting potentials.

For all current formulation attempts, the main issue is to determine whether the drug delivery system is efficient at improving the pharmacokinetic profile of resveratrol and at promoting its therapeutic effects in vivo. Most studies have focused on developing controlled-release forms of resveratrol, and many have shown improved resveratrol solubilization and/or stability and encouraging in vitro release properties. However, to date, of the 28 studies inventoried, only 10 have implemented in vivo evaluations, including 6 pharmacokinetic studies in healthy rats and 4 real assessments of therapeutic effects in pathological experimental models.

From a pharmacokinetic standpoint (Table 2), improving resveratrol aqueous solubility alone was not sufficient to improve its bioavailability. Hence, Das et al. [65] prepared water-soluble i.v. and oral formulations of resveratrol with HP-β-CD and RM-β-CD and studied the impact of aqueous solubility and dose manipulation on the pharmacokinetics of resveratrol in healthy Sprague–Dawley rats. Although complexation with HP-β-CD and RM-β-CD was able to largely increase resveratrol solubility, the pharmacokinetic profile of resveratrol showed no change after i.v. administration. Similarly, the oral bioavailability of resveratrol remained uninfluenced by formulation type (resveratrol-CDs-inclusion complexes in solution and resveratrol in suspension) or by dose escalation (15–50 $mg.kg^{-1}$) [65]. As for the formulations designed to achieve targeted and sustained release of resveratrol, integrating resveratrol metabolism into drug design has been fruitful in developing systems intended for colon-specific delivery in the treatment of colon cancer and colitis [71–74]. Since resveratrol undergoes extensive metabolism in the enterocyte and hepatocyte following oral administration, it proved essential to design adapted formulations preventing early release in the upper gastro-intestinal tract and allowing delayed delivery for local activity in the colon. The multiparticulate formulations based on calcium or zinc-pectinate networks have been modified with glutaraldehyde [71,72], polyethyleneimine [74] and chitosan [73] to successfully achieve a colon-specific drug release profile with delayed plasma appearance, higher $T_{max}$ and lower $C_{max}$ than resveratrol in suspension following a single administration of 25 $mg.kg^{-1}$. Along the same lines, in an attempt to improve resveratrol biodistribution and decrease its metabolism, lipid-core nanocapsules designed for brain delivery in the treatment of Alzheimer's disease demonstrated higher tissue concentrations than free resveratrol after both single and repeat oral and i.p. administration of 5 $mg.kg^{-1}$ of resveratrol [78]. Interestingly, to date, this has been the only study to underline the gastro-intestinal toxicity potential of resveratrol following repeated oral administration and to show improved gastro-intestinal safety with lipid-core nanoencapsulation [78]. These promising formulations warrant further evaluation in disease models in order to determine whether improving the pharmacokinetics of resveratrol is associated with enhanced therapeutic efficacy in vivo.

From a therapeutic standpoint (Table 3), a few resveratrol formulations have been tested in pathological models of cancers [81,82] or endothelial injury [85,86] in rodents. Although these models did not provide pharmacokinetics data on resveratrol, all 4 studies reported significant biological effects of resveratrol in vivo as an anti-cancer [81,82] and anti-atherosclerotic [85,86] drug. Of note, only one study used the oral route, with a relatively high dose of 50 $mg.kg^{-1}$ of resveratrol administered once or repeatedly [81], while the 3 other studies evaluated i.v. or i.p. injections of lower doses, i.e. 1 $mg.kg^{-1}$[85,86] to 5 $mg.kg^{-1}$[82]. While it is essential to gain a complete understanding of resveratrol metabolism in order to design formulations with improved bioavailability, route of administration and relevant therapeutic dose remain to be established depending on the biological effect expected, the organ or tissue to be targeted, and the disease to be treated [92].

The perspectives now lie in the development of innovative formulations that are able to overcome all the limitations governing resveratrol bioavailability as a pre-requisite to securing efficient and sustained delivery in vivo. It is equally important not to lose sight of the potential toxicity issues over the excipients employed in the formulations (particularly organic solvents) as well as over resveratrol itself, whose effects could be either beneficial or detrimental depending on the dose [93,94].

## 6. Conclusion

Resveratrol has been linked to many health-promoting properties in humans, and its favorable effects are now beyond question. However, a combination of several limiting factors including poor water solubility, limited chemical stability and high metabolization means that resveratrol demonstrates very poor bioavailability, especially by oral route. The major challenge now facing successful development of resveratrol therapies for human patients is to enhance its bioavailability. In this context, there are promising perspectives for the development of pharmaceutical formulations geared specifically to resveratrol delivery.

Even though individually correcting some of the above-mentioned shortcomings is not sufficient to impact positively on resveratrol bioavailability, some of the approaches currently in development are posting promising results. Hence, while the enhancement of resveratrol solubility alone through complexation with β-CD does not modify its pharmacokinetic profile, increased solubility through encapsulation in liposomes has the added benefit of also improving resveratrol stability and leads to significant anti-tumor response in vivo following oral and parenteral administration.

Therefore, the future for efficient resveratrol delivery lies in the development of innovative formulation strategies that are able to overcome each of the physicochemical, pharmacokinetic and metabolic limitations that characterize resveratrol. This objective may be achieved via intelligent drug carriers able to associate protection, controlled release, and targeting functionalities.

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**Table 2**
Influence of formulation on resveratrol pharmacokinetics in healthy rats.

| Formulation | Dose of resveratrol and route of administration | Experimental model | Pharmacokinetic characteristics (plasma appearance/$T_{max}$/$C_{max}$) | Reference |
|---|---|---|---|---|
| β-cyclodextrin, hydroxypropyl-β-cyclodextrin and randomly methylated-β-cyclodextrin / resveratrol complexes | 15–25–50 $mg.kg^{-1}$ — single gavage<br>5–10–25 $mg.kg^{-1}$ — single i.v. injection | Sprague–Dawley rats | No improvement of oral bioavailability vs. resveratrol in suspension whatever the dose tested<br>No modification of i.v. bioavailability vs. resveratrol sodium salt solution whatever the dose tested (non-linear elimination at 25 $mg.kg^{-1}$) | [65] |
| Colon-targeted zinc-pectinate microparticles ± glutaraldehyde | 25 $mg.kg^{-1}$ — single surgical intragastric administration | Sprague–Dawley rats | Pharmacokinetic profile typical of a colon-specific release with glutaraldehyde-modified microparticles (4 h/7–8 h/125 $ng.ml^{-1}$) vs. glutaraldehyde-free formulation (2 h/3–4 h/120 $ng.ml^{-1}$) and resveratrol in suspension (5 min/0.08–0.25 h/270 $ng.ml^{-1}$) | [71] |
| Colon-targeted calcium-pectinate microparticles ± glutaraldehyde | 25 $mg.kg^{-1}$ — single surgical intragastric administration | Sprague–Dawley rats | Pharmacokinetic profile typical of colon-specific release with glutaraldehyde-modified microparticles (3 h/7–8 h/116 $ng.ml^{-1}$) vs. glutaraldehyde-free formulation (2 h/3–4 h/150 $ng.ml^{-1}$) and resveratrol in suspension (5 min/0.08–0.25 h/270 $ng.ml^{-1}$) | [72] |
| Colon-targeted zinc–pectin microparticles ± chitosan | 25 $mg.kg^{-1}$ — single surgical intragastric administration | Sprague–Dawley rats | Pharmacokinetic profile typical of a colon-specific release of resveratrol with delayed appearance of drug in plasma (5 h) followed by steady increase in plasma concentration up to 9 h for the composite zinc–pectin–chitosan formulation | [73] |
| Colon-targeted calcium-pectinate beads ± polyethyleneimine | 25 $mg.kg^{-1}$ — single surgical intragastric administration | Sprague–Dawley rats | Pharmacokinetic profile typical of a colon-specific release with polyethyleneimine-modified beads (when pH of the crosslinking solution adjusted to 1.5) (2 h/6–7 h/112 $ng.ml^{-1}$) vs. polyethyleneimine-free beads (2 h/3–4 h/150 $ng.ml^{-1}$) and resveratrol in suspension (5 min/0.08–0.25 h/270 $ng.ml^{-1}$) | [74] |
| Polymeric lipid-core nanocapsules | 5 $mg.kg^{-1}$ — single gavage or i.p. injection<br>5 $mg.kg^{-1}$ daily for 14 days — gavage or i.p. injection | Wistar rats | Significantly higher concentrations of resveratrol in the brain, liver and kidney after oral and i.p. administration ($p<0.001$ to 0.05) vs. free resveratrol<br>Improved gastrointestinal safety | [78] |

**Table 3**
Influence of formulation on resveratrol efficacy in pathological models.

| Formulation | Dose of resveratrol and route of administration | Experimental model | Biological effects | Reference |
|---|---|---|---|---|
| Liposomes | 50 mg.kg$^{-1}$ — single gavage<br>50 mg.kg$^{-1}$ — gavage 3 times a week for 7 weeks | B6C3F1/J mice<br>and prostate-specific PTEN-knockout mice | Synergistic increase of resveratrol and curcumin bioavailability (in B6C3F1/J mice)<br>Significant decrease of total number of adenocarcinomas with the combination of lipo-curcumin and lipo-resveratrol vs. untreated PTEN-knockout mice (100 vs. 400, $p<0.001$) | [81] |
| Liposomes | 5 mg.kg$^{-1}$ each 3 days (duration not specified) — i.v. injection | Balb/c nude mice with subcutaneous head and neck squamous-cell carcinoma | Inhibition of tumor growth by 70% ($p<0.05$ vs. empty liposomes) | [82] |
| Emulsion–liposome blends | 1 mg.kg$^{-1}$ daily for 7 days prior to and 14 days after induction of arterial injury — i.p. injection | Sprague–Dawley rats with common artery-induced restenosis | Significant reduction of vascular intimal thickening ($p<0.05$ vs. saline) | [85] |
| Emulsions | 1 mg.kg$^{-1}$ daily for 7 days prior to and 14 days after induction of arterial injury — i.p. injection | Sprague–Dawley rats with common artery-induced restenosis | Significant reduction of vascular intimal thickening ($p<0.05$ vs. saline) | [86] |

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