Resveratrol and cyclodextrins, an easy alliance: Applications in nanomedicine, green chemistry and biotechnology

Philippe Jeandet, Eduardo Sobarzo-Sánchez, Md. Sahab Uddin, Roque Bru, Christophe Clément, Cédric Jacquard, Seyed Fazel Nabavi, Maryam Khayatkashani, Gaber El-Saber Batiha, Haroon Khan, et al.

Resveratrol and cyclodextrins, an easy alliance: Applications in nanomedicine, green chemistry and biotechnology

Philippe Jeandet,[a,b,*] Eduardo Sobarzo-Sánchez,[c,d] Md. Sahab Uddin,[e,b] Roque Bru,[f] Christophe Clément,[a] Cédric Jacquard[a], Seyed Fazel Nabavi[g], Maryam Khayatkashani[h], Gaber El-Saber Batiha,[i] Haroon Khan,[j] Iwona Morkunas,[k] Franscesco Trotta[l], Adrian Matencio[l] and Seyed Mohammad Nabavi[g]

[a]*University of Reims Champagne-Ardenne, RIBP EA 4707 USC INRAE 1488, SFR Condorcet FR CNRS 3417, 51100 Reims Cedex, France*

[b]*Pharmakon Neuroscience Research Network, Dhaka, Bangladesh*

[c]*Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, Campus Vida, 15782 Santiago de Compostela, Spain,*

[d]*Instituto de Investigación e Innovación en Salud, Facultad de Ciencias de la Salud, Universidad Central de Chile, Chile*

[e]*Department of Pharmacy, Southeast University, Dhaka, Bangladesh*

[f]*Plant Proteomics and Functional Genomics Group, Department of Agrochemistry and Biochemistry, Faculty of Science, University of Alicante, Alicante, Spain*

[g]*Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran 14359-16471, Iran*

[h]*Amol University of Special Modern Technologies, Amol, Iran*

[i]*Department of Pharmacology and Therapeutics, Faculty of Veterinary Medicine, Damanhour University, Damanhour 22511, AlBeheira, Egypt*

[j]*Department of Pharmacy, Faculty of Chemical and Life Sciences, Abdul Wali Khan University Mardan, 23200, Pakistan.*

[k]*Department of Plant Physiology, Poznań University of Life Sciences, Wołyńska 35, 60-637 Poznań, Poland*

[l]*Department of Chemistry, University of Turin, via P. Giuria 7, 10125, Turin, Italy*

*Corresponding author: Philippe Jeandet, philippe.jeandet@univ-reims.fr

Abstract

Most drugs or the natural substances reputed to display some biological activity are hydrophobic molecules that demonstrate low bioavailability regardless of their mode of absorption. Resveratrol and its derivatives belong to the chemical group of stilbenes; while stilbenes are known to possess very interesting properties, these are limited by their poor aqueous solubility as well as low bioavailability in animals and humans. Among the substances capable of forming nanomolecular inclusion complexes which can be used for drug delivery, cyclodextrins show spectacular physicochemical and biomedical implications in stilbene chemistry for their possible application in nanomedicine. By virtue of their properties, cyclodextrins have also demonstrated their possible use in green chemistry for the synthesis of stilbene glucosylated derivatives with potential applications in dermatology and cosmetics. Compared to chemical synthesis and genetically modified microorganisms, plant cell or tissue systems provide excellent models for obtaining stilbenes in few g/L quantities, making feasible the production of these compounds at a large scale. However, the biosynthesis of stilbenes is only possible in the presence of the so-called elicitor compounds, the most commonly used of which are cyclodextrins. We also report here on the induction of resveratrol production by cyclodextrins or combinatory elicitation with methyljasmonate in plant cell systems as well as the mechanisms by which they are able to trigger a stilbene response. The present article therefore discusses the role of cyclodextrins in stilbene chemistry both at the physico-chemical level as well as the biomedical and biotechnological levels, emphasizing the notion of "easy alliance" between these compounds and stilbenes.

1. Introduction

Discovered in 1939 by Takaoka in the roots of the white hellebore and subsequently identified as a phytoalexin, that is, small biocidal molecules produced by plants as a response to stress, in grapevine (Langcake and Pryce, 1976) and peanut (Ingham, 1976), resveratrol, which belongs to the rather restricted chemical group of stilbenes, has mainly been the focus of studies undertaken by the phytopathologists' community until the onset of the 90s (Jeandet et al., 2002; Jeandet et al., 2010; Jeandet et al., 2021). At the time, works mainly targeted its biosynthetic pathway (Langcake and Pryce, 1977), antifungal activity (Adrian et al., 1997) and metabolism *in planta* (Jeandet et al, 1997) as well as by fungi (Breuil et al. 1998). The first reports on the production of resveratrol by grape berries (Creasy and Coffee, 1988; Jeandet et al., 1991) quickly led to the detection of this compound in wine by Siemann and Creasy (1992). The originality of the seminal work of these two authors was to put in relation the already known properties of resveratrol in traditional Chinese and Japanese medicine (Nonomura et al., 1963) and the cardioprotective effects of a moderate consumption of a wine rich in polyphenols in a population subjected to a hyperlipidemic diet, the so called famous "French Paradox" (Renaud and de Lorgeril, 1992). These convergent studies between the concentration of resveratrol in wine and its possible beneficial effects on human health, has led to a real explosion of the research on this compound at the end of the 90s, an interest which has not been denied since. John Pezutto, whose team was the first to demonstrate the cancer chemoprotective activity of this compound even evoked the "phenomenon resveratrol" (Jang et al., 1997; Pezzuto, 2011). Resveratrol and its derivatives, the number of which now exceeds a thousand, have been the subject of relatively recent bibliographic reviews (Jeandet et al., 2021; Keylor et al., 2015; Rivière et al., 2012; Shen et al., 2009).

From a biological point of view, resveratrol exhibits a cytotoxic activity against many cancer cell lines as well as anti-inflammatory properties (Cai et al., 2015; De Sa Coutinho et al., 2018; Rauf et al., 2018; Varoni et al., 2016). There is a certain amount of preclinical and clinical evidence of its efficacy in the treatment of cardiovascular diseases (Zordosky et al., 2015) and of resveratrol action as a blood pressure lowering agent (Prysyazhna et al., 2019). Resveratrol was also described as being able to play a protective role in case of neurodegenerative diseases such as Alzheimer, Huntington and Parkinson, through its antioxidant activity (Bastianetto et al., 2015; Uddin et al., 2020; Uddin et al., 2021). Resveratrol displays antifungal properties against phytopathogens (Adrian et al. 1997; Gabaston et al., 2017) or fungi responsible for candidiasis in humans (Houillé et al., 2014). Finally, resveratrol and its derivatives have excellent cosmetic properties as whitening agents for the treatment of melanin skin spots (Boo, 2019; Jeandet et al., 2016). One can therefore see without being exhaustive, that resveratrol and in general stilbenes, possess many biological activities. However, most of these properties are based on studies conducted *in vitro*. Several obstacles limit the study of the biological activity of resveratrol and its derivatives *in vivo*. The first one is the weak water-solubility of most stilbenes as well as their low bioavailability in humans and rats, as observed after oral administration; these features being quite common with polyphenols (Kapetanovic et al., 2011; Walle, 2011; Walle et al., 2004). In addition, having these compounds in adequate quantities for the design of biological tests *in vivo* is hampered by the difficulty of obtaining them by pure

chemical synthesis, which is a time-consuming as well as an environmentally unfriendly process (Keylor et al., 2016; Snyder et al., 2011). Bio-producing stilbenes using biological systems, mainly plant tissue cultures or cell suspensions in response to molecules capable of eliciting their synthesis, also provides an interesting alternative in terms of available quantities and green processes (Donnez et al., 2009; Jeandet et al., 2020; Martinez-Marquez et al., 2016). To address these fundamental questions, we show in this review how cyclodextrins, which are cyclic molecules built from a few glucose units, constitute valuable allies in the chemistry of stilbenes. The design of nanomolecular sponges using cyclodextrins capable of increasing the solubility, inclusion and delivery of stilbenes to their target cells is a first example. Use of cyclodextrins can also provide interesting applications in the green synthesis of stilbenes, particularly, for obtaining water-soluble glucosylated derivatives. Finally, the eliciting properties of cyclodextrins on the biosynthesis of stilbenes, not only of monomeric stilbenes but also of oligomeric stilbenes, can be applied in plant biotechnology for the natural sourcing of these compounds.

2. Stilbene chemistry and biosynthesis: a condensed overview

Phytostilbenes are generally low molecular weight compounds varying from 212 Da for pinosylvin (3,4-dihydroxystilbene) or 228 Da for resveratrol (3,5,4'-trihydroxystilbene) (Fig. 1) and up to 1587 Da for pauciflorol D, a resveratrol heptamer identified in *Vatica pauciflora* (Ito et al., 2004). All these compounds contain a 1,2-diphenylethylene structure based on the C6-C2-C6 backbone. The work of Stephenson's group has demonstrated very brilliantly that all stilbenes, comprising oligomers varying in number and structure, are derived from a single block, resveratrol, making this compound the iconic molecule of this group (Keylor et al., 2015). Resveratrol biosynthesis hails from the phenylpropanoid pathway, which is common to lignins and flavonoids (Jeandet et al., 2020; Nabavi et al., 2020) (Fig. 2). This pathway begins with the oxidative deamination of phenylalanine, an amino acid which drains 30% of all the carbon assimilated during photosynthesis (Qian et al., 2019). This first reaction, catalyzed by phenylalanine ammonia lyase (PAL), leads to cinnamic acid, the hydroxylation of which at position 4 yielding *para*-coumaric acid, is ensured by cinnamate-4-hydroxylase, an enzyme from the cytochrome P450 hydroxylase superfamily. In a secondary way, *para*-coumaric acid can be obtained directly from tyrosine *via* TAL (tyrosine ammonia lyase) (see Jeandet et al., 2021 for a review). The final condensation between the *para*-coumaroyl-coenzyme A formed by ligation of *p*-coumarate with a coenzyme A (CoA) molecule *via* a CoA ligase and three malonyl-CoA units formed from the glycolysis-derived acetyl-CoA, is catalyzed by stilbene synthase during an iterative condensation process including the loss of four molecules of CO_2 (Austin and Noel, 2003; Austin et al., 2004).

Once the trihydroxystilbene skeleton of resveratrol is built, a high level of chemical diversification of stilbenes is then obtained thanks to various decorating enzymes like prenylases, hydroxylases as well as glucosyl and methyltransferases (Jeandet et al., 2021). These enzymes lead to different monomeric stilbenes, some of which are described in this work: hydroxylated stilbenes, piceatannol and oxyresveratrol; methylated stilbenes, pterostilbene and glucosylated stilbenes, polydatin or piceid and 4'-β-*O*-D-glucosyl resveratrol (Fig. 1). On the other hand, the subsequent polymerization of resveratrol takes place through the action of plant peroxidases. The condensation

of the phenoxyl radicals formed from resveratrol upon the action of peroxidases, does not take place in a randomized manner but in a defined order including various coupling modes (Keylor et al., 2015). Aside from their glucosylated derivatives, stilbenes, like many polyphenols, are poorly water-soluble compounds with low bioavailabilty (Jeandet et al., 2020; Smoliga and Blanchard, 2014).

3. Resveratrol solubility and bioavailability

While being less lipophilic than its demethylated derivative pterostilbene (Fig. 1), resveratrol is a hydrophobic compound as shown by a log P value of 3.0 to compare with that of methylated stilbenes (log P> 4) (Caruso et al., 2011). Due to its relative lipophilic character, resveratrol can easily cross membranes and seems to be well transferred in human bioengineered epithelia (Walle et al., 2006). Although resveratrol displays promising and beneficial properties for human health, most of the data obtained stemmed from *in vitro* experiments carried out with cell cultures, tissues or bioengineered tissues (Walle, 2011). The main problem encountered with drugs displaying poor aqueous solubility is they cannot easily reach the target cells or tissues at sufficient concentrations to exert their action. *In vivo* studies of resveratrol bioactivity have addressed questions regarding its absorption and bioavailability. Some key parameters commonly used in pharmacokinetics are the area under the curve, AUC, the maximal plasmatic concentration, C_{max} (and the maximal time t_{max} to reach C_{max}), half-life value, $t_{1/2}$ and drug bioavailability, *F*. Mathematically, the AUC of a given drug corresponds to the sum of its instantaneous concentrations in the plasma for a given (0 to t) time interval. AUC is described by the following relation in case of a system with one compartment:

$$\mathrm{AUC}_0^{\mathrm{t}} = \int_0^{\mathrm{t}} \mathrm{C}_0\, \mathrm{e}^{-\mathrm{kt}}$$

Here, C_0 is the initial drug concentration in the plasma and k is the elimination constant of the drug

The bioavailability of a drug is the fraction of the drug which reaches the systemic circulation when it is administered *via* non-intravenous routes as compared to the intravenous one. *F* can be calculated (in %) according to the formula given below with an orally administered drug:

$$F = \left[\frac{\mathrm{AUC_{OA}} \times \mathrm{dose_{IVA}}}{\mathrm{AUC_{IVA}} \times \mathrm{dose_{OA}}}\right] \times 100$$

Where AUC_{OA}= AUC oral administration; AUC_{IVA}, AUC intravenous administration; $dose_{IVA}$, drug dose via the intravenous route and $dose_{OA}$, drug dose *via* oral administration.

The pioneering studies of Goldberg et al. (2003) and Walle et al. (2004), respectively, have shown that upon oral administration of 25 mg doses of various wine polyphenols including resveratrol or the single oral administration of 25 mg radiolabelled resveratrol in humans, this compound seemed to display an unusual high absorption rate (70%) at the gastro-intestinal tract level (GIT) when addressing the sum of all its metabolites (both glucuronated and sulfated ones). However, Walle et al. (2004) concluded that the bioavailability of *non-metabolized* resveratrol

remains at a very low level of around 1%. In fact, resveratrol is rapidly transformed in the small intestine by enterocytes where it undergoes either glucuronidation or sulfation implicating glucuronidases (Böhmdorfer et al., 2017; Springer and Moco, 2019) and sulfotransferases (Böhmdorfer et al., 2017; Boocock et al., 2007; Miksits et al., 2005; Springer and Moco, 2019; Wu et al., 2011), a certain fraction of these sulfo- and glucurono-derivatives entering the portal circulation (Springer and Moco, 2019). Some studies have reported moderate *F* values for resveratrol following oral administration as compared to intravenous dosing in rats: 38.8% (Kapetanovic et al., 2011; Lin et al., 2009) and 29.8% (Kapetanovic et al., 2011). Surprisingly, the more hydrophobic and less polar pterostilbene (3,5-dimethoxy-resveratrol) was found to reach substantial *F* values, 12.5% (Lin et al., 2009) and 66.9% (Kapetanovic et al., 2011).

Preclinical and clinical experiments conducted in human groups after oral administration of resveratrol in the form of repeated doses ranging from 30 to 5000 mg per day, revealed varying but generally low resveratrol peak plasma concentrations (C_{max}): 0.56 - 2967.325 ng/mL (Brown et al., 2010; Draijer et al., 2016; Howells et al., 2011; La Porte et al., 2010; Novotny et al., 2017; Springer and Moco, 2019; Wightman et al., 2015; Wong et al., 2011), pterostilbene displaying higher total plasma levels (C_{max}: 2820-7880 ng/mL) (Kapetanovic et al., 2011). All the afore-mentioned works underlined poor bioavailability of resveratrol after oral administration *via* single or repeated dosing. Such limitations have thus opened the way for the search of alternative methods to increase resveratrol/derivative bioavailability. Some of them such as the use of cyclodextrins as nanocarriers for the transport of resveratrol as well as utilization of cyclodextrins for the green synthesis of more polar and soluble resveratrol derivatives, are described in the following sections of this review.

4. Cyclodextrins as nanomolecular carriers and their use

Biological membranes represent a barrier for the penetration, delivery and therapeutic action of many drugs (Bonnet et al, 2015). Targeted drug solubilizers for oral, transdermal, transmucosal or parenteral formulations are thus needed to overcome these limitations (Stella and Rajewski, 2020). Drug vectorization has been achieved through use of various nanocarriers including liposomes, dendrimers and polymeric nanoparticles of range size from 1 to 1000 nm, namely for cancer treatment (Din et al., 2017). Among these, cyclodextrins have revealed very interesting properties as nano-vehicles for many drugs (Bonnet et al, 2015; Giwani and Vyas, 2015; Pinho et al, 2014) as well as themselves displaying antiviral properties (Jones et al., 2020) and cytotoxic effects at high concentrations on diverse cancer cell lines (Argenziano et al., 2020). Cyclodextrins (CDs) have already been used as nanocarriers for established anticancer drugs like camptothecin (prostate cancer) (Gigliotti et al., 2016), paclitaxel (ovarian, breast and lung cancers) (Ansari et al., 2011a), erlotinib (non-small cell lung cancer) (Dora et al., 2016) and tamoxifen (breast cancer) (Torne et al., 2013). Cyclodextrins were also employed for the release of many other drugs, for example, anti-inflammatory drugs such as acetyl salicylic acid (Shende et al., 2012), oxaprozin (Mennini et al., 2016), antivirals such as rilpivirine (Rao et al., 2018), the anti-HIV1 protease inhibitor lopinavir (Adeoye et al., 2020), antifungals like econazole (Sharma et al., 2011) and antibacterial drugs such as norfloxacin (Mendes et al., 2018). Cyclodextrin-mediated drug delivery has been experimented in case of neurodegenerative diseases, as well. Molecularly-imprinted cyclodextrin nanoparticles have

indeed been designed for the dihydroxyphenylalanine (DOPA)-prodrug delivery in the treatment of Parkinson's disease (Trotta et al., 2016a) as well as for facilitating the crossing of the blood-brain barrier of crocetin, a natural inhibitor of amyloid β plaque formation in the treatment of Alzheimer's disease (Wong et al., 2020) among other nanovectors used for anti-Alzheimer's drug delivery (Wong et al., 2019). CDs are safe products approved by the Food and Drug Administration (FDA) (Stella and Rajewski, 2020). CDs themselves do not display any biological activity unless employed at very high concentrations (Argenziano et al., 2020).

The French Chemist Villiers observed in 1891 that potato starch seeded with *Bacillus amylobacter* (*Clostridium butyricum*) yielded, besides dextrins, two carbohydrates forming "beautiful crystals" in low amounts, named cellulosines and which were attributed a multiple of the following formula [$(C_6H_{10}O_5)_2$ + 3 H_2O] (Crini, 2014). A long time after, the two crystals obtained by Villiers were identified by Manor and Saenger (1972) as being more likely α-cyclodextrin with the formula [$(C_6H_{10}O_5)_6.6H_2O$] and β-cyclodextrin. Cyclodextrins form cyclic oligosaccharidic assemblies constituted of several α-1,4-linked glucopyranose units (hereafter named as glucose units). They are mainly composed of six (CD6) (α-cyclodextrins), seven (CD7) (β-cyclodextrins) and eight glucose units (CD8) (γ-cyclodextrins) (Bonnet et al., 2015; Gidwani and Vyas, 2015). This cyclic oligosaccharidic structure delimits at the supramolecular level a sort of truncated cone as imposed by the peculiar location of the primary hydroxyl groups of the α-D-glucopyranose units on one rim of the structure being the secondary hydroxyl groups on the other (Sandilya et al., 2020) (Fig. 3). CDs thus comprise an inner hydrophobic cavity with the sugar hydroxyl groups being externally oriented (Bonnet et al., 2015). Cyclic structures composed of a lower number of glucose units (< CD5) were not known and reputed not to allow stable conformations of glucose units until the recent work of Yamada group demonstrating the feasibility of the synthesis of smaller cyclodextrins such as CD3 (three glucose units) and CD4 (four glucose units), which could be utilizable for the inclusion of therapeutic molecules of very small size (Ikuta et al., 2019).

Cyclodextrins not only improve the solubility and above all the bioavailability of hydrophobic compounds including both synthetic and natural drugs, they provide them with protection against numerous environmental conditions such as light, pH and temperature variations, oxidation and enzymatic degradation (Bonnet et al., 2015; Kanaya et al., 2011; Pinho et al., 2014). Internalization of drugs within cyclodextrins is related to the cyclodextrin cavity size including the inner and outer diameters which are on average the following: 57/137 nm, 78/153 nm and 95/169 for α-, β- and γ-cyclodextrins, respectively (Gidwani and Vyas, 2015; Stella and Rajewski, 2020) (Fig. 3). Torus shape and opening of α-cyclodextrins are thought to be too tight to permit the formation of inclusion complexes with many drugs leading to the preferential use of β-cyclodextrins, even γ-cyclodextrins for high-molecular weight drugs (Stella and Rajewski, 2020). However, measurement of the binding affinity energy of various cyclodextrins for resveratrol reported, for example, very close values (-5.4 Kcal/mol and -5.3 Kcal/mol) for β- and γ-CDs, respectively (Haley et al., 2020).

As surprising as it may seem, β-cyclodextrins (β-CDs) possess an aqueous solubility eight to twelve-fold lower than the other two main cyclodextrin groups (α- and γ-CDs) (Connors, 1997; Sabadini et al., 2006; Saenger et al., 1998; Sandilya et al., 2020; Szejtli, 1998), though they constitute the preferred CDs as drug carriers in many experiments for their low cost of production and cavity

size best suited for numerous drugs (Stella and Rajewski, 2020). The solubility of β-CDs has thus been increased through chemical modifications of the glucose secondary hydroxyl groups. These include methylated β-CDs (mono-, di- and trimethylated CDs as well as randomized methylation of the cyclodextrin core), hydroxy-alkylated β-CDs (mainly hydroxypropyl-β-CDs, HP-β-CDs), various glucosyl-β-CDs (glucosyl-β-CDs, G1-β-CDs and maltosyl-β-CDs, G2-β-CDs) and sulfonic acid-β-CD derivatives (sulfobutylether-β-CDs) (Bonnet et al., 2015; Gidwani and Vyas, 2015; Lucas-Abellan et al., 2007; Pinho et al., 2014; Stella and Rajewski, 2020; Sandilya et al., 2020) (Fig. 4). Substituting groups may be chosen with a specific goal. Some studies have selected CD derivatives not subject to changes of the ionization state of the substituents in relation with pH variations. For instance, sulfobutylether CDs containing sulfonates or sulfates are stable in the anionic state at physiological pH (Stella and Rajewski, 2020). CDs such as HP-β-CDs, have also been used in combination with biopolymer-liposomes (Soo et al., 2016; Tan et al., 2021). All these types of CDs have been employed for the vectorization of resveratrol and its derivatives (see next section).

Cyclodextrin chemistry has switched to other ways including the synthesis of hypercross-linked materials named CD-polymers when consisting of slightly condensed and water soluble cyclodextrins on one hand, or cyclodextrin-based nanosponges, which are highly polymerized and insoluble CDs, on the other. CDs of increased site specificity in drug delivery as a response to a given stimulus are termed stimuli-responsive CD nanosponges and have been developed more recently (Ciesielska et al., 2020; Dhakar et al., 2019; Palminteri et al., 2021; Yasayan et al., 2020). The three-dimensional mesh polymer network generated by the cross linking of the CD monomers thus forms nanocavities for various drug inclusion (Adeoye et al., 2020). Cross linking may occur upon the condensation of CDs with reagents such as carboxylic acid dianhydrides (pyromellitic dianhydride) leading to carboxylate CDs (Adeoye et al., 2020; Ciesielska et al., 2020), carbonyldiimidazole yielding carbonyl-CDs (Ansari et al., 2011b; Dhakar et al., 2019; Yasayan et al., 2020) (Fig. 5) or 1,6-diisocyanatohexane for the fabrication of polymerized CDs (Haley et al., 2020). For example, condensation of two β-CDs with pyromellitic dianhydride yielded a CD polymer increasing by 12 to 14- fold the solubility of the anti-HIV1 drug, lopinavir (Adeoye et al., 2020).

To deliver drugs in a more specific way, a lot of stimuli-responsive nanosystems-based CDs were conceived (Palminteri et al., 2021; Tayo, 2017). Inclusion of photochromic moieties into nanocarriers generates light responsive systems whose light-induced modification can lead to conformational changes of the carrier and consequently drug release (Babin et al., 2009; Wajs et al., 2016). Another option for modifying nanocarriers is the addition of ionizable groups such as carboxylates or amines to build pH-responsive drug transporters (Manchun et al., 2012; Wu et al., 2016). Differences in pH between tumor and inflammation tissue environments and normal healthy tissues, with the tumor microenvironment being more acidic than normal tissues (Boedtjker and Pedersen, 2020), may justify the building of pH-responsive nanosponges for anticancer and anti-inflammatory drug delivery (Lin et al., 2017; Wu et al., 2016). A similar reasoning applies to the synthesis of temperature-responsive nanosystems (Cheng et al., 2008; Kim and Matsunaga, 2017) which is based on the fact that hyperthermia is associated with pathological processes. Redox-responsive nanocarriers are particularly interesting to exploit the property of certain cancer tissues to contain significantly higher levels of glutathione (GSH) than normal ones, where these high GSH

amounts are linked to tumoral progression and resistance to chemotherapy (Kennedy et al., 2020). Disulfide bonds present in some redox-responsive nanocarriers are easily reduced by enzymes of the thioredoxin family localized in the cytoplasm, endoplasmic reticulum or even lysosomes in the presence of GSH (Arunachalam et al., 2000). Disulfide bond-containing nanovehicles have thus appeared as particularly useful for site-specific drug delivery and, namely, for resveratrol (Daga et al., 2016; Trotta et al., 2016b) (Fig. 6).

Before focusing on resveratrol complexation with CDs, let us remember briefly that CD encapsulation has already been reported for many polyphenols (Pinho et al., 2014). In order to improve the water solubility, thermal stability, photostability as well as the bioavailability of these compounds, numerous works have described the synthesis of inclusion complexes between flavonoids and CDs, among others: β-CD–rutin complexes for increased antibacterial activity (Paczkowska et al., 2015), β-CD–quercetin inclusion complexes for establishing potent nose-to-brain drug carriers (Manta et al., 2020), hydroxypropyl-β-CD encapsulation of naringenin for anti-inflammatory effects (Gratieri et al., 2020), daidzein and genistein inclusion complexes with hydroxypropyl- and sulfobutylether-β-CDs as part of a combined therapy for mucopolysaccharidosis (Fumic et al., 2018), and curcumin crosslinked CD nanosponges for cancer treatment (Rafati et al., 2019).

5. Physico-chemical aspects of resveratrol/stilbene complexation by cyclodextrins:

Formation of inclusion complexes between cyclodextrins and “guest” molecules is defined by two important physico-chemical parameters, the stoichiometry of the internalization process and the binding constant *K* between cyclodextrins and guest compounds, which are given by the following equations in case of a 1:1 stoichiometry (Lopez-Nicolas et al., 2009b):

$$\mathrm{CD} + \mathrm{guest} \leftrightarrows \mathrm{CD:guest}$$

$$K = \frac{[\mathrm{CD:guest}]}{[\mathrm{CD}]\ \mathrm{x}\ [\mathrm{guest}]}$$

where [CD], [CD-guest] and [guest] are concentrations at the equilibrium.

A stoichiometry of 1:1 is corresponding to an inclusion formed by one cyclodextrin with one guest. The stoichiometry becomes 1:2 (or more) in case of a cyclodextrin fixing two (or more) guests and 2:1 for one guest molecule being complexed with two (or more) molecules of cyclodextrins (Pinho et al., 2014). A 1:1 stoichiometry in the CD inclusion complexes formed with resveratrol, pinosylvin, oxyresveratrol, piceatannol (Matencio et al., 2016) or pterostilbene is generally the rule (see Table 1 and references therein), except pinosylvin where a 1:2 stoichiometry is observed (Silva et al., 2014). The stability or the complexation constant *K* (notated K_c or K_f) measures the strength of the association between the drug and the ligand. Otherwise speaking, *K* characterizes drug affinity for CDs (Jambhekar and Breen, 2016). The higher this constant, the higher the interaction between stilbenes and CDs (Bertacche et al., 2006). Values of *K* differ according to the structure of the

internalized stilbenes and the type of CDs being in the magnitude order of 10^2-10^4 M^{-1} (see Table 1 and references therein). The lowest K_c value recorded was 606.65 ± 30.18 M^{-1} for oxyresveratrol complexation on methyl-β-CDs (Matencio et al., 2017) and the highest one, 35864.72 ± 3415.89 M^{-1} for oxyresveratrol inclusion on hydroxypropyl-β-CDs (He et al., 2019). According to some authors, high values of *K* may be detrimental to drug release from the inclusion complex (Stella et al., 1999; Venuti et al., 2014). Increase in the observed anticancer effects of resveratrol-loaded CDs was not found to be in line with the gain in resveratrol solubility observed upon resveratrol complexation with various CDs as compared to free resveratrol (Dhakar et al., 2019; Palminteri et al., 2021; Venuti et al., 2014). For example, around only 65% inhibition of cell viability on MCF-7 human breast cancer cells were recorded with 150 μM resveratrol + sulfobutylether- β-CD and 55% inhibition with free resveratrol despite an increased observed solubility of resveratrol of around 37-fold (0.03 mg/mL against 1.1 mg/mL). This was attributed to a high complexation constant *K* of 10114 M^{-1} maybe explaining a higher retention of this compound (Venuti et al., 2014). Almost similar results were obtained regarding inhibition of a DU-145 prostate cell line:75% inhibition with a carbonyl-β-CD and 65% with resveratrol at 100 μM for a 3-fold enhanced solubility of resveratrol (0.04 mg/mL against 0.12 mg/mL) (Dhakar et al., 2019).

Among the various CDs available, the common ones, α-CDs, β-CDs and γ-CDs have been used for the complexation of resveratrol and its derivatives (Fig. 7) (Bertacche et al., 2006; He et al., 2019; Kumpugdee-Vollrath et al., 2012; Li et al., 2018; Lopez-Nicolas et al., 2009a and 2009b; Lu et al., 2009; Lucas-Abellan et al., 2007; Soussi et al., 2019). There are many studies reporting on the application of derivatized CDs to form inclusion complexes with resveratrol: hydroxypropyl-β-CDs (HP-β-CDs) (Berta et al., 2010; Bertacche et al., 2006; He et al., 2019; Kong et al., 2020; Kumpugdee-Vollrath et al., 2012 ; Li et al., 2018; Lim et al., 2020; Lopez-Nicolas et al., 2009a and 2009b; Lu et al., 2009; Matencio et al., 2017; Sapino et al., 2009.; Silva et al., 2021), glucosylated-β–CDs like the maltosyl-β-CD (G2-β-CD) (Lucas-Abellan et al., 2008), methylated or ethylated-β-CDs such as monomethylated/ethylated-β-CDs (Li et al., 2018; Lopez-Nicolas et al., 2009a and 2009b; Matencio et al., 2017; Trollope et al., 2014), dimethylated-β-CDs (DIMEB) (Bertacche et al., 2006; Kumpugdee-Vollrath et al., 2012) and randomly-methylated-β-CDs (RAMEB) (Duarte et al., 2015) (Table 1). As aforementioned, sulfobutylether β-CDs are well suited for both neutral and cationic substrates due to their stability in the anionic state at various pH values (Stella and Rajewski, 2020; Venuti et al., 2014).

Finally, hypercross-linked CD nanosponges where the 3D mesh between CD units is established through carbonyl, carboxylate and disulfide bonds (Ansari et al., 2011b; Dhakar et al., 2019; Matencio et al., 2020; Palminteri et al., 2021; Pushpalatha et al., 2018) or constituted of polymerized α-, β- and γ-CDs with 1,6-diisocyanotohexane (Haley et al., 2020), have been employed for resveratrol vectorization. In these intricated systems, resveratrol is internalized both in the inner cavities of CDs and the interstitial spaces managed between the cross-linked CDs thus increasing resveratrol loading efficiency (Dhakar et al., 2019). The most promising vectors for resveratrol are represented by the so-called bio-responsive nanosponges which constitute site-specific delivery systems for this compound (Ciesielska et al., 2020; Dhakar et al., 2019; Palminteri et al., 2021, Trotta et al., 2016b; Yasayan et al., 2020).

Generally, resveratrol solubility increases in parallel with the resveratrol-CD molar ratio, solubility being optimal for a resveratrol-CD ratio of 1:4 (Pushpalatha et al., 2018; Sapino et al., 2009) (see Table 1). A solubility diagram of resveratrol recorded at pH 6 revealed an increasing solubility of this stilbene with increased CD concentrations approaching a plateau at the 1:4 resveratrol-CD ratio (Sapino et al. 2009). Resveratrol solubility may also depend on chemical modifications of CDs taking place on hydroxyl groups upon its complexation with CDs. Phase solubility diagrams showed an 8.5-fold increase in resveratrol solubility with β-CD and a 24-fold increased solubility with a HP-β-CD, these values almost doubling when the respective CD concentrations underwent a two-fold increase (Lu et al., 2012). Stilbene or resveratrol complexation with CDs always leads to an increase in their water-solubility ranging from 2-fold (Dhakar et al., 2019) to the unbelievably high value of 700,000-fold recorded by Silva et al. (2014) (Table 1). Resveratrol Inclusion complexes formed with γ-CDs were also reported as enhancing its solubility in lemon juices from 4.8% to 43.1%, *i.e.*, a 9-fold increase (Silva et al., 2021). In some studies, a higher solubility of resveratrol (Lu et al., 2009) or polydatin (Li et al., 2018) was observed with HP-β-CDs than with non-derivated β-CDs (Table 1).

Two parameters are particularly useful in drug nanoformulation: drug loading on- and drug release from the nanoparticles. These factors are essential for determining the efficiency of the drug delivery process. Resveratrol loading on nanoparticles which can be expressed as %, is the ratio between entrapped resveratrol and CD weight (Palminteri et al., 2021). Its values vary from 4 to 7% in polymerized α, β and γ-CDs depending on the CD type (Haley et al., 2020), from 9.95 to 16.12% in GSH-responsive nanosponges as a function of the resveratrol/CD weight ratio (Palminteri et al., 2021) and from 30-40% in carbonyl nanosponges (Ansari et al., 2011b; Matencio et al., 2020) to more than 90% in both carboxylate and carbonyl nanosponges (Pushpalatha et al., 2018) (Table 1). The notion of drug loading can also be extended to the determination of the drug encapsulation efficiency (%), which is defined as the ratio between entrapped resveratrol in CDs and total resveratrol concentration in the mobile phase (Palminteri et al., 2021). The values of around 80% obtained for resveratrol and oxyresveratrol confirm a high encapsulation rate of stilbene compounds in nanosponges (Dhakar et al, 2019; Palminteri et al., 2021) though it can be lower (29%) (Wang et al., 2020). Resveratrol loading efficiency is enhanced in conjunction with the stilbene-CD weight ratio of the inclusion complex (Ansari et al., 2011b; Palminteri et al., 2021). Resveratrol loading passed from 9.95% to 16.12% on glutathione-responsive nanosponges for weight ratios of respectively 1:2 and 1:4 (Palminteri et al., 2021) and 11.93% (1:2 weight ratio) to 16.78% (1:6 weight ratio) for oxyresveratrol (Dhakar et al., 2019).

Release of resveratrol (or derivatives) from CDs or CD-nanosponges was expressed as the drug dissolution rate with time using the membrane diffusion method (Dhakar et al, 2019; Palminteri et al., 2021) or determined by measuring resveratrol release from resveratrol-loaded polymerized CDs in a liquid medium (Haley et al., 2020). Release of resveratrol or oxyresveratrol from various CDs and CD-nanosponges increased by 2 to 8 fold at different timing (1, 3 or 24 h) compared to their dissolution rate in the free forms (Bertacche et al., 2006; Dhakar et al., 2019; Palminteri et al., 2021; Pushpalatha et al., 2018). Resveratrol complexation with HP-β-CDs and its further inclusion into biopolymer-liposomes led to a 100% loading, a value superior to its incorporation to both the CD and

the double layer of liposomes (94.4%), though the former complex allowed a two-fold increase in resveratrol delivery (Table 1) (Soo et al., 2016).

6. Pharmacokinetic profile of resveratrol formulated with cyclodextrins

There are numerous *in vitro* studies describing the characteristics of stilbene-CD inclusion complexes (Table 1), however, works on the pharmacokinetic parameters of resveratrol complexed with CDs stemming from *in vivo* studies and following different modes of administration are less numerous (Das et al., 2008; Kong et al., 2020; Pushpalatha et al., 2018) compared to flavonoids (Dos Santos Lima et al., 2019). The seminal work of Das et al. (2008) provided the first pharmacokinetic profiles regarding resveratrol-CD formulations. In this study, intravenous administration of resveratrol was carried out in rats with HP-β-CD while oral absorption of resveratrol was performed using RAMEB-β-CD (randomly methylated-β-CD) and compared to a suspension of this compound in carboxymethylcellulose (CMC). Although resveratrol internalization with CDs increased its solubility by 59,500 fold, the $AUC_{0\rightarrow 5h}$ (505.9 ng x h/mL) following resveratrol-HP-β-CD intravenous administration at a dosing of 10 mg/kg did not significantly differ from intravenous injection of the plain compound (10 mg/kg resveratrol in a sodium salt suspension) with an $AUC_{0\rightarrow 5h}$ of 532.9 ng x h/mL. Oral formulation of resveratrol with RAMEB-β-CD at the dose of 50 mg/kg both increased C_{max} and t_{max} without significantly modifying $AUC_{0\rightarrow 8h}$ (1009 ng x h/mL) nor resveratrol bioavailability (*F*=39.9%) as compared to the CMC resveratrol suspension ($AUC_{0\rightarrow 8h}$= 981 ng x h/ mL; *F* = 38.8%) (Das et al., 2008) (Table 2). However, using two sorts of resveratrol-CD nanosponges, one carbonyl nanosponge formed by crosslinking β-CD with diphenylcarbonate (R-NS I) and a carboxylate one fabricated from β-CD and pyromellitic dianhydride (R-NS II), a significant resveratrol loading efficiency of around 91% (Tables 1 and 2) was recorded in rats following a 20 mg/kg oral absorption of R-NS I and R-NS II compared to resveratrol alone as well as a two-fold increase in C_{max} and AUC values ($AUC_{0\rightarrow 24h}$: 4145 and 3917 ng x h/ mL *vs* 2080 ng x h/ mL) (Pushpalatha et al., 2018) (Table 2).

In a comparative study performed in rats, pulmonary administration (orotracheal intubation) of resveratrol-HP-β-CD inclusion complexes in various dosages were evaluated against intravenous, intra-gastric and nasal inhalation administration (Kong et al., 2020). Reported data showed better pharmacokinetic profiles (C_{max}, $AUC_{0\rightarrow 10h}$, $AUC_{0\rightarrow\infty}$) according to the trans-pulmonary route *vs* all other routes with decreasing *F* values, 92.95% (pulmonary administration), 76.31% (nasal inhalation) and only 16.68% (intra-gastric route) (Table 2). A 5-fold increase in resveratrol bioavailabilty was thus recorded between pulmonary administration and the intra-gastric route.

These studies therefore indicate that resveratrol bioavailability upon inclusion with cyclodextrins can be increased by a factor 2 when using CD-nanosponges compared to oral administration of the unloaded compound (Das et al., 2008; Pushpalatha et al., 2018). It also depends on its mode of administration (Kong et al., 2020).

7. Stilbene/cyclodextrin inclusions increase stilbene photostability

Generally, the complexation of stilbenes with CDs or nanosponges has a positive effect on their photostability (Allan et al., 2009; Bertacche et al., 2006; Cheng et al., 2018; Dhakar et al., 2019; He et

al., 2019; Li et al., 2018; Pushpalatha et al., 2018; Sapino et al., 2009; Silva et al., 2014) and thermostability (He et al., 2019). Light exposure can indeed be very detrimental to highly photosensitive compounds or drugs. Complexation with CDs has namely been described to delay photodegradation of the light versatile vasodilatator nifedipine (Bayomi et al., 2002). It is well established that the natural isomer of resveratrol (and its derivatives) is the *trans* form which easily yields the *cis* isomer within a few minutes of UV or sunlight exposure (Jeandet et al., 1997; Trela and Waterhouse, 1994). Bertacche et al. (2006) reported that only α-CD was efficient in protecting resveratrol from sunlight as compared to the larger β- and γ-CDs, though all CDs were found to confer resveratrol stability against UV radiations of 254 and 365 nm. It was suggested that the three-dimensional network constituted by CDs (Sapino et al., 2009) or nanosponges (Dhakar et al., 2019; Pushpalatha et al., 2018) negatively affects light scattering due to a screening effect.

8. Reported benefits of stilbene/cyclodextrin inclusion complexes

All data tend to demonstrate that inclusion of resveratrol and its derivatives in CDs improves their solubility as well as loading on-and release from CDs (Table 1 and references therein). Most of the experiments conducted *in vitro* or *in vivo* which have been put in place to validate the benefits of stilbene internalization in CDs on their biological activity, may principally resume in the study of the antioxidant capabilities and cytotoxic actions of the complexes obtained. Besides, other works have reported the usefulness of stilbene inclusion with CDs for biomedical applications *in vivo* (Haley et al., 2020; Lacerda et al., 2017; Lacerda et al., 2018; Soussi et al., 2019).

8.1. Antioxidant activity of stilbene-cyclodextrin inclusion complexes

The antioxidant activity of stilbene-CD inclusion complexes was mainly evaluated by their capacity to enhance scavenging of stable radicals such as $DPPH^{\cdot}$ (Dhakar et al., 2019; Duarte et al., 2015; Haley et al., 2020; Li et al., 2018; Lu et al., 2009; Sapino et al., 2009), $ABTS^{+\cdot}$ and $SO^{+\cdot}$ (Silva et al., 2021) or the lipid peroxidation state (Lu et al., 2012). There is converging evidence in some studies that internalization of stilbenes in CDs or nanosponges increases their antioxidant properties compared to the free compounds. For example, the reducing power of polydatin as determined with the Fe^{3+}/ferricyanide complex as well as its $DPPH^{\cdot}$ radical scavenging activity were respectively enhanced by 2 and 1.5-fold upon inclusion with CDs, the best performances being observed with HP-β-CD (Li et al., 2018) (Table 3). Dhakar et al. (2019) recorded a 75% $DPPH^{\cdot}$ radical inhibition activity with resveratrol-carbonyl-β-CD nanosponges *vs* 45% (1.7 fold-increase) with the plain compound at a 100 μM concentration. The same trend was also reported with oxyresveratrol-carbonyl-β-CD nanosponges at the 50 μM level. Supplementation of lemon juice with resveratrol-γ-CD complexes allowed to maintain juices' antioxidant capacity over 28 days compared to free resveratrol supplementation possibly leading to pertinent application in functional food (Silva et al., 2021). In the same way, a strong inhibition of lipid peroxidation was described with resveratrol-CD complexes (Lu et al., 2012). Haley et al. (2020) showed in a pilot study, that localized resveratrol delivery performed with polymerized α-, β- and γ-CDs maintained a significant $DPPH^{\cdot}$ radical scavenging activity in the oxidative stress microenvironment generated by implanted intracortical microelectrodes, which are

used in the treatment of several neurological disorders increasing their operating time. This work thus adds value to the utilization of resveratrol inclusion CD complexes for potential applications in neurology (Table 3).

At the opposite, no beneficial role of resveratrol encapsulation with CDs was demonstrated in other studies, its antioxidant capabilities being unchanged from resveratrol to resveratrol-CD complexes (Duarte et al., 2015; Lu et al. 2009; Sapino et al., 2009). A strong interaction between CDs and stilbenes and possibly low drug release was reported as a plausible cause for the observed non-significant differences in the scavenging radical capacities of free resveratrol and its inclusion complex with methyl-β-CD despite an increase in resveratrol solubility and loading (Duarte et al., 2015) (Tables 1 and 3). Here, a low enhancement (1.5-fold) in resveratrol release may account for this discrepancy (Duarte et al., 2015).

8.2. Anticancer activity of stilbene-cyclodextrin inclusion complexes

All experimental studies conducted *in vitro* have shown a reduction of the cell viability of various malignant cell lines upon inclusion of resveratrol with CDs or nanosponge complexes *vs* free resveratrol (Table 3). For example, Pushpalatha et al. (2018) noted IC_{50} values for the *in vitro* cytotoxicity of resveratrol carbonyl-β-CD or resveratrol carboxylate-β-CD nanosponges, 65% lower (IC_{50}= 110.70 μM and 117.34 μM) than those of the unloaded compound (IC_{50}=169.98 μM) on MCF-7 human breast cancer cells. A reduced IC_{50} value of 20 μM was observed upon resveratrol inclusion with HP-β-CD for inhibiting the proliferation of 7,12-dimethylbenz[a]anthracene-induced oral cancer cells (HCPC-1 oral squamous cell carcinoma) compared to resveratrol alone (45 μM) (Berta et al., 2010). Moreover, a spectacular regression of exophytic lesions displaying oral squamous cell carcinoma characters was recorded in hamster cheek pouches following topical applications of resveratrol-CD complexes *vs* free resveratrol (Berta et al., 2010). A significantly higher inhibition of cell viability was also reported for oxyresveratrol (-75%) and resveratrol (-70%) loaded on carbonyl nanosponges at the 100 μM concentration on DU-145 prostate cancer cells compared to the free compounds (-60 and -50%, respectively) (Dhakar et al., 2019) (Table 3). At the same 100 μM concentration, a 1.5 fold-increase (40 to 60%), a 4 fold-increase (20 to 80%) and a 6 fold-increase (10 to 60%) were observed in the inhibition of cell viability (from unloaded resveratrol to resveratrol nanosponges) for one prostate cancer line (PC-3) and two colon cancer lines (HT-29 and HCT-116), respectively (Matencio et al., 2020). Reduction in the viability of HT-29 colon cancer cells also shifted from 15% with plain resveratrol to 40% with dual liposome-CD-resveratrol encapsulation complexes at a dose of 100 μM (Soo et al., 2016).

Very marked effects of resveratrol-HP-β-CD or resveratrol-β-CD complexes have been reported regarding the cell viability decrease of HeLa cervical carcinoma cells (-40%) and Hep3B hepatocellular liver cancer cells (-43 to -46%) compared to the only 5% recorded with unloaded resveratrol (Lu et al., 2012). Extensive alterations of the cellular morphology including membrane collapse were also observed with CDs loaded with resveratrol though no such alterations were seen with free resveratrol (Lu et al., 2012). Similar reduction of cell viability (> 90%) was reported upon resveratrol inclusion with other types of CDs such as RAMEB-β-CD *vs* resveratrol (70%) in Caco-2 human epithelial colorectal adenocarcinoma cells (Duarte et al., 2015) or sulfobutylether-β-CDs

(65%) in the MCF-7 breast cancer line than with resveratrol alone (55%) (Venuti et al., 2014). In this latter case, the slight difference observed in the reduction of the cell viability of those cancer cells was attributed to a high binding constant between resveratrol and CDs thus limiting resveratrol release efficiency. Resveratrol-sulfobutylether-β-CDs encapsulated in poly (lactic-co-glycolic acid) nanoparticles, which have been proposed as an inhalable system for resveratrol delivery, displayed a remarkable inhibition of the cell viability of non-small cell lung cancer cells, reducing by respectively 15.39 and 50-fold the IC_{50} against the A549 and H358 cell lines compared to plain resveratrol (Wang et al., 2020).

Glutathione (GSH)-responsive nanosponges were used to selectively target cancer cells with elevated contents of GSH such as some ovarian and breast tumorigenic cell lines (Palminteri et al., 2021). The 3-D mesh of these nanosponges is constituted by the CD cavities and the interstitial spaces managed by the cross linkage of the CDs with pyromellitic dianhydride and disulfure bridges (Fig. 6). The latter are lysed by endocellular enzymes of the thioredoxin family in the presence of high amounts of GSH thus facilitating release of resveratrol in the cell. Nanosponges are internalized in the cells through different endocytosis pathways (Palminteri et al., 2021). At resveratrol concentrations from 100 to 200 μM, a 50-80% inhibition of the cell viability of the OVCAR-3 ovarian cancer cell line and the MDA-MB-231 breast cancer cell line was reported with the resveratrol nanosponges, while a lower reduction in cell viability (-15%) was noted with the resveratrol nanosponges on normal human fibroblasts, the human mammary epithelial cell line MCF-10A or the SK-OV-3 human ovarian malignant cells, demonstrating the selective toxicity of these nanosponges (Palminteri et al., 2021).

8.3. Applications of stilbene-cyclodextrin inclusion complexes in vivo

Stilbene inclusion in CDs and its recognized benefits to increasing the solubility, release and bioavailability of these compounds has received some interesting applications in nanomedicine. For example, Vectisol® formulation of resveratrol, *i.e.* its encapsulation in a monopropane diamino-β-CD, turned out to allow the early recovery of proximal tubular function and glomerular filtration as well as a slowdown of loss of the renal functions in a kidney transplantation preclinical study in pigs thanks to the resveratrol antioxidant properties (Soussi et al., 2019). By reducing oxidative stress in the right ventricle of rats displaying monocrotaline-induced pulmonary hypertension in a *cor pulmonale* model, inclusion of pterostilbene with HP-β-CDs ameliorates the systolic function of the ventricle as well as prevents it from structural alterations such as hypertrophy through an increase of pterostilbene bioavailability (Lacerda et al., 2017). Likewise, pterostilbene encapsulation with HP-β-CDs was shown to preserve *via* a decrease of lipid peroxidation and the regulation of some antioxidant mechanisms, the function of the left ventricle following induced myocardial infarction in rats (Lacerda et al., 2018). Additionally, inclusion of stilbenes in CDs may also have a positive effect by increasing their antimicrobial capabilities. These compounds are indeed known for possessing various antifungal and antimicrobial activities (Vestergaard and Ingmer, 2019). Complexation of pterostilbene with HP-β-CDs, which is reputed to display higher fungitoxicity than its non-methylated counterpart resveratrol, was reported to diminish by 7.5-fold the minimum inhibiting concentration and by 4-fold the minimum bactericidal concentration on growth of *Fusobacterium nucleatum*, a

bacterial pathogen associated with periodontitis, compared to unloaded pterostilbene dissolved in DMSO (Lim et al., 2020).

Numerous works have provided a large piece of evidence that stilbene compounds, mainly resveratrol (Aziz et al., 2005; Boo, 2019; Costa et al., 2016, Lin et al. 2021; Osmond et al., 2012) or pterostilbene (Sirerol et al., 2015) are efficient in preventing ultraviolet-B induced damages of skin, treating cutaneous herpes (Docherty et al., 2004), psoriasis (Kjaer et al., 2015), modulating skin cancer mechanisms or improving melanoma treatment with potential applications in onco-dermatology. CDs have been shown to constitute interesting agents as good vehicles for stilbene delivery and for ensuring high levels of compound penetration as well as safety of the tissues for the treatment of skin or mucosal cancers (Ansari et al, 2011b; Berta et al., 2010; Sapino et al., 2009). Experiments with various matrices including rabbit mucosa (Ansari et al., 2011b), porcine skin (Sapino et al., 2009) and porcine ear skin (Pushpalatha et al., 2019), revealed an increased *ex vivo* skin penetration of resveratrol with resveratrol CD or nanosponge formulations. Resveratrol-nanosponges accumulated at a two-fold higher rate (600 $\mu g/cm^2$) than the plain compound (300 $\mu g/cm^2$) in porcine ear skin (Pushpalatha et al., 2019). A similar trend was reported with resveratrol-HP-β-CDs in porcine skin (Sapino et al., 2009) and resveratrol-carbonyl nanosponges in rabbit mucosa (Ansari et al., 2011b).

9. Implication of cyclodextrins for the green synthesis of stilbene glucosides

Glucosylation of stilbene compounds not only increases their aqueous solubility for potential uses in cosmetic and onco-dermatology but substitution by a glucosyl group at the 4'-position of stilbenes also protects them from oxidation by polyphenol-oxidases such as tyrosinases (Regev-Shoshani et al., 2003). A lot of stilbene β-D-glucosides have been identified so far in plants, namely the 3-*O*-β-D-glucosyl-resveratrol (piceid or polydatin), the 4'-*O*-β-D-glucosyl-resveratrol (resveratroloside) and the 4'-*O*-β-D-glucosyl-piceatannol (Fig. 1) (Jeandet et al., 2020). Research has moved over the past few years toward the synthesis of their α-anomeric counterparts whose aqueous solubility and surfactant properties are superior (Gonzalez-Alfonso et al., 2018; Marié et al., 2018; Ioannou et al., 2021; Shimoda et al., 2015).

The major drawback in the green synthesis of stilbene glucosides is the compatibility of the solvent employed for both the glucose acceptor (here the starting stilbenes) and the enzyme used for glucosylation. For this reason, oftentimes, a compromise between enzyme stability and stilbene solubility is necessary (Jeandet et al., 2020). Making use of green solvents could be the right answer to this paradox. The green synthesis of 3-*O*-α-D-glucosyl resveratrol with sucrose and not CDs as a glucose donor, has already been performed under the catalytic action of a phosphorylase from *Bifidobacterium adolescentis* using a combination of an ionic liquid and a buffer, which considerably increases resveratrol solubility (De Winter et al., 2013). Several works have reported achievement of stilbene *O*-glucosylation with cyclodextrin glucosyl-(glucano)-transferases (CGTases) from various sources as biocatalysts utilizing starch or CDs as glucose donors (Gonzalez-Alfonso et al., 2018; Ioannou et al., 2021; Marié et al., 2018; Mathew et al., 2012; Shimoda et al., 2015; Torres et al., 2011) (Table 4). CGTases have indeed often been employed for the biosynthesis of various polyphenolic glucoside derivatives: epicatechin glucosides (Aramsangtienchai et al., 2011),

kaempferol glucoside (Choung et al., 2017), genistein diglucoside (Han et al., 2017), flavonol and flavanone glucosides (Lee et al., 2017), pinoresinol glucoside (Khummanee et al., 2019) or α-arbutin (Mathew et al., 2013). Torres et al. (2011) have described the use of a monophasic solvent system constituted of a mixture of one organic solvent (DMSO) and acetate buffer for the synthesis of a series of glucoside derivatives of resveratrol. In this synthesis, starch was employed as the primary glucose donor, glucosylation being ensured by the CGTases of *Thermoanaerobacter* or *Bacillus macerens*. Under these conditions, various glucosides of resveratrol were obtained with quite good 50% glucosylation yield, suggesting that CDs arising from the partially hydrolyzed starch were directly implicated in the transfer of the glucosyl moiety to stilbene acceptors. In a similar manner, the enzymatic production of a 4'-*O*-α-glucoside of pterostilbene whose solubility is lower than that of hydroxystilbenes, was described in a monophasic solvent system constituted by DMSO and buffer with the CGTase of *Thermoanaerobacter* and starch as the primary source for glucosyl groups (Gonzalez-Alfonso et al., 2018). However, the high proportion of DMSO in the solvent mixture renders this synthetic route unsuitable for the green production of stilbene glucosides.

As aforementioned, CDs allow the increasing of the internalization rate of compounds poorly soluble in water such as stilbene aglycones. Their use is thus particularly conducive to the green synthesis of stilbene glucoside derivatives (Ioannou et al., 2021; Jeandet et al., 2020; Marié et al., 2018). The transfer of an α-glucoside group or more groups from the donor (the cyclodextrin) to the acceptor (the stilbene) may proceed through coupling of the cyclodextrin and the stilbene, which randomly attach to the active site of the CGTase (Lim et al., 2021; Mathew et al., 2012). A plausible mechanism for the formation of a series of piceid (referred as $picG_1$) derivatives considerably varying in the number of the glucosyl groups, has been deciphered under the action of the CGTase of *B. macerans* (Mathew et al., 2012) (Fig. 8). A primary nucleophilic attack of the 4'-hydroxyphenyl group of piceid ($picG_1$) on the Carbon 1 at the reducing end of an opened α-CD, α-maltohexaose, results in an α-(1,4) linkage between piceid and the maltohexaose leading to the release of an initial coupling product called $picG_7$. Following successive disproportionation reactions of $picG_7$, various glucoside derivatives of $picG_1$ like $picG_2$, $picG_3$, etc…are then obtained (Mathew et al., 2012). This mechanism may explain not only the recovery of monoglucosides but also of di and tri-glucosides during resveratrol glucosylation in the presence of CGTases (see below) (Ioannou et al., 2021; Marié et al., 2018, Torres et al., 2011). Polyglucosylated derivatives of 4'-*O*-β-resveratrol-glucoside like 4'-*O*-β-maltoside, 4'-*O*-β-maltotrioside, 4'-*O*-β-maltotetraoside and 4'-*O*-β-maltopentaoside acting as potent inhibitors of phosphodiesterase activity and displaying possible neuroprotective properties, were obtained through a synthetic route including α-CD and a plant CGTase in a medium totally free from organic solvent (Shimoda et al., 2015). One may pay attention to the fact that in this case, only the β-anomeric forms were obtained instead of the commonly recovered α-glucosides (Table 4).

The CGTase-catalyzed synthesis of hundred milligrams of α-*O*-D- mono and diglucosides of resveratrol (3 and 4'-α-*O*-D-glucosyl resveratrol as well as 3 and 4'-α-*O*-D-maltosyl resveratrol) was performed more recently at the 2-L bioreactor scale in water (MES buffer) with the CGTase from *Thermoanaerobacter* sp. (*Toruzyme*) and β-CD as a glucose donor (Marié et al., 2018) (Fig. 9). Maximization of the glucosylation transfer was achieved *via* the optimization of multiple factors such as pH, temperature, enzyme and donor amount as well as the resveratrol:CD ratio, performing a 35%

yield based on molar concentrations. This yield increases up to 50% when a 1 kDa cut-off membrane is coupled to the enzymatic reactor thus allowing retention of the resveratrol β-CD inclusion complex in the medium and increasing the transfer rate of the glucoside derivatives formed in the permeate such that they are protected from further hydrolysis (Ioannou et al., 2021). The production rates of the 3 and the 4'-*O*-α-glucosides of resveratrol were almost similar indicating the absence of any regioselectivity in the glucosylation process on the stilbene moiety (Marié et al., 2018) (Table 4).

Glucosylation of stilbenes increases their water-solubility making them utilizable for topical applications in case of cutaneous disorders for cosmetics and onco-dermatology (Intagliata et al., 2019). Torres et al. (2011) indeed noted a 67-fold increase in the solubility of resveratrol-α-glucosides compared to resveratrol. Likewise, pterostilbene, which is an almost insoluble compound in water, has its solubility reaching 0.1 g per liter upon glucosylation (Gonzalez-Alfonso et al., 2018). Except the study of Shimoda et al. (2015) reporting an increase in the inhibition of phosphodiesterase activity with resveratrol glucosides that suggests their potential for the treatment of neurodegenerative diseases, other works conducted on the biological activity of stilbene glucosides tend to show paradoxically a decrease in their antioxidant and cytotoxic effects with regards to the aglycones (Table 4). By taking resveratrol as the reference compound with an antioxidant activity of 100%, the relative activities of the 3 and the 4'-*O*-α-glucosides of resveratrol were respectively of only 40 and 70% (Marié et al., 2018; Torres et al., 2011) as confirmation that glucosylation on the 4'-position of stilbenes is less detrimental to their biological activity (Regev-Shoshani et al., 2003). Similarly, Gonzalez-Alfonso et al. (2018) reported a near 40% decrease in the antioxidant activity of 4'-*O*-α-glucoside of pterostilbene as well as a significantly lower toxicity on HT-29 colon cancer cells compared to the aglycone.

Apart from the synthesis of stilbene glucosides, use of RAMEB-β–CDs was also found to facilitate hydroxylation of the stilbene core with engineered cytochrome P450 leading to various di- and trihydroxystilbenes and limiting the use of organic solvents to a few percents (Ruhlmann et al., 2017).

10. Cyclodextrins for the induction of stilbene production in plant cell systems

As aforementioned, one major feature of CDs is their ability to form inclusion complexes with poor water-soluble organic molecules due to the hydrophobic character of their central cavity, which thus serve as nano-sized carriers for these molecules in aqueous solutions. In addition to such a remarkable property, CDs are able to interact with plant cells in which they can trigger a defense response. This makes them useful tools to study plant biochemistry and physiology as well as biotechnology aspects. The first evidence for a CD-plant cell interaction arose from experiments run with grapevine cell cultures treated with the phytoalexin resveratrol, either unloaded or complexed with the dimethyl-β-CD (DM-β-CD) in order to evaluate its efficacy as a protecting agent against the phytopathogen *Xylophylus ampelinus*. Although unloaded resveratrol completely disappeared within 48 h, resveratrol loaded on DM-β-CD remained stable in the medium. Unexpectedly, controls treated only with DM-β-CD exhibited an accumulation of resveratrol evidencing for the first time that CDs may act as inducers of *de novo* resveratrol synthesis in grapevine cells (Morales et al., 1998).

As seen before, CDs display a high chemical diversity, including CDs of natural origin with free hydroxyl groups, and the ones of synthetic origin with chemical groups attached to the glucosidic OH groups (Bonnet et al., 2015). The capability of a limited number of β-CDs to induce resveratrol bioproduction was first evaluated in grapevine cell cultures (Bru et al., 2003; Bru et al., 2006). Only chemically modified CDs, *e.g.* methyl- or hydroxypropyl-CDs, induced a strong resveratrol production unlike the natural CDs, which yielded a very weak response. However, sulfated β-CDs, which are frequently used as carriers in pharmaceutical formulations (Stella and Rajewski, 2020), brought about a hypersensitive response in grapevine cells. Bru group's study thus highlighted the importance of the chemical nature of CD-linked groups to raise a cellular response and suggested that one plausible reason for the reported elicitor activity of CDs is their structural similarity to the oligosaccharidic elicitors released from plant cell walls upon plant-fungal interactions. Dimethylated-β-CDs also well-known as DIMEB thus became the gold standard in subsequent research works. Another piece of evidence that CDs differentially interact with plant cells is the species- and genotype-dependent cell resveratrol production observed as a response to a particular cyclodextrin type (Zamboni et al., 2006).

CDs are almost non-toxic for cell cultures and display a superior eliciting activity than other oligosaccharides like chitosan, a major component of fungal cell walls (Ferri et al., 2009). Among the elicitors used to induce stilbene biosynthesis by plant cell or tissue systems, CDs lead to the highest production yields (in the g/L range) (Bru et al., 2003; Bru et al., 2006; Nivelle et al., 2017) compared to other common eliciting molecules derived from jasmonate, like methyljasmonate (MeJA) with reported production levels of only milligrams per liter (Krisa et al., 1999; Tassoni et al., 2005; Santamaria et al. 2010). Further works have shown empirically that combinatory elicitation with CDs and MeJA and, to a lesser extent, CDs plus coronatine, the jasmonate-Ile analog, synergize the effects of each elicitor increasing the production of resveratrol by 5 to 8-fold in grapevine cell suspensions (Almagro et al., 2015; Belchí-Navarro et al., 2012; Lijavetzky et al., 2008; Oilva et al., 2018). Spectroscopic approaches for understanding the synergistic mechanisms existing between CDs and MeJA have reported that resveratrol, CDs and MeJA together in solution formed binary complexes, respectively CD-resveratrol and CD-MeJA but no ternary inclusion complexes (Oliva et al., 2018). CDs were demonstrated to improve the aqueous solubility of the reputed hydrophobic molecule, MeJA, resulting in an increase of resveratrol production by grapevine cells.

Cost is a key issue in biotechnology and the utilization of elicitors like DIMEB and coronatine could turn out to be quite expensive for large scale applications in bioreactors. Attempts to reduce the production costs incurred by CDs have led to a new strategy, such as the use of CD polymers coated with magnetic nanoparticles for the easy recover and reutilization of the elicitor in plant cell cultures for optimizing resveratrol production (Almagro et al., 2020). The obtained results are promising as HP-β-CD coated polymers can be reused up to three times yielding resveratrol levels ranging from 0.3 and 0.5 g/L.

Stilbene production based on the use of CDs has also been accomplished in plant tissue systems like the hairy roots of *Arachis hypogaea*, *Vitis rotundifolia* and *V. vinifera* leading to the accumulation of tens of mg/g dry weight (DW) of resveratrol, piceid and resveratrol dimers in the elicited tissues of grapevine or peanut (Medina-Bolivar et al., 2007; Nopo-Olazabal et al., 2013;

Tisserant et al., 2016). Elicitation resulted in a successful strategy to both enhance the production level of those stilbenes and promote their extracellular accumulation, which is particularly useful for facilitating their extraction from the culture medium. Use of DIMEB was also reported to induce the production as well as modifying the profiles of some isoprenylated stilbenes belonging to the arachidin family (Fig. 1) in the hairy roots of *A. Hypogaea* (Yang et al., 2015; Fang et al., 2020).

Once the feasibility of producing a natural compound or drug by tissue or cell cultures has been demonstrated, the problem arises of transferring the results obtained from the laboratory scale to the industrial production in bioreactors (Donnez et al., 2009; Jeandet et al., 2014; Jeandet et al., 2016). The high stilbene levels recovered in plant cell systems as a response to elicitation with CDs, particularly in grapevine cell cultures, have led to scale up the cultures from shaken flasks to bioreactors. Most grapevine cell cultures well tolerate the typical shear stress of the bioreactor environment, even with a stirred tank (Aumont et al., 2004; Lambert et al., 2019; Nivelle et al., 2017; Vera-Urbina et al., 2013), although some genotypes seem to be more sensitive (Donnez et al., 2011; Ferri et al., 2011). Both bubble column (Vera-Urbina et al., 2013) and disposable bag wave bioreactors (Eibl and Eibl, 2008) are suitable for this purpose. Elicitation of stilbene production with DM-β-CD was successfully performed in bioreactors using the *V. vinifera* and *V. labrusca* cell lines. Recovered stilbene amounts well correlated with the respective achievements in shaken flasks though being slightly higher in bioreactors, most likely due to a better mass transfer. When using DM-β-CD alone, accomplished resveratrol yields were 2.2 and 3 mg/g fresh weight (FW) for *V. vinifera* cv Gamay cultures in V-shaped bubble columns and in stirred tank bioreactors, respectively. Resveratrol amounts rose to 13.5 mg/g FW in each bioreactor (Vera-Urbina et al., 2013) and even reached 14.3 mg/g FW in a 20-litre stirred tank bioreactor upon combinatory elicitation with DM-β-CD and MeJA (Lambert et al., 2019), which further confirms the synergistic effect already mentioned in shaken flasks (Lijavetzky et al., 2008).

Elicitation with cyclodextrins combined with plant metabolic engineering has been disclosed as a successful strategy to diversify the profile of stilbenes and other specialized metabolites produced by cell suspension cultures. For instance, grapevine cells transformed with the *human hydroxylase CYP1B1* (Martinez-Marquez et al., 2016) or the *Rosa hybrida orcinol*-O-*methyltransferase* (Martinez-Marquez et al., 2018) produced significant levels of resveratrol derivatives like piceatannol and pterostilbene, respectively, in addition to resveratrol upon elicitation. Likewise, the transformation of *Sylibum marianum* cultures with the *grapevine stilbene synthase 3* yielded 12 mg/L resveratrol upon elicitation with DM-β-CD, in addition to the accumulation of silymarin and coniferyl alcohol as in the wild lines (Hidalgo et al., 2017).

11. Mechanisms of induction of stilbene production by cyclodextrins

Although CDs, and particularly DM-β-CDs, are known to induce a phytoalexin response in grapevine cells ending up in both the production and the extracellular accumulation of various stilbenes, the understanding of the cellular and molecular mechanisms involved in this response is far from being elucidated. Such events obviously include perception of CDs or their hydrolyzing products at the membrane level and induction of the related signaling pathways, followed by regulation of the key enzymes of stilbene biosynthesis, gene transcription changes as well as modifications of some

membrane transporters. The mechanisms by which CDs are able to trigger the production of resveratrol and related stilbenes in the cell, remain unexplained. A good comparison can be drawn with the induction of a phytoalexin response in soybean cotyledons by middle-chain oligogalacturonides released from the plant cell wall by fungal endo-polygalacturonases (Cervone et al., 1989). It is likely that opening of the CD ring and subsequent hydrolysis of the glucosidic chain may also generate oligosaccharides such as maltoheptaose and maltohexaose with potent eliciting activities on resveratrol biosynthesis.

To decipher the early signaling events taking place during resveratrol biosynthesis induction in the presence of DM-β-CD or DM-β-CD + MeJA, the effect of blockers of extracellular Ca^{2+} fluxes, inhibitors of MAP kinases, NADPH oxidases and Tyr phosphatases as well as NO scavengers was studied in grapevine cell suspensions (Belchi-Navarro et al., 2013). DM-β-CD / MeJA combination turned out to relieve the action of blockers of extracellular Ca^{2+} fluxes, MAPKs inhibitors and NO/H_2O_2 scavengers indicating that Ca^{2+} mobilization, NO and H_2O_2 production, MAP kinases and phosphatases are involved in the early signalization to reach resveratrol production (Fig. 10) (Belchi-Navarro et al., 2013). Remarkably, these effects on signaling pathways resemble those reported for grapevine cell cultures treated with the microbial protein elicitor PG1 (Poinssot et al., 2003, Vandelle et al., 2006).

Transcription factors are major components in the regulation of cellular metabolic events fine-tuning the control of numerous biosynthetic routes including the resveratrol one comprising for example, the *Vitis vinifera* transcription factors VvWRKY24 and VvMyB14 being able to up-regulate *STS* gene expression on one hand, and the negative regulator VvWRKY8 of *STS* gene expression on the other (Fig. 10) (Duan et al., 2016; Jeandet et al., 2019; Jiang et al., 2019; Vanozzi et al., 2018; Wong and Matus, 2017). Transcription factors like MYB15 which activates the transcription of stilbene synthase (STS) (Höll et al., 2013) and the NAC-type which promotes the biosynthesis of phenylpropanoids and monolignols (Mitsuda et al., 2007), are up-regulated by DM-β-CD and further enhanced by DM-β-CD + MeJA (Fig. 10) (Almagro et al., 2014). Numerous biosynthetic enzymes from the connected pathways of shikimate, phenylalanine, phenylpropanoid (PAL, C4H, 4CL), malonyl CoA and stilbene (STS) biosynthesis are up-regulated by DM-β-CD, and DM-β-CD + MeJA to allow a marked carbon flow toward resveratrol biosynthesis (Almagro et al., 2014). Omics analyses conducted on grapevine cell cultures offered an overall picture of the major metabolic events following combined DM-β-CD and MeJA elicitation (Almagro et al., 2014; Martinez-Esteso et al., 2011; Martinez-Marquez et al., 2017). Proteomic changes strongly correlate with transcriptional events, particularly during changes in the activity of the enzymes catalyzing the late resveratrol biosynthetic steps (PAL, STS) (Martinez-Esteso et al., 2011). Taken altogether, it would seem that CDs and combinatory elicitation with CDs and MeJA orchestrate resveratrol accumulation by two strategic actions: (i) activation of *STS* genes transcription; (ii) increase of the precursor supply taking into account that all the precursors of resveratrol biosynthesis are also shared by major competing pathways; *i.e.* monolignol and flavonoid routes. These omic studies also revealed the co-expression of certain glutathione-*S*-transferase isoforms at both the transcript and protein levels. Interestingly, overexpression of a tau class glutathione-*S*-transferase (VvGST U10a) possibly implicated in the transport of resveratrol was observed in grapevine cells upon elicitation with DM-β-CD or DM-β-CD +

MeJA (Martinez-Marquez et al., 2017). Otherwise, combinatory elicitation with DIMEB and MeJA in peanut hairy roots, led to the up-regulation of stilbene dimethylallyltransferases, which are implicated in the transfer of a dimethylallyl pyrophosphate group to various stilbenic compounds, in addition to STS (Yang et al. 2018). This confirms the accumulation of prenylated stilbenes at levels similar with those of resveratrol (Fig. 10) (Yang et al. 2015). Combinatory elicitation is thus also able to activate metabolic steps downstream resveratrol biosynthesis to diversify stilbene profiles.

12. Conclusions and future prospects

The involvement of CDs in the chemistry of resveratrol at both the physico-chemical level as well as the biomedical and biotechnological levels, was underlined in this work. Cyclodextrins can serve as nanomolecular-scale transporters for stilbenes to improve their solubility and bioavailability, thereby ensuring their delivery at the cellular level. Inclusion of resveratrol and stilbenes in cyclodextrins increases their water solubility by a factor of 10 up to 10,000 depending on the studies, allowing them to be used in green chemistry particularly for the synthesis of glucosylated derivatives without the need for organic solvents. Finally, the reported eliciting properties of CDs on the production of stilbenes by tissue or cell cultures in quantities of the order of a few grams, constitutes a third aspect of what we have defined as the easy alliance between stilbenes and cyclodextrins.

As regard the nano-transport of resveratrol and its derivatives, it has generally been shown that CDs improve both their solubility in water and their bioavailability in animal models and, consequently, their anticancer and antioxidant activity as well as their biological properties during experiments carried out *in vivo*, compared to unloaded resveratrol. However, even if the percentage of resveratrol loaded on CDs is elevated, its release from CDs may be hampered in case of high resveratrol-CD association constants. Some authors have indeed suggested that the lack of differences recorded in the biological activity between free and CD-encapsulated resveratrol could be linked to high values of this constant. Regarding bioavailability, it seems that resveratrol inclusion with CDs modifies this parameter increasing it by a factor two when using CD-nanosponges; a significant improvement in bioavailability (more than 5-fold) was also recorded depending on its mode of administration (pulmonary, nasal or intra-gastric) (Das et al., 2008; Kong et al., 2020; Pushpalaha et al., 2018). Further studies are thus needed to study the pharmacokinetic profiles of stilbenes *in vivo* upon nano-encapsulation with CDs.

Stilbene vectorization using CDs is now moving towards the production of more specific systems such as bioresponsive-cyclodextrin nanosponges targeting particular cell types or microenvironments. Trotta's group recently described the inexpensive synthesis of a GSH-responsive CD nanosponge capable of selectively targeting certain types of cancer cells. The crosslinking in this nanosystem contains disulfide bridges whose lysis in the presence of endogenous GSH and endocellular enzymes facilitates drug release. These nanosponges have successfully been studied using the anticancer drug, doxorubicin during *in vitro* experiments (Trotta et al., 2016b). The method was transposed very recently to the design of GSH-bioresponsive nanosponges dedicated to the transport of resveratrol (Palminteri et al., 2021). This type of resveratrol-nanosponges preferentially targets certain models of cancer cells *in vitro* (ovarian, breast and lung cancer cells), which contain higher levels of GSH than other cancer cell types and normal cells. GSH-responsive nanoparticles

transporting resveratrol would therefore have to be further tested *in vivo* for the treatment of specific tumors and the modulation of tumor extracellular matrices in relation to the high GSH levels released by tumor-associated fibroblasts (Palminteri et al., 2021).

Use of CDs for the green synthesis of glucosides of resveratrol and its derivatives has a double benefit, CDs both serve as donors of glucosyl moieties during the complex reactions of transglucosylation in the presence of CGTases and allow the solubilization of these compounds in water and buffer solutions (Ioannou et al., 2021; Marié et al., 2018; Shimoda et al., 2015) or limit to small amounts the incorporation of organic solvents (Gonzalez-Alfonso et al., 2018; Mathew et al., 2012). Quantities of the order of a few hundred milligrams of resveratrol α-glucosides have already been obtained from only 2 g of resveratrol in presence of a β-CD in 2 L-reactors, thus paving the way toward the application to syntheses on a larger scale (Marié et al., 2018). Coupling the enzymatic reactors with membranes with a cut-off threshold of 1 kDa already makes it possible to optimize the accomplished yields (Ioannou et al., 2021).

Unexpectedly, CDs were reported the ability of inducing the production of resveratrol at the gram scale as well as yielding various profiles of stilbenes including hydroxylated, isoprenylated, glucosylated, methylated and oligomeric forms in plant cell or tissue systems. Research in this area will face two challenges: up-scaling the bioproduction of stilbenes at the industrial level and deciphering the mechanisms at the basis of their biosynthesis by plant cells and tissues. There are indeed still many gaps to bridge in the knowledge of the mechanisms by which CDs elicit resveratrol production in grapevine and other plant culture systems. All this requires further efforts, such as the discovery of receptor- and signaling cascade-specific proteins, additional transcriptional regulation players as well as membrane transporters enabling the extracellular accumulation of stilbenes. It would be interesting to carry out a targeted gene expression analysis to explore whether MYB and WRKY transcription factors do respond or not to CD elicitation or combinatory elicitation with MeJA, and which *STS* paralogs are activated to obtain a more complete picture of the regulatory stilbene biosynthesis network in grapevine.

Acknowledgements: Part of this work is the result of an aid to the postdoctoral training and improvement abroad for Dr Adrián Matencio (number 21229/PD/19) and financed by the Fundación Séneca (Región de Murcia, Spain).

Legends of the figures:

Figure 1: Biosynthesis of stilbenes starting from phenylalanine and the alternative route from tyrosine. Abbreviations used: PAL, phenylalanine ammonia lyase; TAL, tyrosine ammonia lyase; C4H, cinnamate-4-hydroxylase; 4CL, 4-cinammoyl-CoA ligase; STS, stilbene synthase; CHS, chalcone synthase; ROMT, resveratrol-*O*-methyltransferase; GT, glucosyltransferases; UDPG, UDP-Glucose; PER, peroxidases

Figure 2: Chemical structures of some stilbene monomers described in this review. Hydroxystilbenes, resveratrol, piceatannol, oxyresveratrol and pinosylvin; stilbene glucosides, piceid, 4'-*O*-β-glucosyl-resveratrol (resveratroloside); methylated stilbenes, pterostilbene; isoprenylated stilbenes; arachidin-1, arachidin-2 and arachidin-3

Figure 3: Schematic representation of the truncated cones formed by the cyclic oligosaccharides of α-(CD6), β-(CD7) and γ-cyclodextrins (CD8). The cyclic oligosaccharidic assembly delimits at the supramolecular level a sort of truncated cone whose inner diameters are increasing according to the CD type.

Figure 4: Simplified structures of some modified β-cyclodextrins (CD7). **1**; R = H, β-cyclodextrin, R= -CH_2-CH[OH]-CH_3, 2-hydroxypropyl-β-cyclodextrin; **2**, R=-CH_3, methyl-β-cyclodextrin; **3**, **3a**, R= -SO_3Na, β-cyclodextrin sulfate, **3b**, R= -$[CH_2]_4$-SO_3Na, sulfobutylether-β-cyclodextrin.

Figure 5: 3D representation of a carbonyl CD nanosponge. This type of nanosponge is obtained by reaction of a β-CD with carbonyldiimidazole yielding the carbonyl CD nanosponge and imidazole. Linking carbonyl groups are colored in red and blue

Figure 6: 3D representation of a GSH-responsive β-CD nanosponge. β-cyclodextrin cycles made of seven α-D-glucose units are linked with the crosslinker pyromellitic dianhydride and ethyldisulfide bridges. Diethylsulfide bridges are colored in yellow, oxygen atoms in red and oxygen-hydrogen bonds in white

Figure 7: Inclusion of resveratrol within the cavity of a β–cyclodextrin (realized by molecular docking)

Figure 8: Hypothetical mechanism of the formation of stilbene glucosides from cyclodextrins. Cleavage of the cycle of the α-cyclodextrin yields an opened α-cyclodextrin named α-maltohexaose. A primary nucleophilic attack of the hydroxyl situated at the 4'-position of piceid on the C1 at the reducing end of maltohexaose leads to an intermediate compound whose disproportionation leads to various piceid glucoside derivatives

Figure 9: Green synthesis of various *O*-α-glucosylated derivatives starting from β-cyclodextrin as a glucose donor with a cyclodextrin glucosyl transferase. **A**, General scheme of the synthesis; **B**, schematic representation of resveratrol inclusion inside the β-cyclodextrin cavity. **1** and **2**, 3 and 4'-α-*O*-D-glucosyl resveratrol; **3** and **4**, 3 and 4'-α-*O*-D-maltosyl resveratrol. Abbreviations: R, resveratrol; β-CD, β-cyclodextrin; CGTase, cyclodextrin glucanotransferase (according to Ioannou et al., 2021)

Figure 10: Regulation of stilbene biosynthesis through combinatory elicitation with dimethyl-β-CD (DIMEB) and MeJA elicitors in grapevine cells. Stilbene biosynthesis involves the production of the early precursors erythrose 4-P (E4P) and phosphenolpyruvate (PEP) from a carbon source through central carbohydrate pathways. The two direct precursors of resveratrol are produced through two diferent pathways: *p-coumaroyl CoA* is a final product of the two early precursors processed *via* the shikimate/aromatic aminoacid biosynthesis/phenylpropanoid serial pathways, and *Malonyl CoA* comes from a parallel processing of PEP through three enzymatic steps. The first stilbene, resveratrol, may undergo derivatization reactions out of which only two have been well characterized to date: methylation by resveratrol-*O*-methyltransferases in grapevine (VvROMT), and prenylation by resveratrol dimethylallyl transferases in peanut (AhR4/3'DT). Resveratrol and prenylated derivatives are found in the extracelular médium, as well. In grapevine cell cultures upon elicitation with DIMEB and DIMEB + MeJA, a tau class glutathione *S*-transferase (VvGSTU2) is putatively involved in the extracelular accumulation of resveratrol as free form or complexed with CDs. Elicitors such as DIMEB and MeJA trigger early signaling events starting from Ca^{2+} income from the apoplastic space that ends up in transcriptional regulation through a only partly established pathway where production of NO, H_2O_2 and participation of protein tyrosine phosphatases (TyrPase) and MAPK is involved. In *Vitis quinquangularis,* a MAPKKK38 transcription factor has been described to enhance the trancription of *STS* genes likely *via* the transcriptional activation of MYB14. In *V. amurensis,* Ca-dependent protein kinases activate the transcription of specific *STS* paralogs. In *V. vinífera,* the best characterized transcriptional activators of *STS* genes are MYB14/15 TFs, that are also able to activate the transcription of shikimate pathway key genes as well as those of *PAL* and *ROMT*. MYB14, WRKY8 and resveratrol are components of a regulatory loop in which MYB14 promotes the production of resveratrol; resveratrol activates the transcription of WRKY8, likely through undisclosed effector proteins, and WRKY8 interacts with MYB14 to block it, thus down-regulating resveratrol levels. Such a negative loop was discovered upon UV light irradiation which activates the transcription of MYB14. Other steps of the phenylpropanoid pathway have also specific transcriptional activators such as WRKY2 and MYB5a, and NAC TFs which are active up-regulators of some key steps of the shikimate pathway. Regulatory entities described in relation with combinatory elicitation with DIMEB and MeJA are shown in orange colour. Blue arrows indicate possible hierarchy between early signaling events. Green and red arrows stand for transcriptional up- and down-regulation respectively; solid lines indicate that the evidence has been validated in targeted experiments while slashed lines means the evidence only comes from omics analysis. Genes encoding for TFs have been labelled in their promoter regions according to the stimulus they respond: elicitor responding (ERE), hormone responding (HRE), UV light responding (UVRE) and resveratrol responding (RRE). DIMEB are symbolized by small troncated structures

1000 **References**

1001

Adeoye, O.; Bartolo, I.; Conceiçao, J.; Da Silva, A.B.; Duarte, N.; Francisco, A.P.; Taveira, N.; Cabral-Marques, H. 2020. Pyromellitic dianhydride crosslinked soluble cyclodextrin polymers: Synthesis, lopinavir release from sub-micron sized particles and anti-HIV-1 activity. Int. J. Pharm. 583, 119356.

Adrian, M.; Jeandet, P.; Veneau, J.; Weston, L.A.; Bessis, R. 1997. Biological activity of resveratrol, a stilbenic compound from grapevine against *Botrytis cinerea*, the causal agent for gray mold. J. Chem. Ecol. 23 1689-1702.

Allan, K.E.; Lenehan, C.E.; Ellis, A.V. 2009. UV light stability of α-cyclodextrin/resveratrol host-guest complexes and isomer stability at varying pH. Aust. J. Chem. 62, 921-926.

Almagro, L.; Belchí-Navarro, S.; Martínez-Marquez, A.; Bru-Martinez, R.; Pedreño, M.A. 2015. Enhanced extracellular production of trans-resveratrol in *Vitis vinifera* suspension cultured cells by using cyclodextrins and coronatine. Plant Physiol. Biochem. 97, 361-367.

Almagro, L.; Carbonell-Bejerano, P.; Belchí-Navarro, S.; Bru-Martinez, R.; Martínez-Zapater, J.M.; Lijavetzky, D.; Pedreño, M.A. 2014. Dissecting the transcriptional response to elicitors in *Vitis vinifera* cells. PLoS ONE 9, e109777.

Almagro, L.; De Gea-Abellán, A.; Rodríguez-López, M.I.; Núñez-Delicado, E.; Gabaldón, J.A.; Pedreño, M.A. 2020. A smart strategy to improve t-resveratrol production in grapevine cells treated with cyclodextrin polymers coated with magnetic nanoparticles. Polymers 12, e991.

Ansari, K.A.; Torne, J.; Vavia, S.; Trotta, F.; Cavalli, R. 2011a. Paclitaxel loaded nanosponges: *in vitro* characterization and cytotoxicity study on MCF-7 cell line culture. Curr. Drug Deliv. 8, 194-202.

Ansari, K.A.; Vavia, P.R.; Trotta, F.; Cavalli, R. 2011b. Cyclodextrin-based nanosponges for delivery of resveratrol: *In vitro* characterization, stability, cytotoxicity and permeation study. AAPS PharmSciTech 12, 279-286.

Aramsangtienchai, P.; Chavasiri, W.; Ito, K.; Pongsawasdi, P. 2011. Synthesis of epicatechin glucosides by a β-cyclodextrin glycosyltransferase. J. Mol. Catal. B Enzym. 73, 27-34.

Argenziano, M.; Foglietta, F.; Canaparo, R.; Spagnolo, R.; Della Pepa, C.; Caldera, F.; Trotta, F.; Serpe, L.; Cavalli, R. 2020. Biological effect evaluation of glutathione-responsive cyclodextrin-based nanosponges: 2D and 3D studies. Molecules 25, 2775.

Arunachalam, B.; Phan, U.T.; Geuze, H.J.; Cresswell, P. 1990. Enzymatic reduction of disulfide bonds in lysosomes: Characterization of a gamma-interferon-inducible lysosomal thiol reductase (GILT). Proc. Natl Acad. Sci. USA 97, 745-750.

Aumont, V.; Larronde, F.; Richard, T.; Budzinski, H.; Decendit, A.; Deffieux, G.; Krisa, S.; Mérillon, J.M. 2004. Production of highly ^{13}C-labeled polyphenols in *Vitis vinifera* cell bioreactor cultures. J. Biotechnol. 109, 287-294.

Austin, M.B.; Bowman, M.E.; Ferrer, J.L.; Schröder, J.; Noel, J.P. 2004. An aldol switch discovered in stilbene synthases mediates cyclisation specificity of type III polyketide synthases. Chem. Biol. 11, 1179-1194.

Austin, M.B.; Noel, J.P. 2003. The chalcone synthase of type III polyketide synthases. Nat. Prod. Rep. 20, 79-110.

Aziz, M.H.; Afaq, F.; Ahmad, N. 2005. Prevention of ultraviolet-B radiation damage by resveratrol in mouse skin is mediated via modulation in survivin. Photochem. Photobiol. 81, 25-31.

Babin, J.; Pelletier, M.; Lepage, M.; Allard, J.F.; Morris, D.; Zhao, Y. 2009. A new two-photon sensitive block copolymer nanocarrier. Angew. Chem. Int Ed. 48, 3329-3332.

Bastianetto, S.; Ménard, C.; Quirion, R. 2015. Neuroprotective action of resveratrol. Biochim. Biophys. Acta Mol. Basis Dis. 1852, 1195-1201.

Bayomi, M.A.; Abanumay, K.A.; Al-Angary, A.A. 2002. Effect of inclusion complexation with cyclodextrins on photostability of nifedipine in solid state. Int. J. Pharm. 243, 107-117.

Belchí-Navarro, S.; Almagro, L.; Lijavetzky, D.; Bru, R.; Pedreño, M.A. 2012. Enhanced extracellular production of trans-resveratrol in *Vitis vinifera* suspension cultured cells by using cyclodextrins and methyljasmonate. Plant Cell Rep. 31, 81-89.

Belchí-Navarro, S.; Almagro, L.; Sabater-Jara, A.B.; Fernández-Pérez, F.; Bru-Martinez, R.; Pedreño, M.A. 2013. Early signaling events in grapevine cells elicited with cyclodextrins and methyl jasmonate. Plant Physiol. Biochem. 62, 107-110.

Berta, G.N.; Salamone, P.; Sprio, A.E.; Di Scipio, F.; Marinos, L.M.; Sapino, S.; Carlotti, M.E.; Cavalli, R.; Di Carlo, F. 2010. Chemoprevention of 7,12-dimethylbenz[a]anthracene (DMBA)-induced oral carcinogenesis in hamster cheek pouch by topical application of resveratrol complexed with 2-hydroxypropyl-β-cyclodextrin. Oral Oncol. 46, 42-48.

Bertacche, V.; Lorenzi, N.; Nava, D.; Pini, E.; Sinico, C. 2006. Host-guest interaction study of resveratrol with natural and modified cyclodextrins. J. Incl. Phenom. Macrocycl. Chem.55, 279-287.

Boedtkjer, E.; Pedersen, S.F. 2020. The acidic tumor microenvironment as a driver of cancer. Annu. Rev. Physiology 83, 103-126.

Böhmdorfer, M.; Szakmary, A.; Schiestl, R.; Vaquero, J.; Riha, J.; Brenner, S.; Thalhammer, T.; Szekeres, T.; Jäger, W. 2017. Involvement of UDP-glucuronosyltransferases and sulfotransferases in the excretion and tissue distribution of resveratrol in mice. Nutrients 9, 1347.

Bonnet, V.; Gervaise, C.; Djedaïni-Pilard, F.; Furlan, A.; Sarazin, C. 2015. Cyclodextrin nanoassemblies: a promising tool for drug delivery. Drug Discov. Today 20, 1120-1126.

Boo, Y. C. 2019. Human skin lightening efficacy of resveratrol and its analogs: From *in vitro* studies to cosmetic applications. Antioxidants 8, 322.

Boocock, D.J.; Faust, G.E.; Patel, K.R.; Schinas, A.M.; Brown, V.A.; Ducharme, M.P.; Booth, T.D.; Crowell, J.A.; Perloff, M.; Gescher, J.A.; Steward, W.P.; Brenner, D.E. 2007. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. Cancer Epidemiol. Biomark. Prev. 16, 1246-1252.

Breuil, A.C.; Adrian, M.; Pirio, N.; Meunier, P.; Bessis, R.; Jeandet, P. 1998. Metabolism of stilbene phytoalexins by *Botrytis cinerea*: Characterization of a resveratrol dehydrodimer. Tetrahedron Lett. 39, 537-540.

Brown, V.A.; Patel, K.R.; Viskaduraki, M.; Crowell, J.A.; Perloff, M.; Booth, T.D.; Vasilinin, G.; Sen, A.; Schinas, A.M.; Piccirilli, G.; Brown, K.; Steward, W.P.; Gescher, A.J.; Brenner, D.E. 2010. Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: Safety, pharmacokinetics, and effect on the insulin-like growth factor axis. Cancer Res. 70, 9003-9011.

Bru, M.R.; Pedreno, M.A. 2003. Method for the production of resveratrol in cell cultures. US patent WO/2003/062406.

Bru, R.; Selles, S.; Casado-Vela, J.; Belchi-Navarro, S.; Pedreño, M.A. 2006. Modified cyclodextrins are chemically defined glucan inducers of defence responses in grapevine cell cultures. J. Agric. Food Chem. 54, 65-71.

Cai, H.; Scott, E.; Kholghi, A.; Andreadi, C.; Rufini, A.; Karmokar, A.; Britton, R.G.; Horner-glister, E.; Greaves, P.; Jawad, D.; James, M.; Howells, L.; Ognibene, T.; Malfatti, M.; Goldring, C;, Kitteringham, N.; Walsh, J.; Viskaduraki, M., West, K.; Miller, A.; Hemingway, D.; Steward, W.P.; Gescher, A.J.; Brown, K. 2015. Cancer chemoprevention: Evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice. Sci. Transl. Med. 7, 298ra117.

Caruso, F.; Mendoza, L.; Castro, P.; Cotoras, M.; Aguirre, M.; Matsuhiro, B.; Isaacs, M.; Rossi, M.; Viglianti, A.; Antonioletti, R. 2011. Antifungal activity of resveratrol against *Botrytis cinérea* is improved using 2-furyl derivatives. PLoS One 6**,** e25421.

Cervone, F.; Hahn, M.G.; De Lorenzo, G.; Darvill, A.; Albersheim, P. 1989. Host-pathogen interactions XXXIII. A plant protein converts a fungal pathogenesis factor into an elicitor of plant defense responses. Plant Physiol. 90, 542-548.

Cheng, J.G.; Tian, B.R.; Huang, Q.; Ge, H.R.; Wang, Z.Z. 2018. Resveratrol functionalized carboxymethyl-β-cyclodextrin: Synthesis, characterization and photostability. J. Chem. 2018**,** 6789076.

Cheng, C.; Wei, H.; Shi, B.X.; Cheng, H.; Li, C.; Gu, Z.W.; Cheng, S.X; Zhang, X.Z.; Zhuo, R.X. 2008. Biotinylated thermoresponsive micelle self-assembled from double-hydrophilic block copolymer for drug delivery and tumor target. Biomaterials 29, 497-505.

Choung, W.J.; Hwang, S.H.; Ko, D.S.; Kim, S.B.; Kim, S.H.; Jeon, S.H.; Choi, H.D.; Lim, S.S.; Shim, J.H. 2017. Enzymatic synthesis of a novel kaempferol-3-*O*-β-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranoside using cyclodextrin glucanotransferase and its inhibitory effects on aldose reductase, inflammation, and oxidative stress. J. Agric. Food Chem. 65, 2760-2767.

Ciesielska, A.; Ciesielski, W.; Girek, B.; Girek, T.; Koziel, K.; Kulawik, D.; Lagiewka, J. 2020. Biomedical application of cyclodextrin polymers cross-linked via dianhydrides of carboxylic acids. Appl. Sci. 10, 8463.

Connors, K.A. 1997. The stability of cyclodextrin complexes in solution. Chem. Rev. 97, 1325-1358.

Costa, A.; Bonner, M.Y.; Arbiser, J.L. 2016. Use of polyphenolic compounds in dermatologic oncology. Am. J. Clin. Dermatol. 17, 369-385.

Creasy, L.L.; Coffee, M. 1988. Phytoalexin production potential of grape berries. J. Am. Soc. Hortic. Sci. 113, 230-234.

Crini, G. 2014. Review: A history of cyclodextrins. Chem. Rev. 114, 10940-10975.

Daga, M.; Ullio, C.; Argenziano, M.; Dianzani, C.; Cavalli, R.; Trotta, F.; Ferretti, C.; Zara, G.P.; Gigliotti, C.L.; Ciamporcero, E.S.; Pettazzoni, P.; Corti, D.; Pizzimenti, S.; Barrera, G. 2016. GSH-targeted nanosponges increase doxorubicin-induced toxicity "*in vitro*" and "*in vivo*" in cancer cells with high antioxidant defenses. Free Radic. Biol. Med. 97, 24-37.

Das, S.; Lin, H.S.; Ho, P.C.; Ng, K.Y. 2008. The impact of aqueous solubility and dose on the pharmacokinetic profiles of resveratrol. Pharm. Res. 25, 2593-2600.

De Sa Coutinho, D.; Pacheco, M.T.; Frozza, R.L.; Bernardi, A. 2018. Anti-inflammatory effects of resveratrol: mechanistic insights. Int. J. Mol. Sci. 19, 1812.

De Winter, K.; Verlinden, K.; Kren, V.; Weignerova, L.; Soetaert, W.; Desmet, T. 2013. Ionic liquids as cosolvents for glycosylation by sucrose phosphorylase: balancing acceptor solubility and enzyme stability. Green Chem. 15, 1949-1955.

Dhakar, N.K.; Matencio, A.; Caldera, F.; Argenziano, M.; Cavalli, R.; Dianzani, C.; Zanetti, M.; Lopez-Nicolas, J.M.; Trotta, F. 2019. Comparative evaluation of solubility, cytotoxicity and photostability studies of resveratrol and oxyresveratrol loaded nanosponges. Pharmaceutics 11, 545.

Din, F.U.; Aman, W.; Ullah, I.; Qureshi, O.S.; Mustapha, O.; Shafique, S.; Zeb, A. 2017. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int. J. Nanomed. 12, 7291-7309.

Docherty, J.J.; Smith, J.S.; Fu, M.M.; Stoner, T.; Booth, T. 2004. Effect of topically applied resveratrol on cutaneous herpes simplex virus infections in hairless mice. Antivir. Res. 61, 19-26.

Donnez, D.; Jeandet, P.; Clément, C.; Courot, E. 2009. Bioproduction of resveratrol and stilbene derivatives by plant cells and microorganisms. Trends Biotechnol. 27, 706-713.

Donnez, D.; Kim, K.H.; Antoine, S.; Conreux, A; De Luca, V.; Jeandet, P.; Clément, C.; Courot, E. 2011. Bioproduction of resveratrol and viniferins by an elicited grapevine cell culture in a 2L stirred bioreactor. Process Biochem. 46, 1056-1062.

Dora, C.P.; Trotta, F.; Kushwah, V.; Devasari, N.; Singh, C.; Suresh, S.; Jain, S. 2016. Potential of erlotinib cyclodextrin nanosponge complex to enhance solubility, dissolution rate, *in vitro* cytotoxicity and oral bioavailability. Carbohydr. Polym. 137, 339-349.

Dos Santos Lima, B.; Shanmugam, S.; de Souza Siqueira Quintans, J.; Quintans Jr, L.J.; De Souza Araujo, A.A. 2019. Inclusion complexes with cyclodextrins enhances the bioavailability of flavonoid compounds: A systematic review. Phytochem. Rev. 18, 1337-1359.

Draijer, R.; Van Dorsten, F.A.; Zebregs, Y.E.; Hollebrands, B.; Peters, S.; Duchateau, G.S.; Grün, C.H. 2016. Impact of proteins on the uptake, distribution, and excretion of phenolics in the human body. Nutrients 8, 814.

Duan, D.; Fischer, S.; Merz, P.; Bogs, J.; Riemann, M.; Nick, P. 2016. An ancestral allele of grapevine transcription factor MYB14 promotes plant defence. J. Exp. Bot. 67, 1795-1804.

Duarte, A.; Martinho, A.; Luis, A.; Figueiras, A.; Oleastro, M.; Domingues, F.C.; Silva, F. 2015. Resveratrol encapsulation with methyl-β-cyclodextrin for antibacterial and antioxidant delivery applications. LWT-Food Sci. Technol. 63, 1254-1260.

Eibl, R.; Eibl, D. 2008. Design of bioreactors suitable for plant cell and tissue cultures. Phytochem. Rev. 7, 593-598.

Fang, L.; Yang, T.; Medina-Bolivar, F. 2020. Production of prenylated stilbenoids in hairy root cultures of peanut (*Arachis hypogaea*) and its wild relatives *A. ipaensis* and *A. duranensis* via an optimized elicitation procedure. Molecules 25, 509.

Ferri, M.; Dipalo, S.C.; Bagni, N.; Tassoni, A. 2011. Chitosan elicits mono-glucosylated stilbene production and release in fed-batch bioreactor cultures of grape cells. Food Chem. 124, 1473-1479.

Fumic, B.; Jablan, J.; Cincic, D.; Zovko Koncic, M.; Jug, M. 2018. Cyclodextrin encapsulation of daidzein and genistein by grinding: implication on the glycosaminoglycan accumulation in mucopolysaccharidosis type II and III fibroblasts. J. Microencapsul. 35, 1-12.

Gabaston, J.; Cantos-Villar, E.; Biais, B.; Waffo-Teguo, P.; Renouf, E.; Corio-Costet, M.F.; Richard, T.; Mérillon, J.M. 2017. Stilbenes from *Vitis vinifera* L. wastes: A sustainable tool for controlling *Plasmopara viticola*. J. Agric. Food Chem. 65, 2711-2718.

Gidwani, B.; Vyas, A. A 2015. comprehensive review on cyclodextrin-based carriers for delivery of chemotherapeutic cytotoxic anticancer drugs. BioMed Res. Int. 2015, 198268.

Gigliotti, C.L.; Minelli, R.; Cavalli, R.; Occhipinti, S.; Barrera G.; Pizzimenti, S.; Cappellano, G.; Boggio, E.; Conti, L.; Fantozzi, R.; Giovanelli, M.; Trotta, F.; Dianzani, U.; Dianzoni, C. 2016. *In vitro* and *in vivo* therapeutic evaluation of campothecin-encapsulated β-cyclodextrin nanosponges in prostate cancer. J. Biomed. Nanotechnol. 12, 114-127.

Goldberg, D.M.; Yann, J.; Soleas, G.J. 2003. Absorption of three-wine-related polyphenols in three different matrices by healthy subjects. Clin Biochem. 36, 79-87.

Gonzalez-Alfonso, J.L.; Rodrigo-Frutos, D.; Belmonte-Reche, E.; Penalver, P.; Poveda, A.; Jimenez-Barbero, J.; Ballesteros, A.O.; Hirose, Y.; Polaina, J.; Morales J.C.; Fernandez-Lobato, M.; Plou, F.J. 2018. Enzymatic synthesis of a novel pterostilbene α-glucoside by the combination of cyclodextrin glucanotransferase and amyloglucosidase. Molecules 23, 1271.

Gratieri, T.; Pinho, L.A.G.; Almeida Oliveira, M.; Sa-Barreto, L.L.; Marreto, R.M., Silva, I.C.; Gelfuso, G.M.; de Souza Siqueira Quintans, J.; Quintans Jr, L.J.; Cunha-Filho, M. 2020. Hydroxypropyl-β-CD-complexed naringenin by solvent change precipitation for improving anti-inflammatory effect *in vivo*. Carbohydr. Polym. 231, 115769.

Haley, R.M.; Zuckerman, S.T.; Dakhlallah, H.; Capadona, J.R.; von Recum, H.A.; Ereifej, E.S. 2020. Resveratrol delivery from implanted cyclodextrin polymers sustained antioxidant effect on implanted neural probes. Int. J. Mol. Sci. 21, 3579.

Han, R.; Ge, B.; Jiang, M.; Xu, G.; Dong, J.; Ni, Y. 2017. High production of genistein diglucoside derivative using cyclodextrin glycosyltransferase from *Paenibacillus macerans*. J. Ind. Microbiol. Biotechnol. 44, 1343-1354.

He, J.; Guo, F.; Lin, L.; Chen, H.; Chen, J.; Cheng, Y.; Zheng, Z.P. 2019. Investigating the oxyresveratrol β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin complexes: The effects on oxyresveratrol solution, stability, and antibrowning activity on fresh grape juice. LWT-Food Sci. Technol. 100, 263-270.

Hidalgo, D.; Martínez-Márquez, A.; Cusidó, R.; Bru-Martínez, R.; Palazón, J.; Corchete, P. 2017. *Silybum marianum* cell cultures stably transformed with *Vitis vinifera* stilbene synthase accumulate t-resveratrol in the extracellular medium after elicitation with methyl jasmonate or methylated β-cyclodextrins. Eng. Life Sci. 17, 686-694.

Höll, J.; Vannozzi, A.; Czemmel, S.; D'Onofrio, C.; Walker, A.R.; Rausch, T.; Lucchin, M.; Boss, P.K.; Dry, I.B.; Bogs, J. 2013. The R2R3-MYB transcription factors MYB14 and MYB15 regulate stilbene biosynthesis in *Vitis vinifera*. Plant Cell 25, 4135-4149.

Houillé, B.; Papon, N.; Boudesocque, L.; Bourdeaud, E.; Besseau, S.; Courdavault, V.; Enguehard-Gueiffier, C.; Delanoue, G.; Guérin, L.; Bouchara, J.P.; Clastre, M.; Giglioli-Guivarc'h, N.; Guillard, J.; Lanoue, A.

2014. Antifungal activity of resveratrol derivatives against Candida species. J. Nat. Prod. 77, 1658-1662.

Howells, L.M.; Berry, D.P.; Elliott, P.J.; Jacobson, E.W.; Hoffmann, E.; Hegarty, B.; Brown, K.; Steward, W.P.; Gescher, A.J. 2011. Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases—safety, pharmacokinetics, and pharmacodynamics. Cancer Prev. Res. 4, 1419-1425.

Ikuta, D.; Hirata, Y.; Wakamori, S.; Shimada, H.; Tomabechi, Y.; Kawasaki, Y.; Ikeuchi, K.; Hagimori, T.; Matsumoto, S.; Yamada, H. 2019. Conformationally supple glucose monomers enable synthesis of the smallest cyclodextrins. Science 364, 674-677.

Ingham, J. L. 1976. 3,5,4′-trihydroxystilbene as a phytoalexin from groundnuts (*Arachis hypogaea*). Phytochemistry 15, 1791-1793.

Intagliata, S.; Modica, M.N.; Santagati, L.; Montenegro, L. 2019. Strategies to improve resveratrol systemic and topical bioavailability: An update. Antioxidants 8, 244.

Ioannou, I.; Barboza, E.; Willig, G.; Marié, T.; Texeira, A.; Darme, P.; Renault, J.H.; Allais, F. 2021. Implementation of an enzyme membrane reactor to intensify the α-*O*-glycosylation of resveratrol using cyclodextrins. Pharmaceuticals 14, 319.

Ito, T.; Tanaka, T.; Iinuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. 2004. Three new stilbene oligomers from the stem bark of *Vatica pauciflora*. J. Nat. Prod. 67, 932-937.

Jambhekar, S.S.; Breen, P. 2016. Cyclodextrins in pharmaceutical formulations II: solubilization, binding constant, and complexation efficiency. Drug Discov. Today 21, 363-368.

Jang, M.; Cai, L.; Udeani, G.O.; Slowing, K.V.; Thomas, C.F.; Beecher, C.W.W.; Fong, H.H.S.; Farnsworth, N.R.; Kinghorn, A.D.; Metha, R.G.; Moon, R.C.; Pezzuto, J.M. 1997. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 275, 218-220.

Jeandet, P.; Bessis, R.; Gautheron, B. 1991. The Production of resveratrol (3,5,4′-trihydroxystilbene) by grape berries in different developmental stages. Am. J. Enol. Vitic. 42, 41-46.

Jeandet, P.; Breuil, A.C.; Adrian, M.; Weston, L.A.; Debord, S.; Meunier, P.; Maume, G.; Bessis, R. 1997. HPLC analysis of grapevine phytoalexins coupling photodiode array detection and fluorometry. Anal. Chem. 69, 5172-5177.

Jeandet, P.; Clément, C.; Cordelier, S. 2019. Regulation of resveratrol biosynthesis in grapevine: new approaches for disease resistance? J. Exp. Bot. 70, 375-378.

Jeandet, P.; Clément, C.; Courot, E. 2014. Use of plant cell suspensions as a basis for large-scale production of resveratrol in bioreactors. Eng. Life Sci. 14, 622–632.

Jeandet, P.; Clément, C.; Tisserant, L.P.; Crouzet, J.; Courot, E. 2016. Use of grapevine cell cultures for the production of phytostilbenes of cosmetic interest. C.R. Chimie 19, 1062-1070.

Jeandet, P.; Delaunois, B.; Conreux, A.; Donnez, D.; Nuzzo, V.; Cordelier, S.; Clément, C.; Courot, E. 2010. Biosynthesis, metabolism, molecular engineering and biological functions of stilbene phytoalexins in plants. BioFactors 36, 331-341. 933.

Jeandet, P.; Douillet, A.C.; Weston, L.A.; Debord, S.; Sbaghi, M.; Bessis, R.; Adrian, M. 2002. Phytoalexins from the Vitaceae: biosynthesis, phytoalexin gene expression in transgenic plants, antifungal activity, and metabolism. J. Agric. Food Chem. 50, 2731-2741.

Jeandet, P.; Sobarzo-Sánchez, E.; Sanches Silva, A.; Clément, C.; Nabavi, S.F.; Battino, M.; Rasekhian, M.; Belwal, T.; Habtemariam, S.; Koffas, M.; Nabavi, S.M. 2020. Whole-cell biocatalytic, enzymatic and green chemistry methods for the production of resveratrol and its derivatives. Biotechnol. Adv. 38, 107461.

Jeandet, P.; Vannozzi, A.; Sobarzo-Sanchez, E.; Uddin, M.S.; Bru, R.; Martinez-Marquez, A.; Clément, C.; Cordelier, S.; Manayi, A.; Nabavi, S.F.; Rasekhian, M.; Batiha, G.E.S.; Khan, H.; Morkunas, I.; Belwal, T.; Jiang, J.; Koffas, M.; Nabavi, S.M. 2021. Phytostilbenes as agrochemicals: biosynthesis, bioactivity, metabolic engineering and biotechnology. Nat. Prod. Rep., 28, 1282-1329.

Jiang, J.; Xi, H.; Dai, Z.; Lecourieux, F.; Yuan, L.; Liu, X.; Patra, B.; Wei, Y.; Li, S.; Wang, L. 2019. VvWRKY8 negatively regulates VvSTS through direct interaction with VvMYB14 to balance resveratrol biosynthesis in grapevine. J. Exp. Bot. 70, 715-729.

Jones, T.J.; Cagno, V.; Janecek, M.; Ortiz, D.; Gasilova, N.; Piret, J.; Gasbarri, M.; Constant, D.A.; Han, Y.; Vukovic, L.; Kral, P.; Kaiser, L.; Huang, S.; Constant, S.; Kirkegaard, K.; Boivin, G.; Stellacci, F.; Tapparel, C. 2020. Modified cyclodextrins as broad-spectrum antivirals. Sci. Adv. 6, eaax9318.

Kanaya, A.; Takashima, Y.; Harada, A. 2011. Double-threated dimer and supramolecular oligomer formed by stilbene modified cyclodextrin: Effect of acyl migration and photostimuli. J. Org. Chem. 76, 492-499.

Kapetanovic, I.M.; Muzzio, M.; Huang, Z.H.; Thompson, T.N.; McCormick, D.L. 2011. Pharmacokinetics, oral bioavailability, and metabolic profile of resveratrol and its dimethylether analog, pterostilbene, in rats. Cancer Chemother Pharm. 68, 593-601.

Kennedy, L.; Sandhu, J.K; Harper, M.E.; Cuperlovic-Culf, M. 2020. Role of glutathione in cancer: from mechanisms to therapies. Biomolecules 10, 1429.

Keylor, M.H.; Matsuura, B.S.; Griesser, M.; Chauvin, J.P.; Harding, R.A.; Kirillova, M.S.; Zhu, X.; Fischer, O.J.; Pratt, D.K.; Stephenson, C.R.J. 2016. Synthesis of resveratrol tetramers via a stereoconvergent radical equilibrium. Science 354, 1260-1265.

Keylor, M.H.; Matsuura, B.S.; Stephenson, C.R.J. 2015. Chemistry and biology of resveratrol-derived natural products. Chem. Rev. 115, 8976-9027.

Khummanee, N.; Rudeekulthamrong, P.; Kaulpiboon, J. 2019. Cyclodextrin glycosyltransferase-catalyzed synthesis of pinoresinol-α-D-glucoside having antioxidant and anti-inflammatory activities. Appl. Biochem. Microbiol. 55, 360-370.

Kim, Y.J.; Matsunaga, Y.T. 2017. Thermo-responsive polymers and their application as smart biomaterials. J**.** Mater. Chem. B 5**,** 4307-4321.

Kjaer, T.N.; Thorsen, K.; Jessen, N.; Stenderup, K.; Pedersen, S.B. 2015. Resveratrol ameliorates imiquimod-induced psoriasis-like skin inflammation in mice. PLoS One 10, e0126599.

Kong, D.; Ren, C.; Ning, C.; Cheng, Y.; Cai, H.; Xing, H.; Zhang, Y.; Li, N.; Lu, Y.; Chen, X.; Zhao, D. 2020. Pulmonary administration of resveratrol/hydroxyproplyl-β-cyclodextrin inclusion complex: *in vivo* disposition and *in vitro* metabolic study. J. Drug Deliv. Sci. Technol. 60, 101995.

Krisa, S.; Larronde, F; Budzinski, H.; Decendit, A.; Deffieux, G.; Mérillon, J.M. 1999. Stilbene production by *Vitis vinifera* cell suspension cultures: methyl jasmonate induction and ^{13}C biolabeling. J. Nat. Prod. 62, 1688-1690.

Kumpugdee-Vollrath, M.; Ibold, Y.; Sriamornsak, P. 2012. Solid state characterization of trans resveratrol complexes with different cyclodextrins. JAASP 1, 125-136.

Lacerda, D.; Ortiz, V.; Türck, P.; Campos-Carraro, C.; Zimmer, A.; Teixeira, R.; Bianchi, S.; Luz de Castro, A.L.; Schenkel, P.C.; Bello-Klein, A.; Bassani, V.L.; da Rosa Araujo, A.S. 2018. Stilbenoid pterostilbene complexed with cyclodextrin preserves left ventricular function after myocardial infarction in rats: possible involvement of thiol proteins and modulation of phosphorylated GSK-3β. Free Rad. Res. 52, 988-999.

Lacerda, D.; Türck, P.; de Lima-Seolin, B.G.; Colombo, R.; Duarte Ortiz, V.; Poletto Bonetto, J.H.; Campos-Carraro, C.; Bianchi, S.E.; Bello-Klein, A.; Bassani, V.L.; da Rosa Araujo, A.S. 2017. Pterostilbene reduces oxidative stress, prevents hypertrophy and preserves systolic function of right ventricle in *cor pulmone* model. Br. J. Pharmacol. 174, 3302-3314.

Lambert, C.; Lemaire, J.; Auger, H.; Guilleret, A.; Reynaud, R.; Clément, C.; Courot, E.; Taidi, B. 2019. Optimize, modulate, and scale-up resveratrol and resveratrol dimers bioproduction in *Vitis labrusca* L. cell suspension from flasks to 20 l bioreactor. Plants 8, e567.

Langcake, P.; Pryce, R.J. 1976. The production of resveratrol by *Vitis vinifera* and other members of the Vitaceae as a response to infection or injury. Physiol. Plant Pathol. 9, 77-86.

Langcake, P.; Pryce, R.J. 1977. The production of resveratrol and the viniferins by grapevines in response to ultraviolet irradiation. Phytochemistry 16, 1193-1196.

La Porte, C.; Voduc, N.; Zhang, G.; Seguin, I.; Tardiff, D.; Singhal, N.; Cameron, D.W. 2010. Steady-state pharmacokinetics and tolerability of trans-resveratrol 2000mg twice daily with food, quercetin and alcohol (ethanol) in healthy human subjects. Clin. Pharmacokinet. 49*,* 449-454.

Lee, Y.S.; Woo, J.B.; Ryu, S.I.; Moon, S.R.; Han, N.S.; Lee, S.B. 2017. Glucosylation of flavonol and flavanones by *Bacillus* cyclodextrin glucosyltransferase to enhance their solubility and stability. Food Chem. 229, 75-83.

Li, S.; Yuan, L.; Zhang, B.; Zhou, W.; Wang, X.; Bai, D. 2018. Photostability and antioxidant activity studies on the inclusion complexes of *trans*-polydatin with β-cyclodextrin and derivatives. RSC Adv. 8, 25941.

Lijavetzky, D.; Almagro, L.; Belchí-Navarro, S.; Martinez-Zapater, J.M.; Bru, R.; Pedreño, M.A. 2008. Synergistic effect of methyljasmonate and cyclodextrin on stilbene biosynthesis pathway gene expression and resveratrol production in Monastrell grapevine cell cultures. BMC Res. Notes 1, e132.

Lim, H.C.; Rasti, B.; Sulistyo, J.; Hamid, M. A. 2021. Comprehensive study on transglucosylation of CGTase from various sources. Helyon 7, e06305.

Lim, Y.R.I.; Preshaw, P.M.; Lim, L.P.; Ong, M.M.A.; Lin, H.S.; Tan, K.S. 2020. Pterostilbene complexed with cyclodextrin exerts antimicrobial and anti-inflammatory effects. Sci. Rep. 10, 9072.

Lin, J.T.; Du, J.K.; Yang, Y.Q.; Li, L.; Zhang, D.W.; Liang, C.L.; Wang, J.; Mei, J.; Wang, G.H. 2017. pH and redox dual stimulate-responsive nanocarriers based on hyaluronic acid coated mesoporous silica for targeted drug delivery. Mater. Sci. Eng. C Mater. Biol. Appl. 81, 478-484.

Lin, M.H.; Hung, C.F.; Sung, H.C.; Yang, S.C.; Yu, H.P.; Fang, J.Y. 2011. The bioactivities of resveratrol ant its naturally occurring derivatives on skin. J. Food Drug Anal. 29, 15-38.

Lin, H.S.; Yue, B.D.; Ho, P.C. 2009. Determination of pterostilbene in rat plasma by a simple HPLC-UV method and its application in pre-clinical pharmacokinetic study. Biomed. Chromatogr. 23, 1308-1315.

Lopez-Nicolas, J.M.; Rodriguez-Bonilla, P.; Garcia-Carmona, F. 2009a. Complexation of pinosylvin, an analogue of resveratrol with high antifungal and antimicrobial activity, by different types of cyclodextrins. J. Agric. Food Chem. 57, 10175-10180.

Lopez-Nicolas, J.M.; Rodriguez-Bonilla, P.; Mendez-Carzola, L.; Garcia-Carmona, F. 2009b. Physicochemical study of the complexation of pterostilbene by natural and modified cyclodextrins. J. Agric. Food Chem. 57, 5294-5300.

Lu, Z.; Chen, R.; Fu, R.; Xiong, J.; Hu, Y. 2012. Cytotoxicity and inhibition of lipid peroxidation activity of resveratrol/cyclodextrin inclusion complexes. J. Incl. Phenom. Macrocycl. Chem.73, 313-320.

Lu, Z.; Cheng, B.; Hu, Y.; Zhang, Y.; Zou, G. 2009. Complexation of resveratrol with cyclodextrins: Solubility and antioxidant activity. Food Chem. 113, 17-20.

Lucas-Abellan, C.; Fortea, M.I.; Gabaldon, J.A.; Nunez-Delicado, E. 2008. Complexation of resveratrol by native and modified cyclodextrins: Determination of complexation constant by enzymatic, solubility and fluorimetric assays. Food Chem. 111, 262-267.

Lucas-Abellan, C.; Fortea, M.I.; Lopez-Nicolas, J.M.; Nunez-Delicado, E. 2007. Cyclodextrins as resveratrol carrier system. Food Chem. 104, 39-44 (2007).

Manchun, S.; Dass, C.R.; Sriamornsak, P. 2012. Targeted therapy for cancer using pH-responsive nanocarrier systems. Life Sci. 90, 381-387.

Manor, P.; Saenger, W. 1972. Water molecule in hydrophobic surroundings: structure of α-cyclodextrin-hexahydrate $(C_6H_{10}O_5)_6.6H_2O$. Nature 237, 392-393.

Manta, K.; Papakyriakopoulou, P.; Chountoulesi, M.; Diamantis, D.A.; Spaneas, D.; Valaki, V.; Naziris, N.; Chatziathanasiadou, M.V.; Andreadelis, I.; Moschovou, K.; Athanasiadou, I.; Dallas, P.; Rekkas, D.M.; Demetzos, C.; Colombo, G.; Banella, S.; Javornik, U.; Plavec, J.; Mavromoustakos, T.; Tzakos, A.G.; Valsami, G. 2020. Preparation and biophysical characterization of quercetin inclusion complexes with β-cyclodextrin derivatives to be formulated as possible nose-to-brain quercetin delivery systems. Mol. Pharmaceutics 17, 4241-4255.

Marié, T.; Willig, G.; Teixeira, A.R.S.; Barboza, E.G.; Kotland, A.; Gratia, A.; Courot, E.; Hubert, J.; Renault, J.H.; Allais, F. 2018. Enzymatic synthesis of resveratrol α-glycosides from β-cyclodextrin-resveratrol complex in water. ACS Sustainable Chem. Eng. 6, 5370-5380.

Martínez-Esteso, M.J.; Sellés-Marchart, S.; Vera-Urbina, J.C.; Pedreño, M.A.; Bru-Martinez, R. 2011. DIGE analysis of proteome changes accompanying large resveratrol production by grapevine (*Vitis vinifera* cv. Gamay) cell cultures in response to methyl-β-cyclodextrin and methyl jasmonate elicitors. J. Proteomics 74, 1421–1436.

Martínez-Márquez, A.; Martínez-Esteso, M.J.; Vilella-Antón, M.T.; Sellés-Marchart, S.; Morante-Carriel, J.A.; Hurtado, E.; Palazon, J.; Bru-Martínez, R. 2017. A tau class glutathione-S-transferase is involved in trans-resveratrol transport out of grapevine cells. Front. Plant Sci. 8, e1457.

Martínez-Márquez, A.; Morante-Carriel, J.A.; Palazon, J.; Bru-Martínez, R. 2018. *Rosa hybrida* orcinol O-methyl transferase-mediated production of pterostilbene in metabolically engineered grapevine cell cultures. N. Biotechnol. 42, 62-70.

Martínez-Márquez, A.; Morante-Carriel, J.A.; Ramírez-Estrada, K.; Cusidó, R.M.; Palazon, J.; Bru-Martínez, R. 2016. Production of highly bioactive resveratrol analogues pterostilbene and piceatannol in metabolically engineered grapevine cell cultures. Plant Biotechnol. J. 14, 1813-1825.

Matencio, A.; Dhakar, N.K.; Bessone, F.; Musso, G.; Cavalli, R.; Dianzani, C.; Garcia-Carmona, F.; Lopez-Nicolas, J.M.; Trotta, F. 2020. Study of oxyresveratrol complexes with insoluble cyclodextrin based nanosponges: Developing a novel way to obtain their complexation constants and application in an anticancer study. Carbohydr. Polym. 231, 115763.

Matencio, A.; Garcia-Carmona, F.; Lopez-Nicolas, J.M. 2016. Encapsulation of piceatannol, a naturally occurring hydroxylated analogue of resveratrol, by natural and modified cyclodextrins. Food Funct. 7, 2367.

Matencio, A.; Garcia-Carmona, F.; Lopez-Nicolas, J.M. 2017. The inclusion complex of oxyresveratrol in modified cyclodextrins: A Thermodynamic, structural, physicochemical, fluorescent and computational study. Food Chem. 232, 117-184.

Mathew, S.; Adlercreutz, P. 2013. Regioselective glycosylation of hydroquinone to α-arbutin by cyclodextrin glucanotransferase from *Thermoanaerobacter* sp. Biochem. Eng. J. 79, 187-193.

Mathew, S.; Hedström, M.; Adlercreutz, P. 2012. Enzymatic synthesis of piceid glycosides by cyclodextrin glucanotransferase. Process Biochem. 47, 528-532.

Medina-Bolivar, F.; Condori, J.; Rimando, A.M.; Hubstenberger, J.; Shelton, K.; O'Keefe, S.F.; Bennett, S.; Dolan, M.C. 2007. Production and secretion of resveratrol in hairy root cultures of peanut. Phytochemistry 68, 1992-2003.

Mendes, C.; Meirelles, G.C.; Barp, C.G.; Assreuy, J.; Silva, M.A.S.; Ponchel, G. 2018. Cyclodextrin based nanosponge of norfloxacin: Intestinal permeation enhancement and improved antibacterial activity? Carbohydr. Polym. 195, 586-592.

Mennini, N.; Cirri, M.; Maestrelli, F.; Mura, P. 2016. Comparison of liposomal and NLC (nanostructured lipid carrier) formulations for improving the transdermal delivery of oxaprozin: Effect of cyclodextrin complexation. Int. J. Pharm. 515, 684-691.

Miksits, M.; Maier-Salamon, A.; Aust, S.; Thalhammer, T.; Reznicek, G.; Kunert, O.; Haslinger, E.; Szekeres, T.; Jaeger, W. 2005. Sulfation of resveratrol in human liver: Evidence of a major role for the sulfotransferases SULT1A1 and SULT1E1. Xenobiotica 35, 1101-1119.

Mitsuda, N.; Iwase, A.; Yamamoto, H.; Yoshida, M.; Seki, M.; Shinozaki, K.; Ohme-Takagi, M. 2007. NAC transcription factors, NST1 and NST3, are key regulators of the formation of secondary walls in woody tissues of Arabidopsis. Plant Cell 19, 270-280.

Morales, M.; Bru, R.; García-Carmona, F.; Ros-Barceló, A.; Pedreño, M.A. 1998. Effect of dimethyl-β-cyclodextrins on resveratrol metabolism in Gamay grapevine cell cultures before and after inoculation with *Xylophilus ampelinus*. Plant Cell Tiss. Org. Cult. **53**, 179-187.

Nabavi, S.; Samec, D.; Tomczyk, M.; Milella, L.; Russo, D.; Habtemariam, S.; Suntar, I.; Rastrelli, L.; Daglia, M.; Xiao, J.; Giampieri, F.; Battino, M.; Sobarzo-Sánchez, E.; Nabavi, S.F.; Yousefi, B.; Jeandet, P.; Xu, S.; Shirooie, S. 2020. Flavonoid biosynthetic pathways in plants: versatile targets for metabolic engineering. Biotechnol. Adv. 39, 107461.

Nivelle, L.; Hubert, J.; Courot, E.; Jeandet, P.; Aziz, A.; Nuzillard, J.M.; Renault, J.H.; Clément, C.; Martiny, L.; Delmas, D.; Tarpin, M. 2017. Anti-cancer activity of resveratrol and derivatives produced by grapevine cell suspensions in a 14 L stirred bioreactor. Molecules 22, 474.

Nonomura, S.; Kanagawa, H.; Makimoto, A. 1963. Chemical constituents of polygonaceous plants. I. Studies on the components of Ko-jo-kon (*Polygonum cuspidatum* Sieb Et Zucc.). Yakugaku Zasshi 83, 988-990.

Nopo-Olazabal, C.; Hubstenberger, J.; Nopo-Olazabal, L.; Medina-Bolivar, F. 2013. Antioxidant activity of selected stilbenoids and their bioproduction in hairy root cultures of Muscadine grape (*Vitis rotundifolia* Michx.). J. Agric. Food Chem. 61, 11744-11758.

Novotny, J.A.; Chen, T.Y.; Terekhov, A.I.; Gebauer, S.K.; Baer, D.J.; Ho, L.; Pasinetti, G.M.; Ferruzzi, M.G. 2017. The effect of obesity and repeated exposure on pharmacokinetic response to grape polyphenols in humans. Mol. Nutr. Food Res. 61, 1700043.

Oliva, E.; Mathiron, D.; Bertaut, E.; Landy, D.; Cailleu, D.; Pilard, S.; Clément, C.; Courot, E.; Bonnet, V.; Djedaini-Pilard, F. 2018. Physico-chemical studies of resveratrol, methyl-jasmonate and cyclodextrins interactions : an approach to resveratrol bioproduction optimization. RSC Adv. 8, 1528-1538.

Osmond, G.W.; Augustine, C.K.; Zipfel, P.A.; Padussis, J.; Tyler, D.S. 2012. Enhancing melanoma treatment with resveratrol. J. Surg. Res. 172, 109-115.

Paczkowska, M.; Mizera, M.; Piotrowska, H.; Szymanowska-Powalowska, D.; Lewandowska, K.; Goscianska, J.; Pietrzak, R.; Bednarski, W.; Majka, Z.; Cielecka-Piontek, J. 2015. Complex of rutin with β-cyclodextrin as potential delivery system. PLoS ONE 10, e0120858.

Palminteri, M.; Dhakar, N.K.; Ferraresi, A.; Caldera, F.; Vidoni, C.; Trotta, F.; Isidoro, C. 2021. Cyclodextrin nanosponge for the GSH-mediated delivery of resveratrol in human cancer cells. Nanotheranostics 5, 197-212.

Pezzuto, J.M. 2011. The phenomenon of resveratrol: redefining the virtues of promiscuity. Ann. NY Acad. Sci. 1215, 123-130.

Pinho, E.; Grootveld, M.; Soares, G.; Henriques, M. 2014. Cyclodextrins as encapsulation agents for plant bioactive compounds. Carbohydr. Polym. 101, 121-135.

Poinssot, B.; Vandelle, E.; Bentéjac, M.; Adrian, M.; Levis, C.; Brygoo, Y.; Garin, J.; Sicilia, F.; Coutos-Thévenot, P.; Pugin, A. 2003. The endopolygalacturonase 1 from *Botrytis cinerea* activates grapevine defense reactions unrelated to its enzymatic activity. Mol. Plant Microbe Interact. 16, 553-564.

Prysyazhna, O.; Wolhuter, K.; Switzer, C.; Santos, C.; Yang, X.; Lynham, S.; Shah, A.M.; Eaton, P.; Burgoyne, J.R. 2019. Blood pressure-lowering by the antioxidant resveratrol is counter-intuitively mediated by oxidation of cGMP-dependent protein kinase. Circulation 140, 126-137.

Pushpalatha, R.; Selvamuthukumar, S.; Kilimozhi, D. 2018. Carbonyl and carboxylate crosslinked cyclodextrin as a nanocarrier for resveratrol: *in silico*, *in vitro* and *in vivo* evaluation. J. Incl. Phenom. Macrocycl. Chem. 92, 261-272.

Pushpalatha, R.; Selvamuthukumar, S.; Kilimozhi, D. 2019. Cyclodextrin nanosponge based hydrogel for the transdermal co-delivery of curcumin and resveratrol: Development, optimization, *in vitro* and *ex vivo* evaluation. J. Drug Deliv. Sci. Technol. 52, 55-64.

Qian, Y.; Lynch, J.H.; Guo, L.; Rhodes, D.; Morgan, J.A.; Dudareva, N. 2019. Completion of the cytosolic post-chorismate phenylalanine biosynthetic pathway in plants. Nat. Comm. 10, 15.

Rafati, N.; Zarrabi, A.; Caldera, F.; Trotta, F.; Ghias, N. 2019. Pyromellitic dianhydride crosslinked cyclodextrin nanosponges for curcumin-controlled release: formulation, physicochemical characterization and cytotoxicity investigations. J. Microencapsul. 36, 715-727.

Rao, M.R.; Chaudhari, J.; Trotta, F.; Caldera, F. 2018. Investigation of cyclodextrin-based nanosponges for solubility and bioavailability enhancement of rilpivirine. AAPS PharmSciTech. 19, 1-12.

Rauf, A.; Imran, M.; Butt, M.S.; Nadeem, M.; Peters, D.G.; Mubarak, M.S. 2018. Resveratrol as an anti-cancer agent: A review. Crit. Rev. Food Sci. Nutr. 58, 1428-1447.

Regev-Shoshani, G.; Shoseyov, O.; Bilkis, I.; Kerem, Z. 2003. Glycosylation of resveratrol protects it from enzymic oxidation. Biochem. J. 374, 157-163.

Renaud, S.; De Lorgeril, M. 1992. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 339, 1523-1526.

Rivière, C.; Pawlus, A.D.; Mérillon, J.M. 2012. Natural stilbenoids: Distribution in the plant kingdom and chemotaxonomic interest in Vitaceae. Nat. Prod. Rep. 29, 1317-1333.

Ruhlmann, A.; Antovic, D.; Muller, T.; Urlacher, V.B. 2017. Regioselective hydroxylation of stilbenes by engineered cytochrome P450 from *Thermobifida fusca* YX. Adv. Synth. Catal. 359, 984-994.

Sabadini, E.; Cosgrove, T.; do Carmo Edigio, F. 2006. Solubility of cyclomaltooligosaccharides (cyclodextrins) in H_2O and D_2O: A comparative study. Carbohydr. Res. 341, 270-274.

Saenger, W.; Jacob, J.; Gessler, K.; Steiner, T.; Hoffmann, D.; Sanbe, H.; Koizumi, K.; Smith, S.M.; Takaha, T. 1998. Structures of the common cyclodextrins and their larger analogues - beyond the doughnut. Chem. Rev. 98, 1787-1802.

Sandilya, A.A.; Natarajan, U.; Priya, M.H. 2020. Molecular view into the cyclodextrin cavity: Structure and hydration. ACS Omega 5, 25655-25667.

Santamaria, A.R.; Antonacci, D.; Caruso, G.; Cavaliere, C.; Gubbiotti, R.; Laganà, A.; Valletta, A.; Pasqua, G. 2010. Stilbene production in cell cultures of *Vitis vinifera* L. cvs Red Globe and Michele Palieri elicited by methyl jasmonate. Nat. Prod. Res. 24, 1488-1498.

Sapino, S.; Carlotti, M.E.; Caron, G.; Ugazio, E.; Cavalli, R. 2009. *In silico* design, photostability and biological properties of the complex resveratrol/hydroxypropyl-β-cyclodextrin. J. Incl. Phenom. Macrocycl. Chem. 63, 171-180.

Sharma, R.; Pathak, K. 2011. Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation. Pharm. Dev. Technol. 16, 367-376.

Shen, T.; Wang, X.N.; Lou, H.X. 2009. Natural stilbenes: An overview. Nat. Prod. Rep. 26, 916-935.

Shende, P.K.; Trotta, F.; Gaud, R.S.; Deshmukh, K.; Cavalli, R.; Biasizzo, M. 2012. Influence of different techniques on formulation and comparative characterization of inclusion complexes of ASA with β-cyclodextrin and inclusion complexes of ASA with PMDA cross-linked β-cyclodextrin nanosponges. J. Incl. Phenom. Macrocycl. Chem. 74, 447-454.

Shimoda, K.; Kubota, N.; Hamada, H.; Hamada, K. 2015. Synthesis of resveratrol glycosides by plant glucosyltransferase and cyclodextrin glucanotransferase and their neuroprotective activity. Nat. Prod. Comm. 10, 995-996.

Siemann, E.H.; Creasy, L.L. 1992. Concentration of the phytoalexin resveratrol in wine. Am. J. Enol. Vitic. 43, 49-52.

Silva, F.; Figueiras, A.; Gallardo, E.; Nerin, C.; Domingues, F.C. 2014. Strategies to improve the solubility and stability of stilbene antioxidants: A comparative study between cyclodextrins and bile acids. Food Chem. 145, 115-125.

Silva, A.F.R.; Monteiro, M.; Resende, D.; Braga, S.S.; Coimbra, M.A.; Silva, A.M.S.; Cardoso, S.M. 2021. Inclusion complex of resveratrol with γ-cyclodextrin as a functional ingredient for lemon juices. Foods 10, 16.

Sirerol, J.A.; Feddi, F.; Mena, S.; Rodriguez, M.L.; Sirera, P.; Aupi, M.; Perez, S.; Asensi, M.; Ortega, A.; Estrela, J.M. 2015. Topical treatment with pterostilbene, a natural phytoalexin, effectively protects hairless mice against UVB radiation-induced skin damage and carcinogenesis. Free Radic. Biol. Med. 85, 1-11.

Smoliga, J.M.; Blanchard, O. 2014. Enhancing the delivery of resveratrol in humans: if low bioavailability is the problem, what is the solution? Molecules 19, 17154-17172.

Snyder, S.A.; Goliner, A.; Chiriac, M. 2011. Regioselective reactions for programmable resveratrol oligomer synthesis. Nature 474, 461-464.

Soo, E.; Thakur, S.; Qu, Z.; Jambhrunkar, S.; Parekh, H.S.; Popat, A. 2016. Enhancing delivery and cytotoxicity of resveratrol through a dual nanoencapsulation approach. J. Colloid Interface Sci. 462, 368-374.

Soussi, D.; Danion, J.; Baulier, E.; Favreau, F.; Sauvageon, Y.; Bossard, V.; Matillon, X.; Turpin, F.; Belgsir, E.M.; Thuillier, R.; Hauet, T. 2019. Vectisol formulation enhances solubility of resveratrol and brings its benefits to kidney transplantation in a preclinical porcine model. Int. J. Mol. Sci. 20, 2268.

Springer, M.; Moco, S. 2019. Resveratrol and its human metabolites - Effects on metabolic health and obesity. Nutrients, 11, 143.

Stella, V.J.; Rajewski, R.A. 2020. Sulfobutylether-β-cyclodextrin. Int. J. Pharm. 583, 119396.

Stella, V.J.; Rao, V.M.; Zannou, E.A.; Zia, V. 1999. Mechanisms of drug release from cyclodextrin complexes. Adv. Drug Deliv. Rev. 36, 3-16.

Szejtli, J. 1998. Introduction and general overview of cyclodextrin chemistry. Chem. Rev. 98, 1743-1754.

Takaoka, M. 1939. Resveratrol, a new phenolic compound, from *Veratrum grandiflorum*. J. Chem. Soc. Jpn. 60, 1090-1100.

Tan, C.; Wang, J.; Sun, B. 2021. Biopolymer-liposome hybrid systems for controlled delivery of bioactive compounds: Recent advances. Biotechnol. Adv. 48, 107727.

Tassoni, A.; Fornale, S.; Franceschetti, M.; Musiani, F.; Michael, A.J.; Perry, B.; Bagni, N. 2005. Jasmonates and Na-orthovanadate promote resveratrol production in *Vitis vinifera* cv. Barbera cell cultures. New Phytol. 166, 895-905.

Tayo, L. 2017. Stimuli-responsive nanocarriers for intracellular delivery. Biophys. Rev. 9, 931-940.

Tisserant, L.P.; Aziz, A.; Jullian, N.; Jeandet, P.; Clément, C.; Courot, E.; Boitel-Conti, M. 2016. Enhanced stilbene production and excretion in *Vitis vinifera* cv. Pinot Noir hairy root cultures. Molecules 21,1703-1720.

Torne, S.; Darandale, S.; Vavia, P.; Trotta, F.; Cavalli, R. 2013. Cyclodextrin-based nanosponges: effective nanocarrier for tamoxifen delivery. Pharm. Dev. Technol. 18, 619-625.

Torres, P.; Poveda, A.; Jimenez-Barbero, J.; Parra, J.L.; Comelles, F.; Ballesteros, A.O.; Plou, F.J. 2011. Enzymatic synthesis of α-glycosides of resveratrol with surfactant activity. Adv. Synth. Catal. 353, 1077-1086.

Trela, B.C.; Waterhouse, A.L. 1994. Resveratrol: Isomeric molar absorptivities and stability. J. Agric. Food Chem. 44, 1253-1257.

Trollope, L.; Cruickshank, D.L.; Noonan, T.; Bourne, S.A.; Sorrenti, M.; Catenacci, L.; Caira, M. 2014. Inclusion of *trans*-resveratrol in methylated cyclodextrins: synthesis and solid-state structures. Beilstein J. Org. Chem. 10, 3136-3151.

Trotta, F.; Caldera, F.; Cavalli, R.; Soster, M.; Riedo, C.; Biasizzo, M.; Barretta, G.C.; Balzano, F.; Brunella, V. 2016a. Molecularly imprinted cyclodextrin nanosponges for the controlled delivery of L-DOPA: Perspectives for the treatment of Parkinson's disease. Expert Opin. Drug Deliv. 13, 1671-1680.

Trotta, F.; Caldera, F.; Dianzani, C.; Argenziano, M.; Barrera, G.; Cavalli, R. 2016b. Glutathione bioresponsive cyclodextrin nanosponges. ChemPlusChem 81, 439-443.

Uddin, M.S.; Al Mamun, A.; Rahman, M.M.; Jeandet, P.; Alexiou, A.; Behl, T.; Sarwar, M.S.; Sobarzo-Sanchez, E.; Ashraf, G.M.; Sayed, A.A.; Albadrani, G.M.; Peluso, I.; Abdel-Daim, M.M. 2021. Natural products for neurodegeneration: Regulating neurotrophic signals. Oxid. Med. Cell. Longev. 2021, 8820406.

Uddin, M.S.; Al Mamun, A.; Tanvir Kabir, M.; Ahmad, J.; Jeandet, P.; Sarwarf, M.S.; Ashraf, G.M.; Aleya, L. 2020. Neuroprotective role of polyphenols against oxidative stress-mediated neurodegeneration. Eur. J. Pharmacol. 886, 173412.

Vandelle, E.; Poinssot, B.; Wendehenne, D.; Bentéjac, M.; Pugin, A. 2006. Integrated signaling network involving calcium, nitric oxide, and active oxygen species but not mitogen-activated protein kinases in BcPG1-elicited grapevine defenses. Mol. Plant Microbe Interact. 19, 429-440.

Vannozzi, A.; Wong, D.C.J.; Höll, J.; Hmmam, I.; Matus, J.T.; Bogs, J.; Ziegler, T.; Dry, I.; Barcaccia, G.; Lucchin, M. 2018. Combinatorial regulation of stilbene synthase genes by WRKY and MYB transcription factors in grapevine (*Vitis vinifera* L.). Plant Cell Physiol. 59, 1043-1059.

Varoni, E.M.; Lo Faro, A.F; Sharifi-Rad, J.; Iriti, M. 2016. Anticancer molecular mechanisms of resveratrol. Front. Nutr. 3, 8.

Venuti, V.; Cannava, C.; Cristiano, M.C.; Fresta, M.; Majolino, D.; Paolino, D.; Stancanelli, R.; Tommasini, S.; Ventura, C.A. 2014. A characterization study of resveratrol/sulfobutylether-β-cyclodextrin inclusion complex and *in vitro* cancer activity. Colloids Surf. B 115, 22-28.

Vera-Urbina, J.C.; Selles-Marchart, S.; Martinez-Esteso, M.J.; Pedreño, M.A.; Bru-Martinez, R. 2013. Production of grapevine cell biomass and resveratrol in custom and commercial bioreactors using cyclodextrins and methyl jasmonate as elicitors, in: Delmas, D. (Ed.), Resveratrol: source, production, and health benefits. Nova Science Publishers Inc, New York, pp. 19-39.

Vestergaard, M.; Ingmer H. 2019. Antibacterial and antifungal properties of resveratrol. Int. J. Antimicrob. Agents 53, 716-723.

Wajs, E.; Nielsen, T.T.; Larsen, K.L.; Fragoso, A. 2016. Preparation of stimuli-responsive nano-sized capsules based on CD polymers with redox or light switching properties. Nano Research 9, 2070-2078.

Walle, T. 2011. Bioavailability of resveratrol. Ann. N. Y. Acad. Sci. 1215, 9-15.

Walle, T.; Hsieh, F.; DeLegge, M.H.; Oatis, J.E.; Walle, K. 2004. High absorption but very low bioavailability of oral resveratrol in humans. Drug Metab. Dispos. 32, 1377-1382.

Walle, T.; Walle, U.K.; Sedmerer, D.; Klausner, M. 2006. Benzo[A]pyrene-induced oral carcinogenesis and chemoprevention: studies in bioengineered human tissue. Drug Metab. Dispos. 34, 346-350.

Wang, X.; Parvathaneni, V.; Shukla, S.K.; Kulkarni, N.; Muth, A.; Kunda, N.K.; Gupta, V. 2020. Inhalable resveratrol-cyclodextrin complex loaded biodegradable nanoparticles for enhanced efficacy against non-small cell lung cancer. Int. J. Biol. Macromol. 164, 638-650.

Wightman, E.L.; Haskell-Ramsay, C.F.; Reay, J.L.; Williamson, G.; Dew, T.; Zhang, W.; Kennedy, D.O. 2015. The effects of chronic trans-resveratrol supplementation on aspects of cognitive function, mood, sleep, health and cerebral blood flow in healthy, young humans. Br. J. Nutr. 114, 1427-1437.

Wong, R.H.X.; Howe, P.R.C.; Buckley, J.D.; Coates, A.M.; Kunz, I.; Berry, N.M. 2011. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. Nutr. Metab. Cardiovasc. Dis. 21, 851-856.

Wong, D.C.J.; Matus, J.T. 2017. Constructing integrated networks for identifying new secondary metabolic pathway regulators in grapevine: recent applications and future opportunities. Front. Plant Sci. 8, e505.

Wong, K.H.; Riaz, M.K.; Xie, Y.; Zhang, X.; Liu Q.; Chen, H.; Bian, Z.; Chen, X.; Lu, A.; Yang, Z. 2019. Review of current strategies for delivering Alzheimer's disease drugs across the blood-brain barrier. Int. J. Mol. Sci. 20, 381.

Wong, K.H.; Xie, Y.; Huang, X.; Kadota, K.; Yao X.S.; Yu, Y.; Chen, X.; Lu, A.; Yang, Z. 2020. Delivering crocetin across the blood-brain barrier by using γ-cyclodextrin to treat Alzheimer's disease. Sci. Rep. 10, 3654.

Wu, B.; Basu, S.; Meng, S.; Wang, X.; Hu, M. 2011. Regioselective sulfation and glucuronidation of phenolics: Insights into the structural basis. Curr. Drug Metab. 12, 900-916.

Wu, M.; Cao, Z.; Zhao, Y.; Zeng, R.; Tu, M.; Zhao, J. 2016. Novel self-assembled pH-responsive biomimetic nanocarriers for drug delivery. Mater. Sci. Eng. C Mater. Biol. Appl. 64, 346-353.

Yang, T.; Fang, L.; Nopo-Olazabal, C.; Condori, J.; Nopo-Olazabal, L.; Balmaceda, C.; Medina-Bolivar, F. 2015. Enhanced production of resveratrol, piceatannol, arachidin-1, and arachidin-3 in hairy root cultures of peanut co-treated with methyl jasmonate and cyclodextrin. J. Agric. Food Chem. 63, 3942-3950.

Yang, T.; Fang, L.; Sanders, S.; Jayanthi, S.; Rajan, G.; Podicheti, R.; Thallapuranam, S.K.; Mockaitis, K.; Medina-Bolivar, F. 2018. Stilbenoid prenyltransferases define key steps in the diversification of peanut phytoalexins. J. Biol. Chem. 293, 28-46.

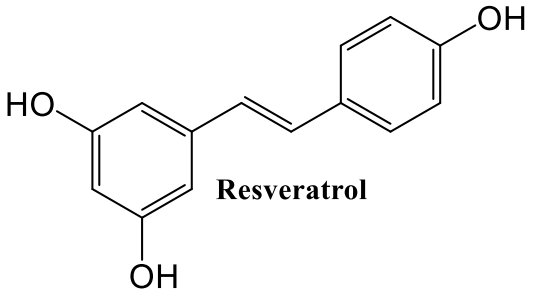
Yasayan, G.; Sert, B.S.; Tatar, E.; Küçükgüzel, I. 2020. Fabrication and characterization studies of cyclodextrin-based nanosponges for sulfamethoxazole delivery. J. Incl. Phenom. Macrocycl. Chem.97, 175-186.

Zamboni, A.; Vrhovsek, U.; Kassemeyer, H.H.; Mattivi, F.; Velasco, R. 2006. Elicitor-induced resveratrol production in cell cultures of different grape genotypes (*Vitis* spp.). Vitis 45, 63-68.

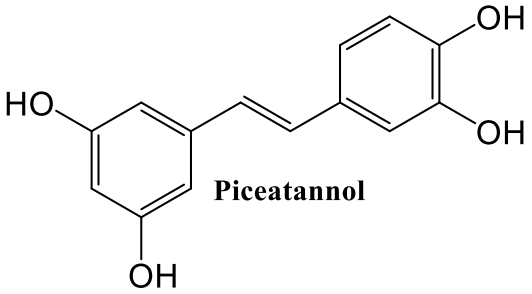
Zordosky, B.N.M.; Robertson, I.M.; Dyck, J.R.B. 2015. Preclinical and clinical evidence for the role of resveratrol in the treatment of cardiovascular diseases. Biochim. Biophys. Acta Mol. Basis Dis. 1852, 1155-1177.

1002

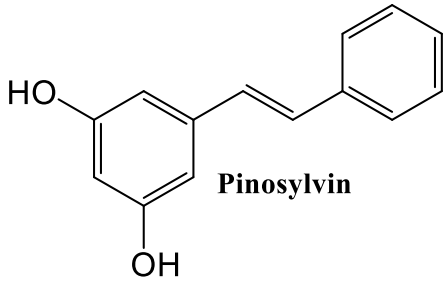
1003



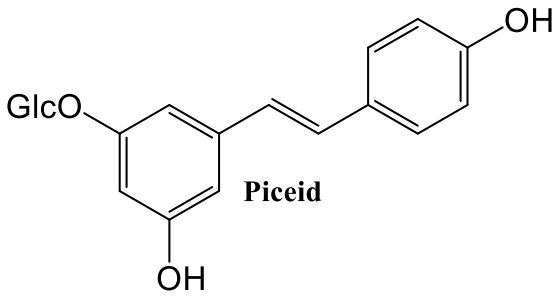
Resveratrol



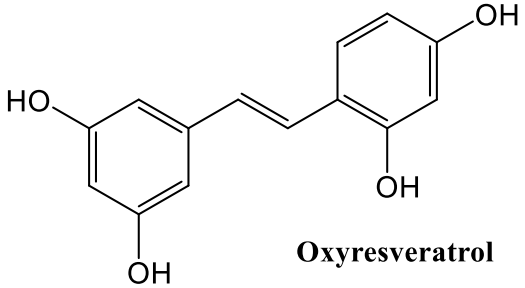
Piceatannol



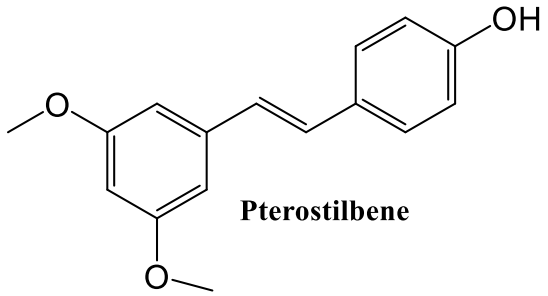
Pinosylvin



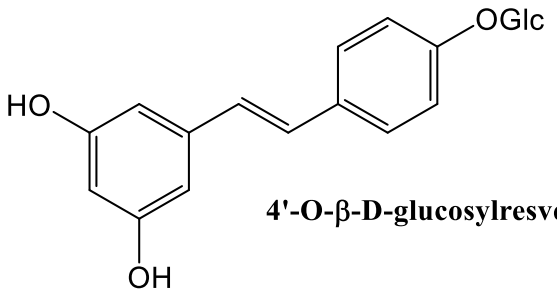
Piceid



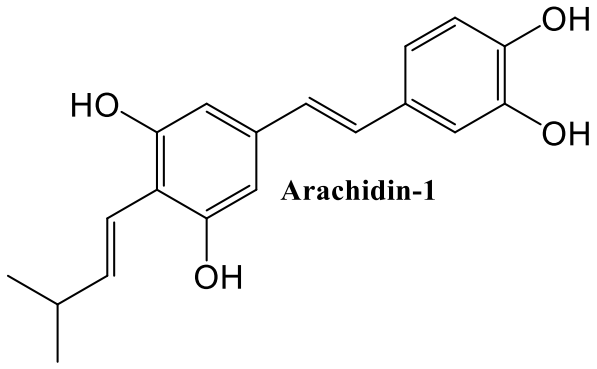
Oxyresveratrol



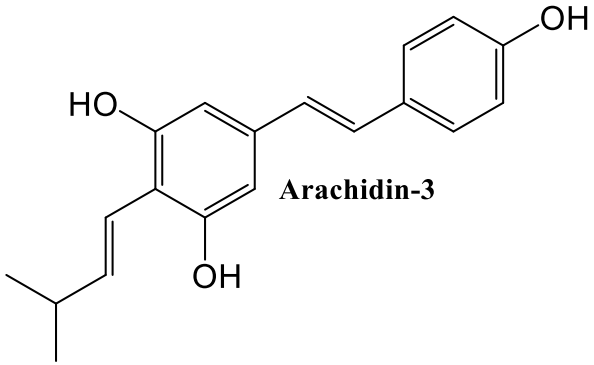
Pterostilbene



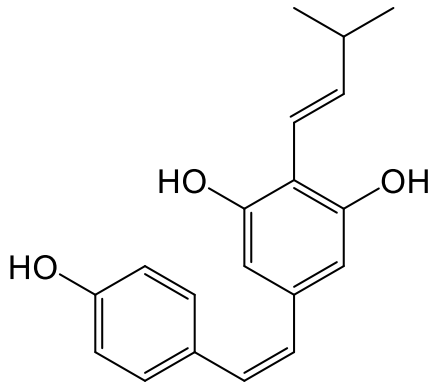
4'-O-β-D-glucosylresveratrol



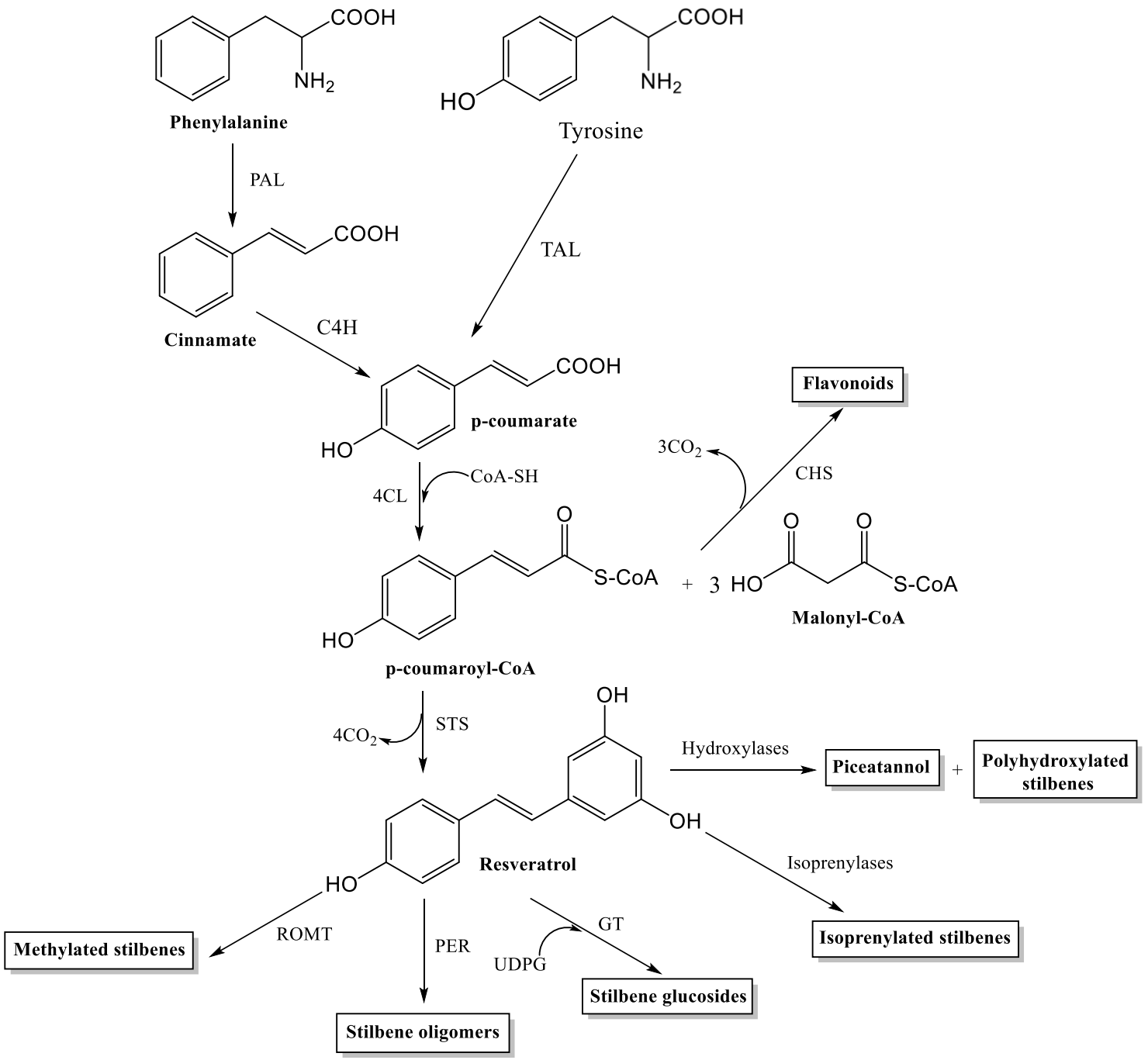
Arachidin-1

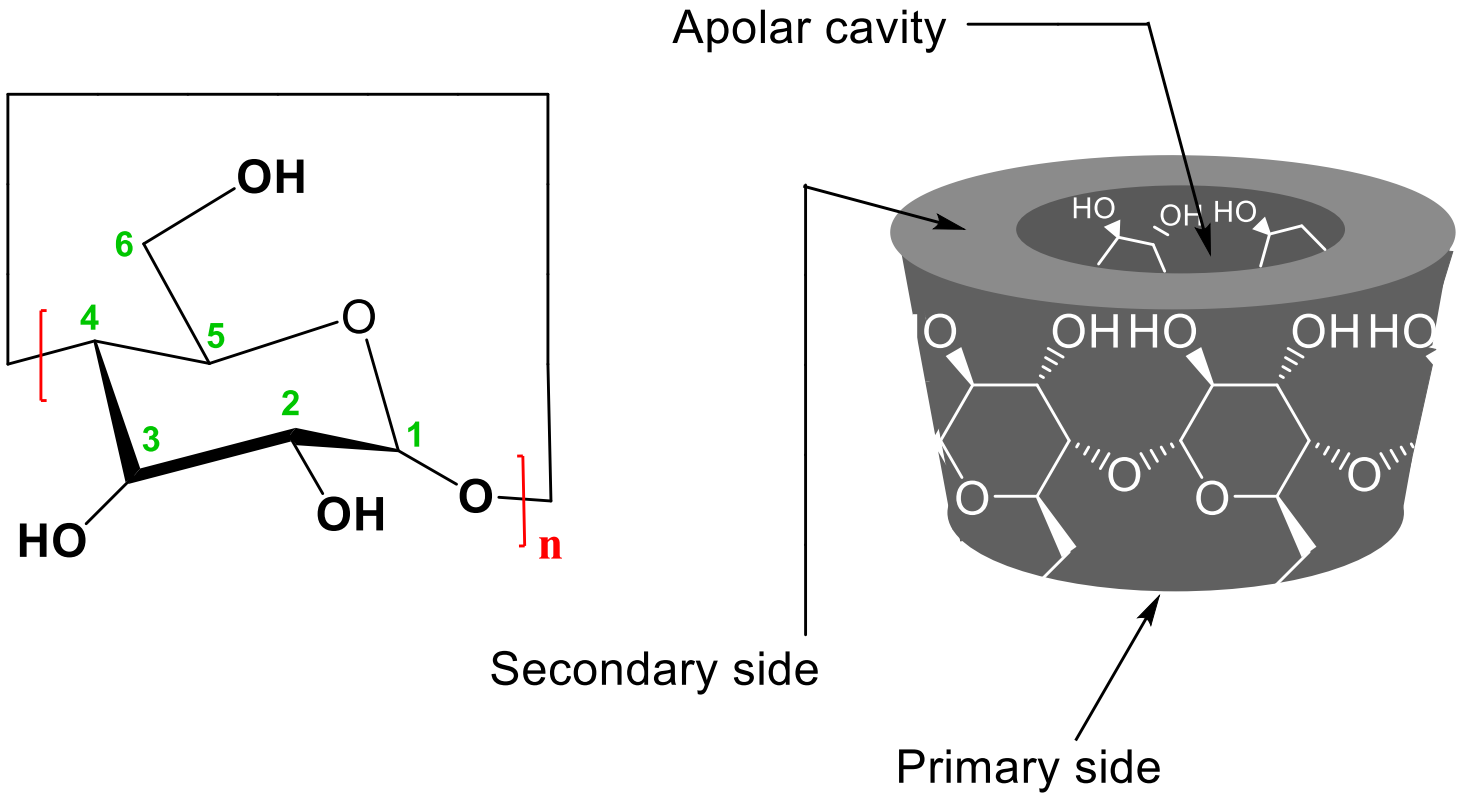


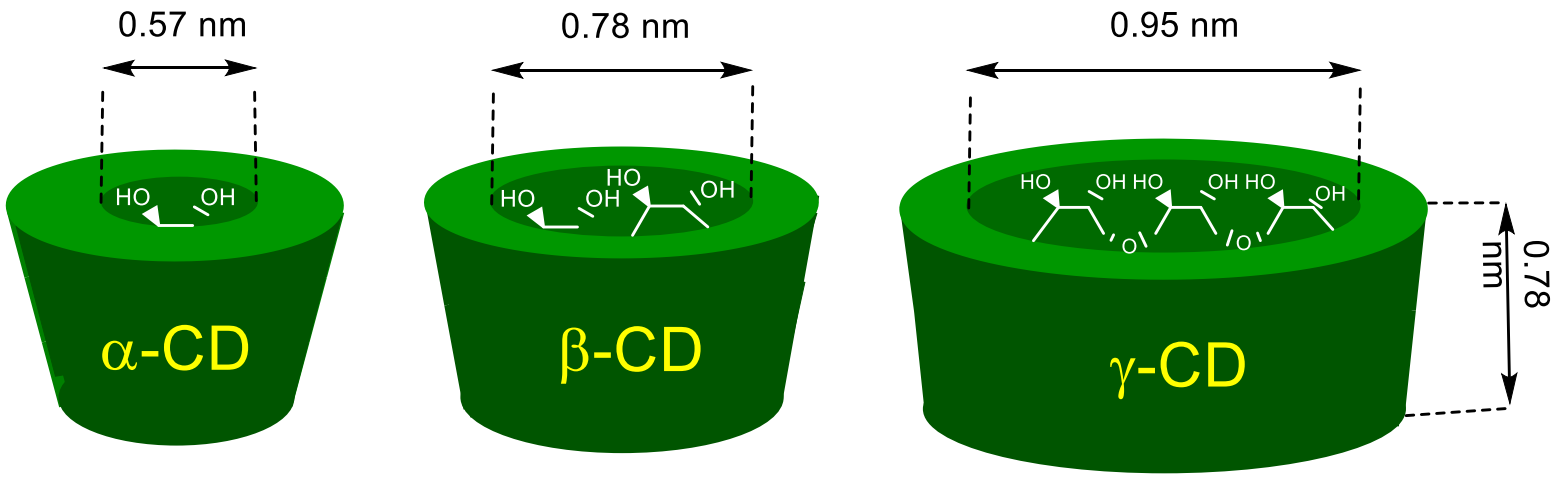
Arachidin-3

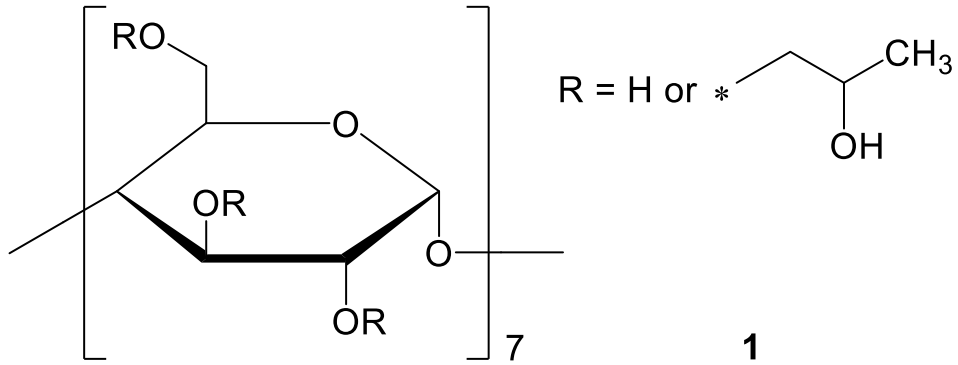


Arachidin-2

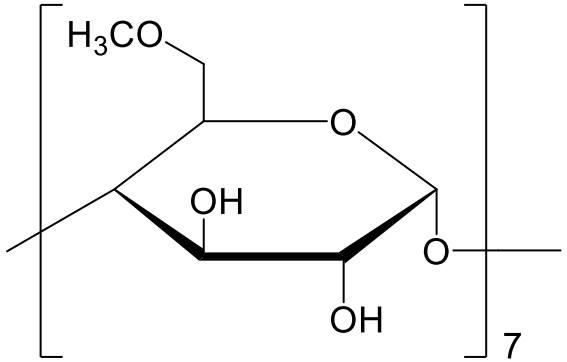

COOH
NH2
Phenylalanine
HO
Tyrosine
PAL
TAL
Cinnamate
C4H
p-coumarate
Flavonoids
3CO2
CHS
4CL
CoA-SH
S-CoA
+ 3 HO
Malonyl-CoA
p-coumaroyl-CoA
4CO2
STS
OH
Hydroxylases
Piceatannol
+
Polyhydroxylated stilbenes
Resveratrol
Isoprenylases
Isoprenylated stilbenes
ROMT
Methylated stilbenes
PER
GT
UDPG
Stilbene glucosides
Stilbene oligomers


Apolar cavity
OH
6
4
5
O
3
2
1
HO
OH
O
n
HO
OH HO
OH HO
OH HO
O
O
O
O
O
Secondary side
Primary side

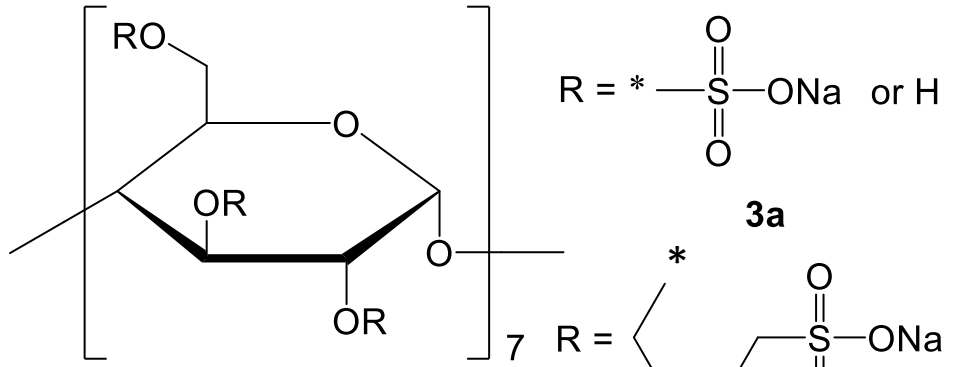

0.57 nm
HO
OH
α-CD
0.78 nm
HO
OH
HO
OH
β-CD
0.95 nm
HO
OH HO
OH HO
OH
O
O
γ-CD
0.78 nm


RO
O
OR
O
OR
7
R = H or *
CH3
OH

1

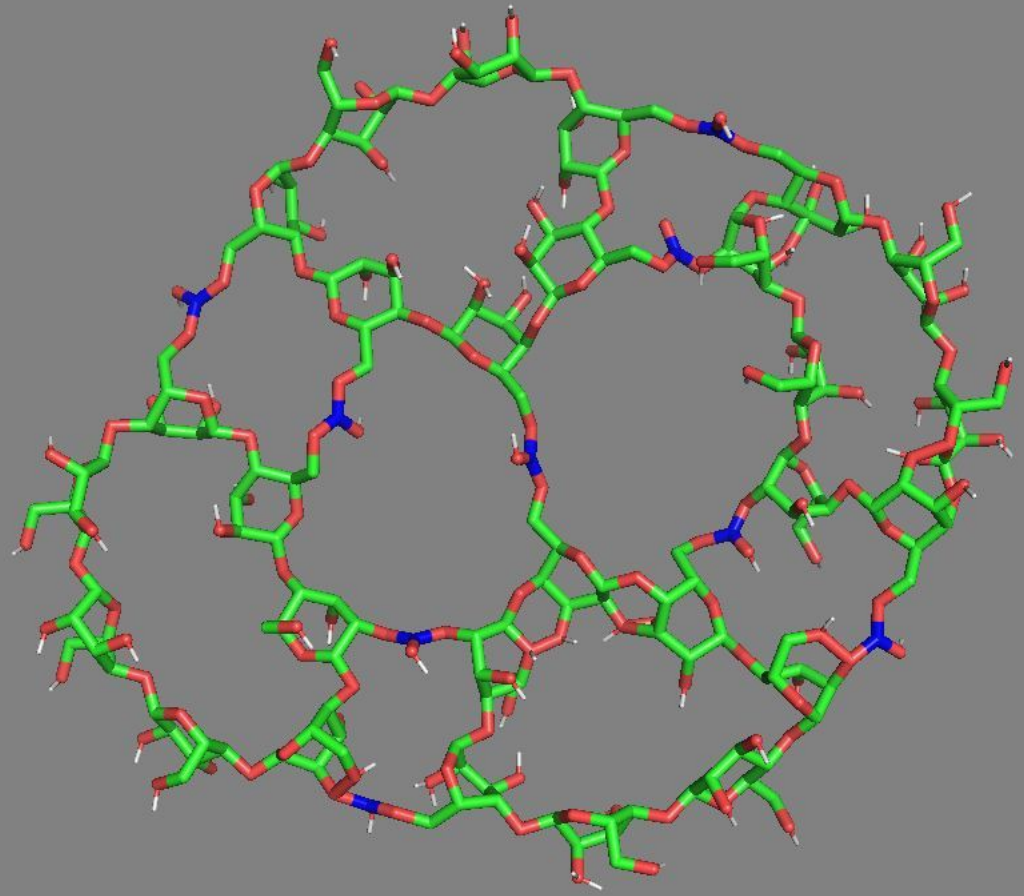

H3CO
O
OH
O
OH
7

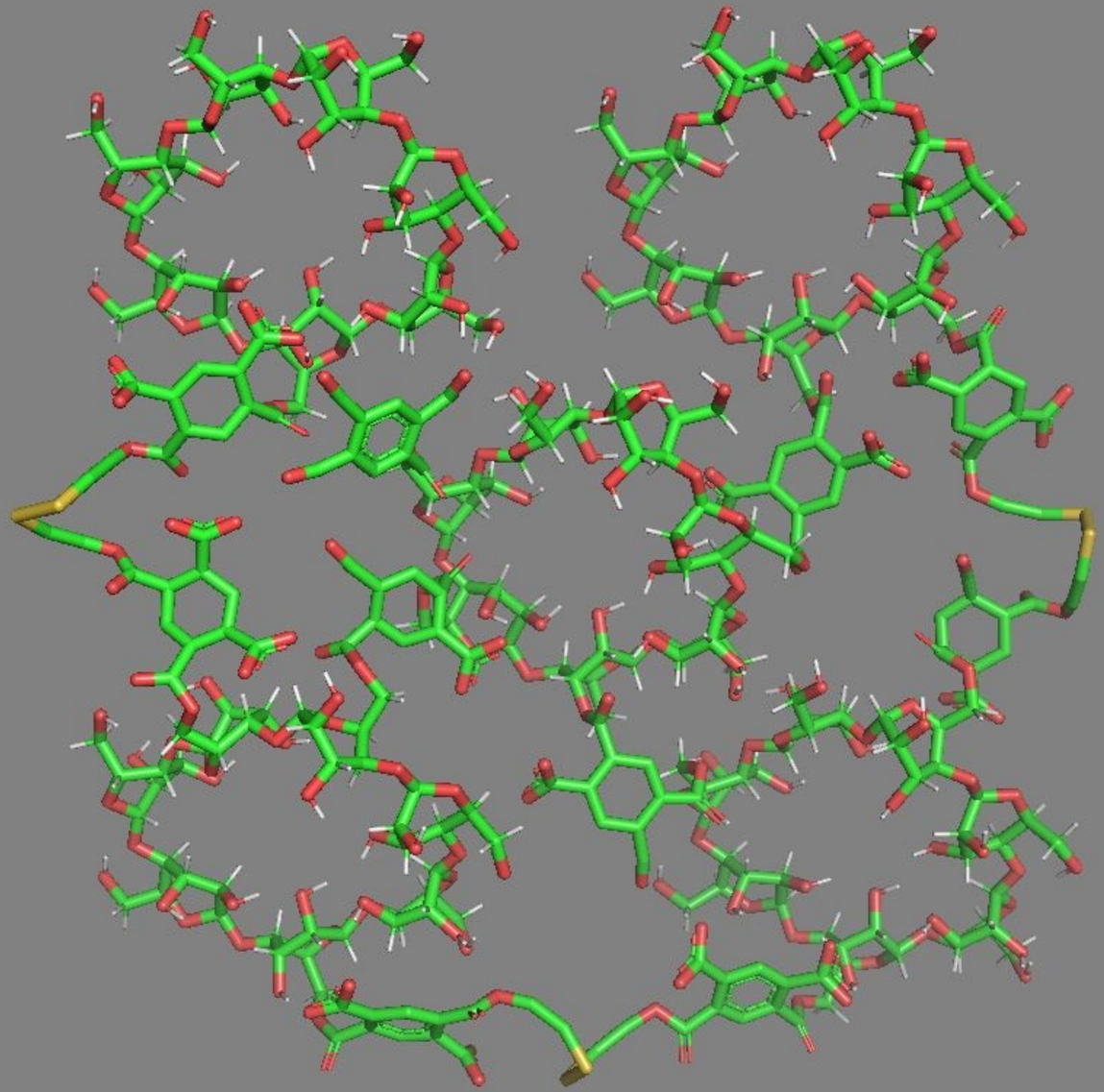
2

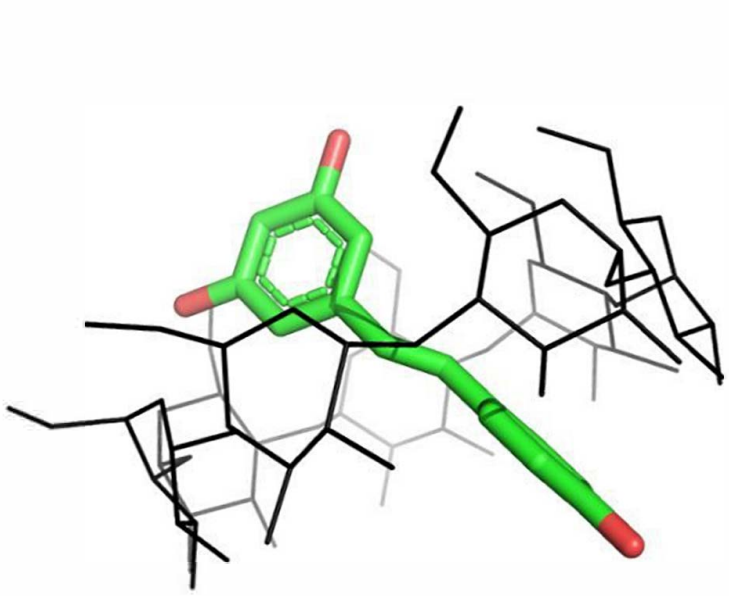
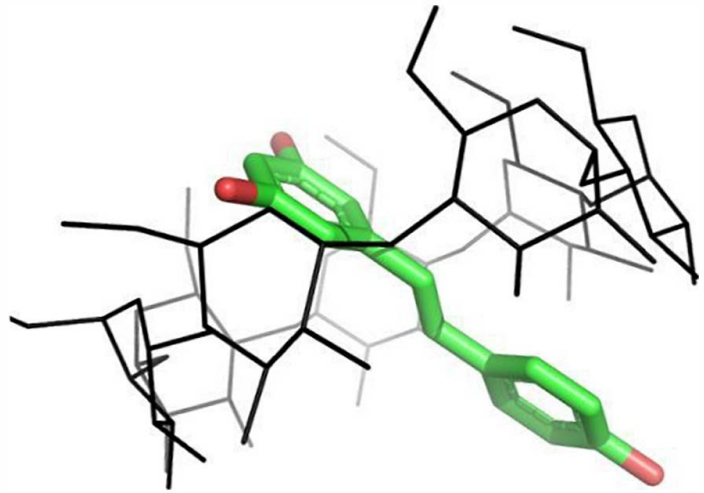
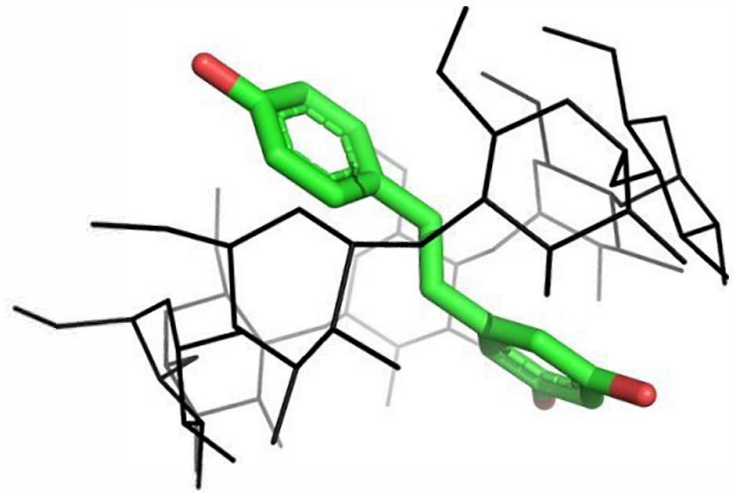
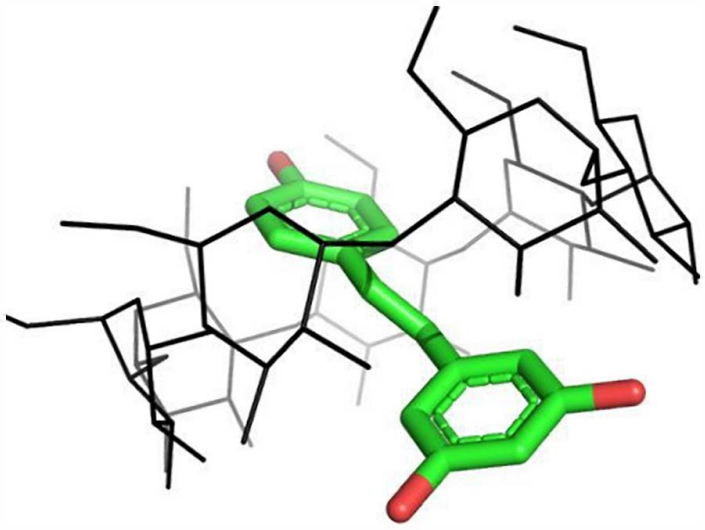
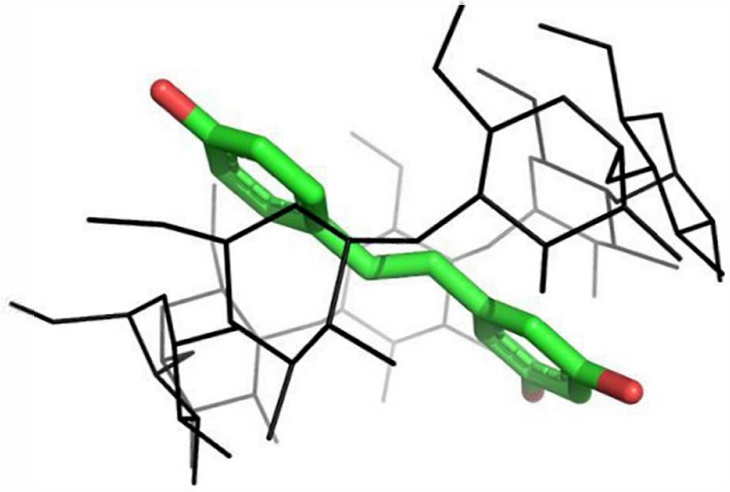
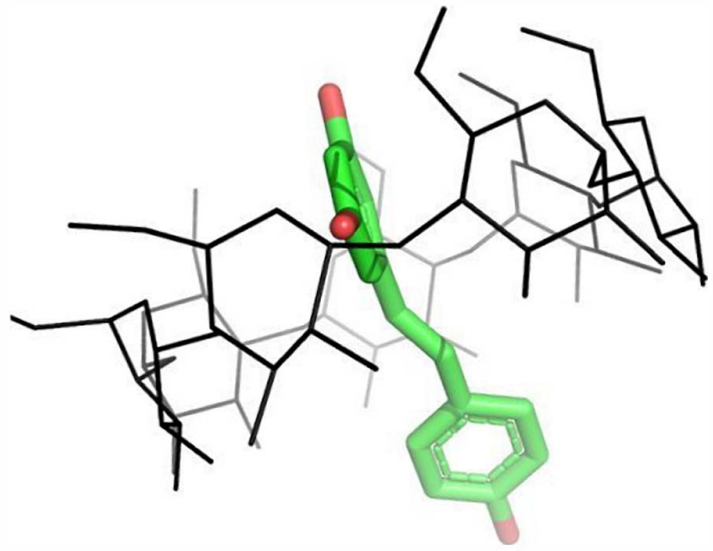

RO
O
OR
O
OR
7
R = *
S
O
ONa
or H
O
O
R =
*
S
O
ONa
O
O

3a

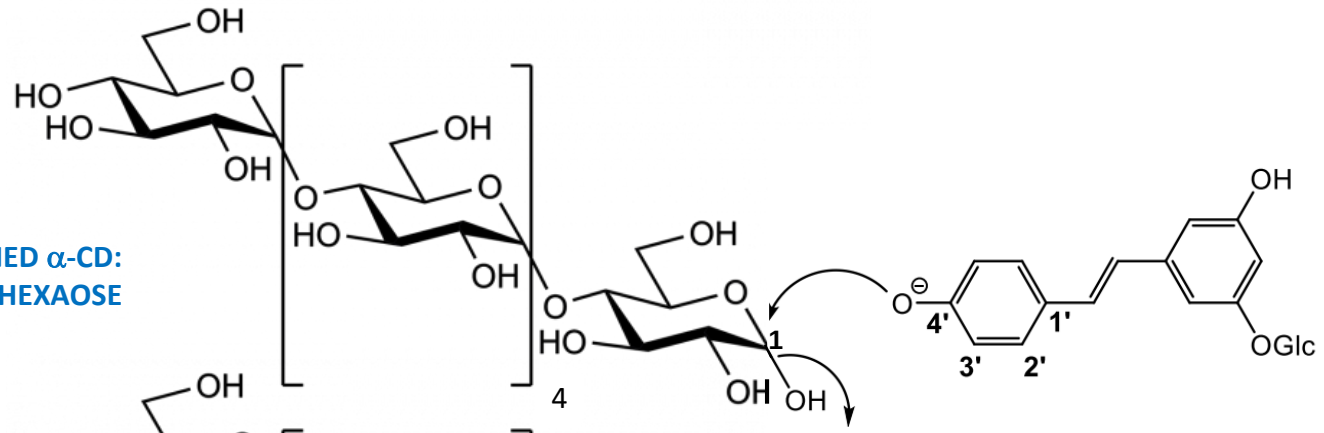
3b



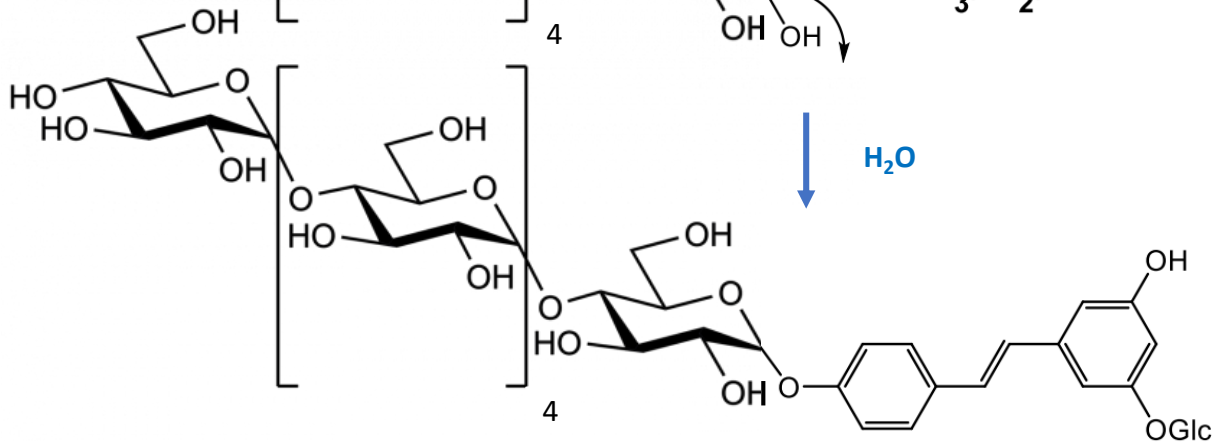


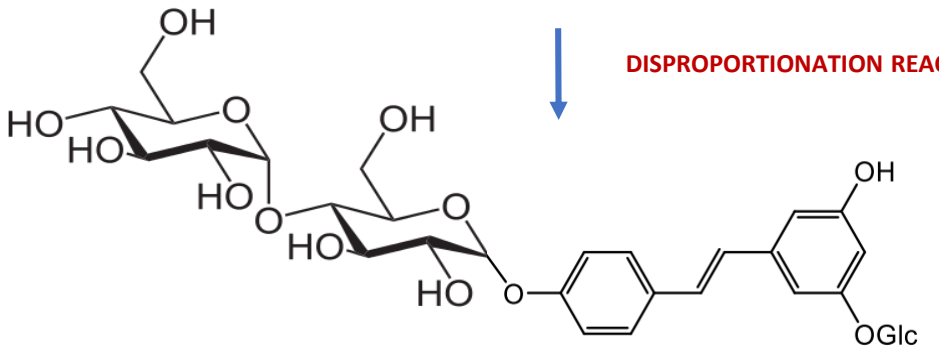
OPENED α-CD:
α- MALTOHEXAOSE



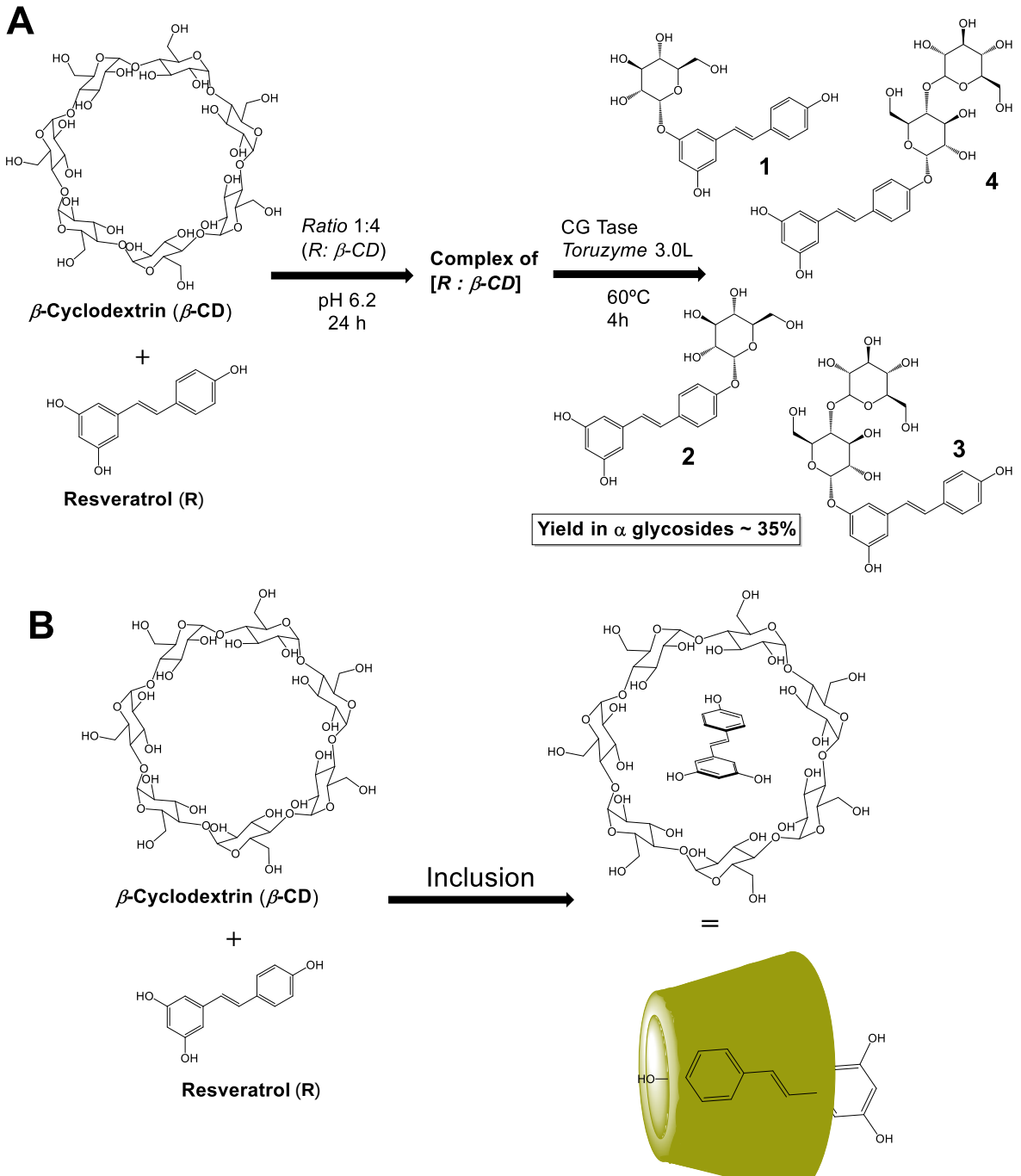
H_2O



DISPROPORTIONATION REACTIONS



PicG3 + various glucosides


A
β-Cyclodextrin (β-CD)
+
Resveratrol (R)
Ratio 1:4
(R: β-CD)
pH 6.2
24 h
Complex of
[R : β-CD]
CG Tase
Toruzyme 3.0L
60ºC
4h
1
2
3
4
Yield in α glycosides ~ 35%
B
β-Cyclodextrin (β-CD)
+
Resveratrol (R)
Inclusion
=

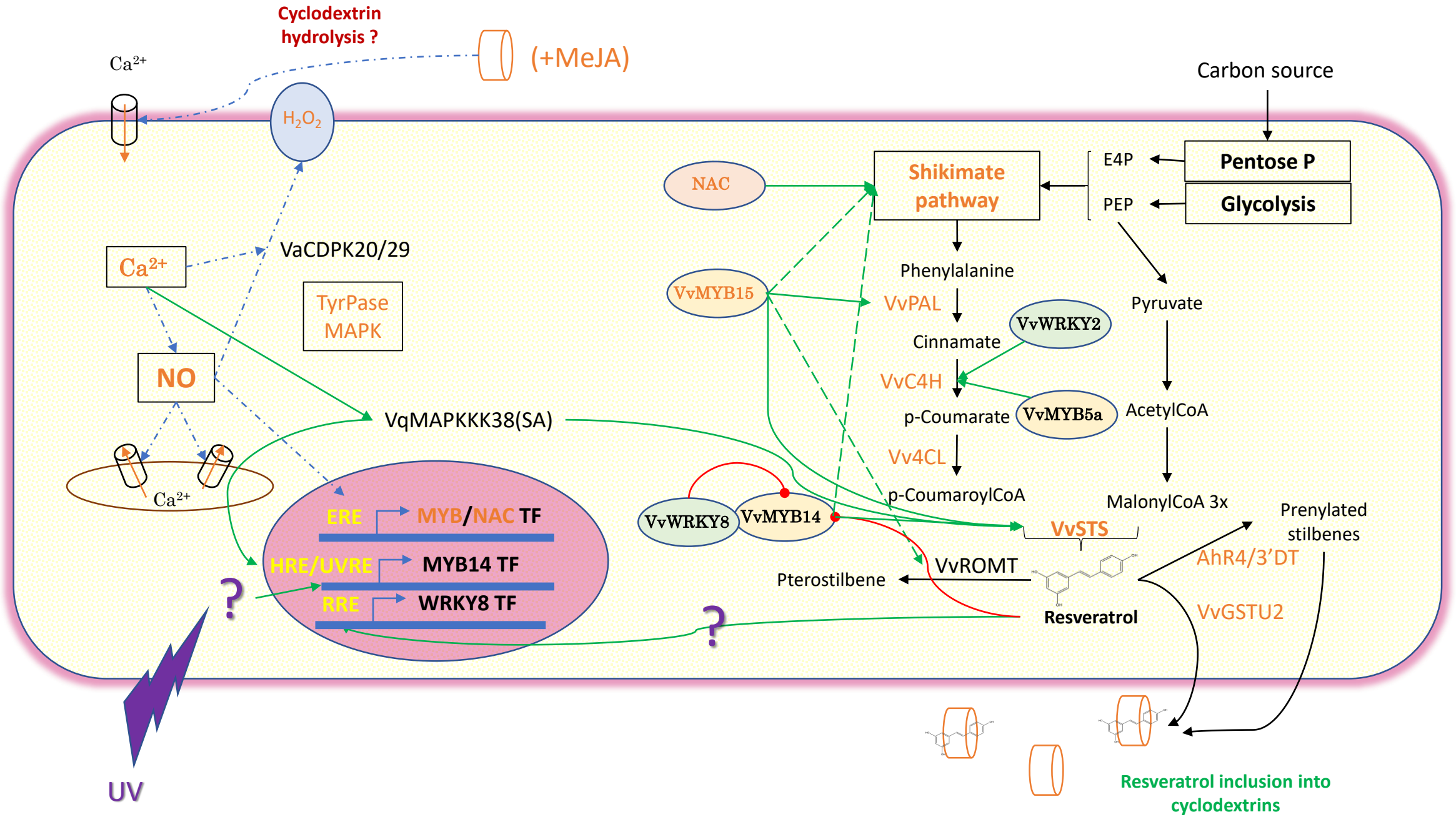

Cyclodextrin hydrolysis ?
(+MeJA)
Ca2+
H2O2
Carbon source
Pentose P
Glycolysis
E4P
PEP
Shikimate pathway
NAC
VvMYB15
Phenylalanine
VvPAL
Cinnamate
VvC4H
p-Coumarate
Vv4CL
p-CoumaroylCoA
VvWRKY2
VvMYB5a
Pyruvate
AcetylCoA
MalonylCoA 3x
VaCDPK20/29
TyrPase MAPK
NO
VqMAPKKK38(SA)
ERE
MYB/NAC TF
HRE/UVRE
MYB14 TF
RRE
WRKY8 TF
VvWRKY8
VvMYB14
VvSTS
VvROMT
Pterostilbene
Resveratrol
Prenylated stilbenes
AhR4/3'DT
VvGSTU2
UV
Resveratrol inclusion into cyclodextrins

Table 1: Some parameters of stilbenes/cyclodextrins inclusion complexes

Abbreviations: K_s: stability constant; CD, cyclodextrin; β-CD, β-cyclodextrin; G2-β-CD, maltosyl- β-cyclodextrin; HP-β-CD, 2-hydroxypropyl-β-cyclodextrin; DM-β-CD, dimethylated-β-cyclodextrin; RAMEB-β-CD, randomized methylated- β-CD, Me-β-CD, methylated β-cyclodextrin; nr, not reported; PLGA, Poly (lactic-co-glycolic) acid; EE, entrapment efficiency; DL, drug loading; Resv-NS,resveratrol-nanosponge; Oxyresv-NS, oxyresveratrol-nanosponge; w/w,weight/weight ratio; GSH, glutathione

Type of CD	Stilbenes	Stoichio -metry	K_s values	Stilbene solubility increase	Stilbene loading	Stilbene release	Refs
β-CD	Resveratrol	1:1	2057 M^{-1}	2-fold	nr	nr	Bertache et al. (2006)
HP-β-CD	Resveratrol	1:1	1588 M^{-1}	nr	nr	nr	
DM-β-CD	Resveratrol	1:1	2604 M^{-1}	8-fold	nr	nr	
β-CD	Resveratrol	nr	4317 ± 338 M^{-1}	nr	nr	nr	Lucas-Abellan et al. (2007)
G2-β-CD	Resveratrol	nr	5130 ± 421 M^{-1}	nr	nr	nr	
HP-β-CD	Resveratrol	1:1	3.17 x 10^5 M^{-1}	59500-fold	nr	nr	Das et al. (2008)
RAMEB-β-CD	Resveratrol	1:1	4.41 x 10^5 M^{-1}		nr	nr	
β-CD	Pinosylvin	1:1	5181 ± 233 M^{-1}	nr	nr	nr	Lopez-Nicolas et al. (2009a)
HP-β-CD	Pinosylvin	1:1	12112 ± 761 M^{-1}	nr	nr	nr	
β-CD	Pterostilbene	1:1	8120 ± 440 M^{-1}	nr	nr	nr	Lopez-Nicolas et al. (2009b)
HP-β-CD	Resveratrol	1:1	24880 ± 1020 M^{-}	nr	nr	nr	
HP-β-CD	Pterostilbene	1:1	17520 ± 981 M^{-1}	8-fold	nr	nr	
β-CD	Resveratrol	1:1	1815 M^{-1}	nr	nr	nr	Lu et al. (2009)
HP-β-CD	Resveratrol	1:1	6778 M^{-1}	nr	nr	nr	
HP-β-CD	Resveratrol	1:1	3189 M^{-1}	increases with CD concentration	nr	nr	Sapino et al. (2009)
HP-β-CD	Resveratrol	nr	nr	nr	nr	nr	Berta et al. (2010)
β-CD	Resveratrol	nr	nr	8.55 to 12.57-fold depending on CD concentration	nr	nr	Lu et al. (2012)
HP-β-CD	Resveratrol	nr	nr	24.31 to 50.49-fold depending on CD concentration	nr	nr	

HP-β-CD HP-β-CD HP-β-CD	Resveratrol Pterostilbene Pinosylvin	1:1 1:1 1:2	1682 ± 49 M^{-1} 11730 ± 13 M^{-1} 14 ± 2.3 M^{-1}	4-6 log fold-increase	nr nr nr	nr nr nr	Silva et al. (2014)
Sulfobutylether-β-CD	Resveratrol	1:1	10114 M^{-1}	37-fold (from 0.03 mg/mL to 1.1 mg/mL)	nr	nr	Venuti et al. (2014)
RAMEB-β-CD	Resveratrol	1:1	1482.9 ± 13.7 M^{-1}	400-fold	80%	Increased by 1.5-fold within 60 min	Duarte et al. (2015)
HP-β-CD	Piceatannol	1:1	14048 ± 702 M^{-1}	nr	nr	nr	Matencio et al. (2016)
HP-β-CD HP-β-CD	Resveratrol loaded in liposomes Resveratrol complexed with HP-β-CD and inclusion in liposomes Both complexation of resveratrol in liposomes and in HP-β-CD included in liposomes	nr nr nr	nr nr nr	nr nr nr	+3.08% +6.23% +11.6%	67.7% within 24h 100% within 24h 94.4% within 24h	Soo et al. (2016)
β-CD Me-β-CD HP-β-CD	Oxyresveratrol Oxyresveratrol Oxyresveratrol	1:1 1:1 1:1	590.00 M^{-1} 606.65 M^{-1} 435.53 M^{-1}	nr nr nr	nr nr nr	nr nr nr	Matencio et al. (2017)
β-CD Me-β-CD HP-β-CD	Polydatin Polydatin Polydatin	1:1 1:1 1:1	798M^{-1} 1106 M^{-1} 1308 M^{-1}	6.4-fold increase 7.9-fold increase 9-fold increase	nr nr nr	nr nr nr	Li et al. (2018)
β-CD HP-β-CD	Oxyresveratrol Oxyresveratrol	1:1 1:1	1897.54 ± 81.14 M^{-1} 35864.72 ± 3415.89 M^{-1}	30-fold increase (0.47 mg/mL to 14.44 mg/mL) 100-fold increase (0.47 mg/mL to 47.33 mg/mL)	20% increase 20% increase	nr nr	He et al. (2019)
HP-β-CD HP-β-CD HP-β-CD HP-β-CD	Resveratrol Oxyresveratrol Piceatannol Pterostilbene	nr	nr	nr	nr	nr	Lim et al. (2020)

Sulfobutylether-β-CD + PLGA	Resveratrol	nr	nr	66-fold (from 0.03 mg/mL to 2.0 mg/mL)	EE: 29.1% DL: 0.72%	95.7% resv release within 30 min	Wang et al. (2020)
γ-CD	Resveratrol	1:1	nr	9-fold increase in lemon juice	nr	nr	Silva et al. (2021)
NANOSPONGES							
Carbonyl nanosponge	Resveratrol	1:2/1:4	nr	33-fold increase (Resv-NS 1:2) 48-fold increase (Resv-NS 1:4)	30% increase (Resv-NS 1:2) 40% increase (Resv-NS 1:4)	5-fold increase (Resv-NS 1:2) 9-fold increase (Resv-NS 1:4) within 2h	Ansari et al. (2011b)
Carbonyl nanosponge (NS-I) Carboxylate nanosponge (NS-II)	Resveratrol	nr	nr	51 to 161 and 167 μg/mL (NS-I 1:2;1:4) 51 to 152 and 156 μg/mL (NS-II 1:2;1:4)	91.52% (NS-I) 90.81 (NS-II)	3-fold increases (NS-I and NS-II)	Pushpalatha et al. (2018)
Carbonyl nanosponge in hydrogels	Curcumin and resveratrol	nr	nr	nr	nr	10-fold increase including a lag phase with curcumin and 2.5 fold-increase with no lag phase with resveratrol compared to unloaded compounds	Pushpalatha et al. (2019)
Carbonyl nanosponge	Resveratrol Oxyresveratrol	-	nr	3-fold for resveratrol (40 to 120 μg/mL) 2-fold for oxyresveratrol (600 to >1000 μg/mL)	9.47 to 14% increase (Resv-NS 1:2 and 1:6 w/w ratio) 11.93 to 16.78% increase (Oxyresv-NS 1:2 and 1:6 w/w ratio)	5-fold increase (47.74% increase for resveratrol within 24h) *ca* 60% increase for oxyresveratrol within 24h	Dhakar et al. (2019)
Carbonyl nanosponge	Resveratrol Oxyresveratrol	1:4	K_{app} (apparent association constant) values: Oxyresv-β-CD 1:4, 3917.89 ± 392.79 M^{-1} Resv-β-CD 1:4, 4466.48 ± 446.65 M^{-1}	nr	39.75% increase (Oxyresv-β-CD-NS 1:4)	Diffusion profile of Oxyresv-NS slower than that of free oxyresveratrol within 12h, pH dependent	Mattencio et al. (2020)
α, β anr γ-CD polymers	Resveratrol	nr	nr	nr	4.5% increase for α and γ-CD polymers 6.7% increase for β-CD polymers	Respectively 11%, 6% and 12% resveratrol release for α, β and γ-CD polymers within 24h	Haley et al. (2020)

GSH-responsive nanosponge	Resveratrol	nr	nr	4-fold increase (46 to 201 μg/mL)	9.95% increase for Resv-β-CD-NS 1:2 (w/w) and 16.12% increase increase for Resv-β-CD-NS 1:4 (w/w)	2-fold increase 5-fold increase with 10 mM GSH 8-fold increase with 20 mM GSH	Palminteri et al. (2021)

Table 2: Some pharmacokinetic parameters of stilbenes or stilbene-cyclodextrin complexes

Abbreviations: C_{max}; maximum plasma concentration; T_{max}, maximal time to reach C_{max}; AUC, area under the curve; CMC, carboxymethyl cellulose; CD, cyclodextrin; β-CD, β-cyclodextrin; RAMEB-β-CD, randomized methylated- β-CD, Carbonyl-NS, carbonyl-nanosponge; Carboxylate-NS, carboxylate-nanosponge; HP-β-CD, 2-hydroxypropyl-β-cyclodextrin

Stilbene formulation	Doses (mg/kg)	Mode of administration	C_{max} (ng/mL)	T_{max} (min)	$AUC_{0\rightarrow t}$ (ng x h/mL)	Bioavailability, F (%)	Refs
CMC suspension	Resveratrol (25)	Oral	270 ± 60	5-15	485 ± 114	38.4 ± 9.02	Das et al. (2008)
CMC suspension	Resveratrol (50)	Oral	430 ± 90	60-90	981 ± 49	38.8 ± 1.96	
RAMEB-β-CD	Resveratrol (25)	Oral	860 ± 190	5-15	480 ± 24	38.0 ± 1.91	
RAMEB-β-CD	Resveratrol (50)	Oral	1750 ± 720	5-15	1009 ± 186	39.9 ± 7.38	
Resveratrol alone	Resveratrol (20)	Oral	496 ± 49	120	2080 ± 56	nr	Pushpalatha et al. (2018)
Carbonyl-NS	Resveratrol (20)	Oral	1107 ± 105	36	4145 ± 155	199.33 ($F_{relative}$)	
Carboxylate-NS	Resveratrol (20)	Oral	1225 ± 111	30	3917 ± 263	188.37 ($F_{relative}$)	
HP-β-CD	Resveratrol (10)	Intravenous	15720 ± 3192	2	2836 ± 223	--	Kong et al. (2020)
HP-β-CD	Resveratrol (50)	Oral	1997 ± 1167	22	2352 ± 1737	16.68 ± 12.16	
HP-β-CD	Resveratrol (20)	Orotracheal	7156 ± 1637	7.8	5280 ± 565	92.95 ± 9.69	
HP-β-CD	Resveratrol (2.3)	Inhalation	148 ± 86	142	390 ± 104	76.31 ± 10.74	

Table 3: Reported bioactivities of stilbenes/cyclodextrins inclusion complexes

Abbreviations: CD, cyclodextrin; NS, nanosponge; β-CD, β-cyclodextrin; HP-β-CD, 2-hydroxypropyl-β-cyclodextrin; DMBA, 7,12-dimethylbenz[a] anthracene; DM-β-CD, dimethylated-β-cyclodextrin; RAMEB-β-CD, randomized methylated-β-CD, Me-β-CD, methylated β-cyclodextrin; nr, not reported; PLGA, poly (lactic-co-glycolic) acid; Resv-NS, resveratrol-nanosponge; Oxyresv-NS, oxyresveratrol-nanosponge; DMSO, dimethylsulfoxide; w/w, weight/weight ratio; GSH-Resv-NS, glutathione responsive nanosponge

Stilbenes	Type of study	Type of CD or NS	Biological input	Refs
Resveratrol	*in vitro*	β-CD HP-β-CD	No significant increase in DPPH radical scavenging and antioxidant activities between resveratrol and Resv-β-CD or resveratrol and Resv-HP-β-CD Better efficiency of Resv-HP-β-CD against Resv- β-CD regarding antiradical and antioxidant activities	Lu et al. (2009)
Resveratrol	*in vitro*	HP-β-CD	No significant increase in antiradical and lipoperoxidation activities between resveratrol and Resv-HP-β-CD Significant increase in resveratrol accumulation in porcine skins with use of Resv-HP-β-CD	Sapino et al. (2009)
Resveratrol	*in vitro* and *in vivo*	HP-β-CD in suspension in a cream (Resv-HP-β-CD-cream) or in a mouthwash (Resv- HP-β-CD-mouthwash)	Higher cytotoxicity of Resv-CD formulations compared to resveratrol on DMBA-induced oral squamous cell carcinoma (HCPC-I cell line) *in vitro* (24-72 h) *In vivo* prevention of exophytic lesions displaying oral squamous cell carcinoma characters. Order efficiency was: Resv-HP-β-CD-cream> Resv- HP-β-CD-mouthwash> free Resv	Berta et al. (2010)
Resveratrol	*in vitro*	Carbonyl-β-CD-NS	Higher cytotoxicity of Resv-NS compared to resveratrol on DMBA-induced cancer cells of buccal mucosa (HCPC-I cell line) Higher permeation of Resv-NS through pig skin Two-fold higher accumulation of Resv-NS in rabbit mucosa	Ansari et al. (2011b)
Resveratrol	*in vitro*	β-CD HP-β-CD	Dramatic morphological alterations of cell membranes of HeLa (human cervical carcinoma) cells with CD formulations of resveratrol but not with free resveratrol Decreased viability of HeLa cells and Hep3B (human hepatocellular liver cancer) cells with CD resveratrol formulations *vs* low cell viability inhibition with free resveratrol	Lu et al. (2012)
Resveratrol	*in vitro*	Sulfobutylether-β-CD	Weak decrease (-65%) in the cell viability of human breast cancer cells (MCF-7 cell line) with the CD resveratrol inclusion complex when compared to resveratrol alone (-50%) within 72 h	Venuti et al. (2014)
Resveratrol	*in vitro*	RAMEB-β-CD	Strong antioxidant activity of resveratrol and Resv-CD but without any significant differences between free and internalized resveratrol No significant differences reported in the reduction in cell viability of Caco-2 cells (human epithelial colorectal carcinoma) cells between free and CD-included resveratrol	Duarte et al. (2015)
Resveratrol	*in vitro*	i) Resveratrol loaded in liposomes (RL) ii) Resveratrol complexed with HP-β-CD and inclusion in liposomes (RCL) iii) Both internalization of resveratrol in liposomes and in HP-β-CD and inclusion in liposomes (RL-CL)	Antiproliferative effect on HT-29-colon cancer cells within 24 h. All inclusion complexes (RL, RCL and RL-CL) displayed higher antiproliferative activities than free resveratrol. The increase in cytotoxicity was in the following order: RL-CL> RCL>RL>R	Soo et al. (2016)

Pterostilbene	*in vivo*	HP-β-CD	Preservation of left ventricular function in infarcted rats following oral administration of the pterostilbene-HP-β-CD. No comparison with free pterostilbene was made precluding any conclusion regarding the effect of the inclusion process	Lacerda et al. (2018)
Polydatin (3-*O*-β-D-resveratrol glucoside)	*in vitro*	β-CD Me-β-CD HP-β-CD	Increased antioxidant activity (as determined by measuring reducing power values) of inclusion complexes with polydatin compared to free polydatin in the following order: HP-β-CD>Me-β-CD>β-CD Increased DPPH radical scavenging activity of inclusion complexes with polydatin compared to free polydatin in the following order: HP-β-CD> Me-β-CD> β-CD	Li et al. (2018)
Resveratrol	*in vitro*	Carbonyl-β-CD nanosponge (Resv-NS-I) Carboxylate-β-CD nanosponge (Resv-NS-II)	Decrease of the cell viability (1.7-fold lower IC_{50} values) of human breast adenocarcinoma cells (MCF-7 cell line) with the CD resveratrol nanosponges, Resv-NS-I and Resv-NS-II, when compared to resveratrol alone	Pushpalatha et al. (2018)
Resveratrol and oxy-resveratrol	*in vitro*	Carbonyl-β-CD nanosponge for resveratrol (Resv-NS) and oxyresveratrol (Oxyresv-NS)	Increased DPPH radical scavenging activity of inclusion nanosponges (Resv-NS and Oxyresv-NS) compared to free stilbenes Decrease of the cell viability of DU-145 prostate cancer cells upon stilbene inclusion with nanosponges compared to free stilbenes	Dhakar et al. (2019)
Resveratrol and curcumin	*in vitro*	Carbonyl-β-CD nanosponge	Dose-dependent decrease in the cell viability of MCF-7 human breast adenocarcinoma cells with Resv-NS and curcumin-NS, respectively	Pushpalatha et al. (2019)
Resveratrol	*in vivo*	Vectisol® (β-CD)	Beneficial effects upon kidney transplantation in a porcine model: slow-down of the loss of renal functions and beginning of histological lesions, decrease of apoptosis and oxidative stress Improvement of kidney preservation	Soussi et al. (2019)
Resveratrol	*in vivo*	Polymerized α, β and γ-CDs	Prolonged antioxidant effect of resveratrol on intracortical microelectrodes used for neurological diseases' treatment	Haley et al. (2020)
Pterostilbene	*in vitro*	HP-β-CD	7.5-fold decrease of the minimum inhibiting concentration and 4 fold-decrease of the minimum bactericidal concentration with pterostilbene CD-inclusion *vs* free pterostilbene in DMSO against *Fusobacterium nucleatum*, a periodontitis-associated pathogen	Lim et al. (2020)
Oxy-resveratrol	*in vitro*	Carbonyl-nanosponge	1.5-fold increase, 4 fold-increase and 6 fold-increase in the inhibition of cell viability of, respectively, prostate (PC-3) cancer cell line and colon (HT-29 and HCT-116) cancer cell lines with oxyresveratrol nanosponges *vs* free oxyresveratrol	Matencio et al. (2020)
Resveratrol	*in vitro*	Sulfobutylether-CDs + PLGA	15.39-fold decrease in the IC_{50} against cell viability of non-small cell lung cancer (NSCLC) A549 cell line and 50 fold-decrease for the H358 cell line *vs* unloaded resveratrol. 1.7-fold increase in caspase-3 levels in the A549 cancer cell line *vs* unloaded resveratrol.	Wang et al. (2020)

Resveratrol	*in vitro*	GSH-responsive nanosponge	Preferential entry of GSH-Resv-NS in cancer cells No toxicity of unloaded nanosponges on normal human fibroblasts Decreased viability of OVCAR-3 human ovarian cancer cells and MDA-MB-231 human triple-negative breast cancer cells with GSH-Resv-NS compared to normal human fibroblasts and normal MCF10-A human mammary epithelial cells	Palminteri et al. (2021)
Resveratrol	*in vitro*	γ-CD	Conservation over time of the antiradical $ABTS^{\cdot+}$ capacity of lemon juice with γ-CD resveratrol complexation compared to juice supplemented with free resveratrol	Silva et al. (2021)

Table 4: Green synthesis of stilbene glucosides using cyclodextrins

Abbreviations: CD, cyclodextrin; α-CD, α-cyclodextrin; β-CD, β-cyclodextrin; CGTase, Cyclodextrin glucosyltransferase; nr, not reported; Pic, piceid; DMSO, dimethylsulfoxide

Reaction conditions	Stilbene acceptor	Glucosides obtained	Biological input and effect on solubility	Refs
Starch → CD as glucose donor in DMSO/Na acetate buffer 10:34 (V/V) at pH 5.6 and 60°C with the CGTase from *Thermoanaerobacter*	Resveratrol (200 mg)	3-*O*-α-D-glucosyl-resveratrol (28.4 mg); 4'-*O*- α-D-glucosyl-resveratrol (20.5 mg); 3-*O*-α-D-maltosyl-resveratrol (12 mg); 4'-*O*-α-D-maltosyl-resveratrol (10.5 mg); 4'-*O*-α-D-maltotriosyl-resveratrol (6.1 mg) and 3,4'-*O*-α-D-diglucosyl-resveratrol (4.1 mg)	Glucoside solubilities: 2 g/L, that is, 5.4-fold increase and 67 fold-increase in solubility compared to piceid (0.37 g/L) and resveratrol (0.03 g/L). Decrease in the antioxidant activity of glucosides compared to resveratrol	Torres et al. (2011)
α-CD as glucose donor in 0.02 M citrate phosphate buffer with 5% methanol (V/V) at pH 6.0 and 40°C with the CGTase from *Bacillus macerans*	Piceid (2.56 mM)	Numerous glucosylated derivatives of piceid ($PicG_2$, $PicG_3$, etc…) not quantified (peak areas)	nr	Mathew et al. (2012)
α-CD as glucose donor in 50 mM citrate buffer at pH 5.6 and 37°C with a CGTase of unspecified origin	4'-*O*-β-D-glucosyl resveratrol (50 mg)	4'-*O*-β-D-maltosyl-resveratrol; (30% yield); 4'-*O*-β-D-maltotriosyl-resveratrol; (22% yield); 4'-*O*-β-D-maltotetraosyl-resveratrol (12% yield) and 4'-*O*-β-maltopentaosyl-resveratrol (6% yield)	Increase in the Inhibition of the phosphodiesterase activity (IC_{50}= 112 μM for 4'-*O*-β-D-maltosyl-resveratrol) compared to resveratrol (187 μM). Potent applications in neurology	Shimoda et al. (2015)
Starch → CD as glucose donor in water + DMSO 20% (V/V) at 60°C with the CGTase from *Thermoanaerobacter*	Pterostilbene (5 mg)	4'-*O*-α-D-glucosyl pterostilbene (0.12 mg) and an uncharacterized pterostilbene diglucoside (0.06 mg)	Increase in pterostilbene aqueous solubility from 0 to 0.1 g/L. 40% decrease in the antioxidant activity of 4'-*O*-α-D-glucoside of pterostilbene as well as a significantly lower toxicity on HT-29 colon cancer cells compared to the aglycone	Gonzalez-Alfonso et al. (2018)
β-CD as glucose donor in 2-[*N*-morpholino-] ethanesulfonic acid buffer at pH 6.2 and 80°C with the CGTase from *Thermoanaerobacter*	Resveratrol (2 g)	Resveratrol (89.22 mg); 3-*O*-α-D-glucosyl-resveratrol (366.6 mg); 4'-*O*- α-D-glucosyl-resveratrol (255.5 mg); 3-*O*-α-D-maltosyl-resveratrol (137.9 mg); 4'-*O*-α-D-maltosyl-resveratrol (85.16 mg)	Reduced antioxidant activities of the 3 and the 4'-*O*-α-D-glucosides of resveratrol (respectively 40 and 70% of that of resveratrol)	Marié et al. (2018)
β-CD as glucose donor in phosphate buffer at pH 6.2 and 80°C with the CGTase from *Thermoanaerobacter.* Reaction mixture coupled to a membrane process	Resveratrol	Shift of the glucosylation yield from 35% to 50% compared to the results of Marié et al. (2018)	nr	Ioannou et al. (2021)