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

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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:

$$\mathrm{AUC}_0^t = \int_0^t C_0\, e^{-kt}$$

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

192 remains at a very low level of around 1%. In fact, resveratrol is rapidly transformed in the small
193 intestine by enterocytes where it undergoes either glucuronidation or sulfation implicating
194 glucuronidases (Böhmdorfer et al., 2017; Springer and Moco, 2019) and sulfotransferases
195 (Böhmdorfer et al., 2017; Boocock et al., 2007; Miksits et al., 2005; Springer and Moco, 2019; Wu et
196 al., 2011), a certain fraction of these sulfo- and glucurono-derivatives entering the portal circulation
197 (Springer and Moco, 2019). Some studies have reported moderate *F* values for resveratrol following
198 oral administration as compared to intravenous dosing in rats: 38.8% (Kapetanovic et al., 2011; Lin et
199 al., 2009) and 29.8% (Kapetanovic et al., 2011). Surprisingly, the more hydrophobic and less polar
200 pterostilbene (3,5-dimethoxy-resveratrol) was found to reach substantial *F* values, 12.5% (Lin et al.,
201 2009) and 66.9% (Kapetanovic et al., 2011).
202 Preclinical and clinical experiments conducted in human groups after oral administration of
203 resveratrol in the form of repeated doses ranging from 30 to 5000 mg per day, revealed varying but
204 generally low resveratrol peak plasma concentrations (C_{max}): 0.56 - 2967.325 ng/mL (Brown et al.,
205 2010; Draijer et al., 2016; Howells et al., 2011; La Porte et al., 2010; Novotny et al., 2017; Springer
206 and Moco, 2019; Wightman et al., 2015; Wong et al., 2011), pterostilbene displaying higher total
207 plasma levels (C_{max}: 2820-7880 ng/mL) (Kapetanovic et al., 2011). All the afore-mentioned works
208 underlined poor bioavailability of resveratrol after oral administration *via* single or repeated dosing.
209 Such limitations have thus opened the way for the search of alternative methods to increase
210 resveratrol/derivative bioavailability. Some of them such as the use of cyclodextrins as nanocarriers
211 for the transport of resveratrol as well as utilization of cyclodextrins for the green synthesis of more
212 polar and soluble resveratrol derivatives, are described in the following sections of this review.
213
214 **4. Cyclodextrins as nanomolecular carriers and their use**
215 Biological membranes represent a barrier for the penetration, delivery and therapeutic
216 action of many drugs (Bonnet et al, 2015). Targeted drug solubilizers for oral, transdermal,
217 transmucosal or parenteral formulations are thus needed to overcome these limitations (Stella and
218 Rajewski, 2020). Drug vectorization has been achieved through use of various nanocarriers including
219 liposomes, dendrimers and polymeric nanoparticles of range size from 1 to 1000 nm, namely for
220 cancer treatment (Din et al., 2017). Among these, cyclodextrins have revealed very interesting
221 properties as nano-vehicles for many drugs (Bonnet et al, 2015; Giwani and Vyas, 2015; Pinho et al,
222 2014) as well as themselves displaying antiviral properties (Jones et al., 2020) and cytotoxic effects at
223 high concentrations on diverse cancer cell lines (Argenziano et al., 2020). Cyclodextrins (CDs) have
224 already been used as nanocarriers for established anticancer drugs like camptothecin (prostate
225 cancer) (Gigliotti et al., 2016), paclitaxel (ovarian, breast and lung cancers) (Ansari et al., 2011a),
226 erlotinib (non-small cell lung cancer) (Dora et al., 2016) and tamoxifen (breast cancer) (Torne et al.,
227 2013). Cyclodextrins were also employed for the release of many other drugs, for example, anti-
228 inflammatory drugs such as acetyl salicylic acid (Shende et al., 2012), oxaprozin (Mennini et al.,
229 2016), antivirals such as rilpivirine (Rao et al., 2018), the anti-HIV1 protease inhibitor lopinavir
230 (Adeoye et al., 2020), antifungals like econazole (Sharma et al., 2011) and antibacterial drugs such as
231 norfloxacin (Mendes et al., 2018). Cyclodextrin-mediated drug delivery has been experimented in
232 case of neurodegenerative diseases, as well. Molecularly-imprinted cyclodextrin nanoparticles have

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

240 The French Chemist Villiers observed in 1891 that potato starch seeded with *Bacillus*
241 *amylobacter* (*Clostridium butyricum*) yielded, besides dextrins, two carbohydrates forming "beautiful
242 crystals" in low amounts, named cellulosines and which were attributed a multiple of the following
243 formula [$(C_6H_{10}O_5)_2$ + 3 H_2O] (Crini, 2014). A long time after, the two crystals obtained by Villiers were
244 identified by Manor and Saenger (1972) as being more likely α-cyclodextrin with the formula
245 [$(C_6H_{10}O_5)_6.6H_2O$] and β-cyclodextrin. Cyclodextrins form cyclic oligosaccharidic assemblies
246 constituted of several α-1,4-linked glucopyranose units (hereafter named as glucose units). They are
247 mainly composed of six (CD6) (α-cyclodextrins), seven (CD7) (β-cyclodextrins) and eight glucose units
248 (CD8) (γ-cyclodextrins) (Bonnet et al., 2015; Gidwani and Vyas, 2015). This cyclic oligosaccharidic
249 structure delimits at the supramolecular level a sort of truncated cone as imposed by the peculiar
250 location of the primary hydroxyl groups of the α-D-glucopyranose units on one rim of the structure
251 being the secondary hydroxyl groups on the other (Sandilya et al., 2020) (Fig. 3). CDs thus comprise
252 an inner hydrophobic cavity with the sugar hydroxyl groups being externally oriented (Bonnet et al.,
253 2015). Cyclic structures composed of a lower number of glucose units (< CD5) were not known and
254 reputed not to allow stable conformations of glucose units until the recent work of Yamada group
255 demonstrating the feasibility of the synthesis of smaller cyclodextrins such as CD3 (three glucose
256 units) and CD4 (four glucose units), which could be utilizable for the inclusion of therapeutic
257 molecules of very small size (Ikuta et al., 2019).

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

270 As surprising as it may seem, β-cyclodextrins (β-CDs) possess an aqueous solubility eight to
271 twelve-fold lower than the other two main cyclodextrin groups (α- and γ-CDs) (Connors, 1997;
272 Sabadini et al., 2006; Saenger et al., 1998; Sandilya et al., 2020; Szejtli, 1998), though they constitute
273 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):

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

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

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

355 internalized stilbenes and the type of CDs being in the magnitude order of 10^2-10^4 M^{-1} (see Table 1
356 and references therein). The lowest K_c value recorded was 606.65 ± 30.18 M^{-1} for oxyresveratrol
357 complexation on methyl-β-CDs (Matencio et al., 2017) and the highest one, 35864.72 ± 3415.89 M^{-1}
358 for oxyresveratrol inclusion on hydroxypropyl-β-CDs (He et al., 2019). According to some authors,
359 high values of *K* may be detrimental to drug release from the inclusion complex (Stella et al., 1999;
360 Venuti et al., 2014). Increase in the observed anticancer effects of resveratrol-loaded CDs was not
361 found to be in line with the gain in resveratrol solubility observed upon resveratrol complexation
362 with various CDs as compared to free resveratrol (Dhakar et al., 2019; Palminteri et al., 2021; Venuti
363 et al., 2014). For example, around only 65% inhibition of cell viability on MCF-7 human breast cancer
364 cells were recorded with 150 μM resveratrol + sulfobutylether- β-CD and 55% inhibition with free
365 resveratrol despite an increased observed solubility of resveratrol of around 37-fold (0.03 mg/mL
366 against 1.1 mg/mL). This was attributed to a high complexation constant *K* of 10114 M^{-1} maybe
367 explaining a higher retention of this compound (Venuti et al., 2014). Almost similar results were
368 obtained regarding inhibition of a DU-145 prostate cell line:75% inhibition with a carbonyl-β-CD and
369 65% with resveratrol at 100 μM for a 3-fold enhanced solubility of resveratrol (0.04 mg/mL against
370 0.12 mg/mL) (Dhakar et al., 2019).
371 Among the various CDs available, the common ones, α-CDs, β-CDs and γ-CDs have been used
372 for the complexation of resveratrol and its derivatives (Fig. 7) (Bertacche et al., 2006; He et al., 2019;
373 Kumpugdee-Vollrath et al., 2012; Li et al., 2018; Lopez-Nicolas et al., 2009a and 2009b; Lu et al.,
374 2009; Lucas-Abellan et al., 2007; Soussi et al., 2019). There are many studies reporting on the
375 application of derivatized CDs to form inclusion complexes with resveratrol: hydroxypropyl-β-CDs
376 (HP-β-CDs) (Berta et al., 2010; Bertacche et al., 2006; He et al., 2019; Kong et al., 2020; Kumpugdee-
377 Vollrath et al., 2012 ; Li et al., 2018; Lim et al., 2020; Lopez-Nicolas et al., 2009a and 2009b; Lu et al.,
378 2009; Matencio et al., 2017; Sapino et al., 2009.; Silva et al., 2021), glucosylated-β–CDs like the
379 maltosyl-β-CD (G2-β-CD) (Lucas-Abellan et al., 2008), methylated or ethylated-β-CDs such as
380 monomethylated/ethylated-β-CDs (Li et al., 2018; Lopez-Nicolas et al., 2009a and 2009b; Matencio et
381 al., 2017; Trollope et al., 2014), dimethylated-β-CDs (DIMEB) (Bertacche et al., 2006; Kumpugdee-
382 Vollrath et al., 2012) and randomly-methylated-β-CDs (RAMEB) (Duarte et al., 2015) (Table 1). As
383 aforementioned, sulfobutylether β-CDs are well suited for both neutral and cationic substrates due
384 to their stability in the anionic state at various pH values (Stella and Rajewski, 2020; Venuti et al.,
385 2014).
386 Finally, hypercross-linked CD nanosponges where the 3D mesh between CD units is
387 established through carbonyl, carboxylate and disulfide bonds (Ansari et al., 2011b; Dhakar et al.,
388 2019; Matencio et al., 2020; Palminteri et al., 2021; Pushpalatha et al., 2018) or constituted of
389 polymerized α-, β- and γ-CDs with 1,6-diisocyanotohexane (Haley et al., 2020), have been employed
390 for resveratrol vectorization. In these intricated systems, resveratrol is internalized both in the inner
391 cavities of CDs and the interstitial spaces managed between the cross-linked CDs thus increasing
392 resveratrol loading efficiency (Dhakar et al., 2019). The most promising vectors for resveratrol are
393 represented by the so-called bio-responsive nanosponges which constitute site-specific delivery
394 systems for this compound (Ciesielska et al., 2020; Dhakar et al., 2019; Palminteri et al., 2021, Trotta
395 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

436 the double layer of liposomes (94.4%), though the former complex allowed a two-fold increase in
437 resveratrol delivery (Table 1) (Soo et al., 2016).
438
439 **6. Pharmacokinetic profile of resveratrol formulated with cyclodextrins**
440 There are numerous *in vitro* studies describing the characteristics of stilbene-CD inclusion complexes
441 (Table 1), however, works on the pharmacokinetic parameters of resveratrol complexed with CDs
442 stemming from *in vivo* studies and following different modes of administration are less numerous
443 (Das et al., 2008; Kong et al., 2020; Pushpalatha et al., 2018) compared to flavonoids (Dos Santos
444 Lima et al., 2019). The seminal work of Das et al. (2008) provided the first pharmacokinetic profiles
445 regarding resveratrol-CD formulations. In this study, intravenous administration of resveratrol was
446 carried out in rats with HP-β-CD while oral absorption of resveratrol was performed using RAMEB-β-
447 CD (randomly methylated-β-CD) and compared to a suspension of this compound in
448 carboxymethylcellulose (CMC). Although resveratrol internalization with CDs increased its solubility
449 by 59,500 fold, the $AUC_{0\rightarrow5h}$ (505.9 ng x h/mL) following resveratrol-HP-β-CD intravenous
450 administration at a dosing of 10 mg/kg did not significantly differ from intravenous injection of the
451 plain compound (10 mg/kg resveratrol in a sodium salt suspension) with an $AUC_{0\rightarrow5h}$ of 532.9 ng x
452 h/mL. Oral formulation of resveratrol with RAMEB-β-CD at the dose of 50 mg/kg both increased C_{max}
453 and t_{max} without significantly modifying $AUC_{0\rightarrow8h}$ (1009 ng x h/mL) nor resveratrol bioavailability
454 (*F*=39.9%) as compared to the CMC resveratrol suspension ($AUC_{0\rightarrow8h}$= 981 ng x h/ mL; *F* = 38.8%) (Das
455 et al., 2008) (Table 2). However, using two sorts of resveratrol-CD nanosponges, one carbonyl
456 nanosponge formed by crosslinking β-CD with diphenylcarbonate (R-NS I) and a carboxylate one
457 fabricated from β-CD and pyromellitic dianhydride (R-NS II), a significant resveratrol loading
458 efficiency of around 91% (Tables 1 and 2) was recorded in rats following a 20 mg/kg oral absorption
459 of R-NS I and R-NS II compared to resveratrol alone as well as a two-fold increase in C_{max} and
460 AUC values ($AUC_{0\rightarrow24h}$: 4145 and 3917 ng x h/ mL *vs* 2080 ng x h/ mL) (Pushpalatha et al., 2018)
461 (Table 2).
462 In a comparative study performed in rats, pulmonary administration (orotracheal intubation)
463 of resveratrol-HP-β-CD inclusion complexes in various dosages were evaluated against intravenous,
464 intra-gastric and nasal inhalation administration (Kong et al., 2020). Reported data showed better
465 pharmacokinetic profiles (C_{max}, $AUC_{0\rightarrow10h}$, $AUC_{0\rightarrow\infty}$) according to the trans-pulmonary route *vs* all
466 other routes with decreasing *F* values, 92.95% (pulmonary administration), 76.31% (nasal inhalation)
467 and only 16.68% (intra-gastric route) (Table 2). A 5-fold increase in resveratrol bioavailabilty was thus
468 recorded between pulmonary administration and the intra-gastric route.
469 These studies therefore indicate that resveratrol bioavailability upon inclusion with
470 cyclodextrins can be increased by a factor 2 when using CD-nanosponges compared to oral
471 administration of the unloaded compound (Das et al., 2008; Pushpalatha et al., 2018). It also depends
472 on its mode of administration (Kong et al., 2020).
473
474 **7. Stilbene/cyclodextrin inclusions increase stilbene photostability**
475 Generally, the complexation of stilbenes with CDs or nanosponges has a positive effect on their
476 photostability (Allan et al., 2009; Bertacche et al., 2006; Cheng et al., 2018; Dhakar et al., 2019; He et

477 al., 2019; Li et al., 2018; Pushpalatha et al., 2018; Sapino et al., 2009; Silva et al., 2014) and
478 thermostability (He et al., 2019). Light exposure can indeed be very detrimental to highly
479 photosensitive compounds or drugs. Complexation with CDs has namely been described to delay
480 photodegradation of the light versatile vasodilatator nifedipine (Bayomi et al., 2002). It is well
481 established that the natural isomer of resveratrol (and its derivatives) is the *trans* form which easily
482 yields the *cis* isomer within a few minutes of UV or sunlight exposure (Jeandet et al., 1997; Trela and
483 Waterhouse, 1994). Bertacche et al. (2006) reported that only α-CD was efficient in protecting
484 resveratrol from sunlight as compared to the larger β- and γ-CDs, though all CDs were found to
485 confer resveratrol stability against UV radiations of 254 and 365 nm. It was suggested that the three-
486 dimensional network constituted by CDs (Sapino et al., 2009) or nanosponges (Dhakar et al., 2019;
487 Pushpalatha et al., 2018) negatively affects light scattering due to a screening effect.
488

489 **8. Reported benefits of stilbene/cyclodextrin inclusion complexes**

490 All data tend to demonstrate that inclusion of resveratrol and its derivatives in CDs improves their
491 solubility as well as loading on-and release from CDs (Table 1 and references therein). Most of the
492 experiments conducted *in vitro* or *in vivo* which have been put in place to validate the benefits of
493 stilbene internalization in CDs on their biological activity, may principally resume in the study of the
494 antioxidant capabilities and cytotoxic actions of the complexes obtained. Besides, other works have
495 reported the usefulness of stilbene inclusion with CDs for biomedical applications *in vivo* (Haley et al.,
496 2020; Lacerda et al., 2017; Lacerda et al., 2018; Soussi et al., 2019).
497

498 *8.1. Antioxidant activity of stilbene-cyclodextrin inclusion complexes*

499 The antioxidant activity of stilbene-CD inclusion complexes was mainly evaluated by their capacity to
500 enhance scavenging of stable radicals such as $DPPH^{\cdot}$ (Dhakar et al., 2019; Duarte et al., 2015; Haley
501 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
502 the lipid peroxidation state (Lu et al., 2012). There is converging evidence in some studies that
503 internalization of stilbenes in CDs or nanosponges increases their antioxidant properties compared to
504 the free compounds. For example, the reducing power of polydatin as determined with the
505 Fe^{3+}/ferricyanide complex as well as its $DPPH^{\cdot}$ radical scavenging activity were respectively enhanced
506 by 2 and 1.5-fold upon inclusion with CDs, the best performances being observed with HP-β-CD (Li et
507 al., 2018) (Table 3). Dhakar et al. (2019) recorded a 75% $DPPH^{\cdot}$ radical inhibition activity with
508 resveratrol-carbonyl-β-CD nanosponges *vs* 45% (1.7 fold-increase) with the plain compound at a 100
509 μM concentration. The same trend was also reported with oxyresveratrol-carbonyl-β-CD
510 nanosponges at the 50 μM level. Supplementation of lemon juice with resveratrol-γ-CD complexes
511 allowed to maintain juices' antioxidant capacity over 28 days compared to free resveratrol
512 supplementation possibly leading to pertinent application in functional food (Silva et al., 2021). In the
513 same way, a strong inhibition of lipid peroxidation was described with resveratrol-CD complexes (Lu
514 et al., 2012). Haley et al. (2020) showed in a pilot study, that localized resveratrol delivery performed
515 with polymerized α-, β- and γ-CDs maintained a significant $DPPH^{\cdot}$ radical scavenging activity in the
516 oxidative stress microenvironment generated by implanted intracortical microelectrodes, which are

517 used in the treatment of several neurological disorders increasing their operating time. This work
518 thus adds value to the utilization of resveratrol inclusion CD complexes for potential applications in
519 neurology (Table 3).
520 At the opposite, no beneficial role of resveratrol encapsulation with CDs was demonstrated
521 in other studies, its antioxidant capabilities being unchanged from resveratrol to resveratrol-CD
522 complexes (Duarte et al., 2015; Lu et al. 2009; Sapino et al., 2009). A strong interaction between CDs
523 and stilbenes and possibly low drug release was reported as a plausible cause for the observed non-
524 significant differences in the scavenging radical capacities of free resveratrol and its inclusion
525 complex with methyl-β-CD despite an increase in resveratrol solubility and loading (Duarte et al.,
526 2015) (Tables 1 and 3). Here, a low enhancement (1.5-fold) in resveratrol release may account for
527 this discrepancy (Duarte et al., 2015).
528
529 *8.2. Anticancer activity of stilbene-cyclodextrin inclusion complexes*
530 All experimental studies conducted *in vitro* have shown a reduction of the cell viability of various
531 malignant cell lines upon inclusion of resveratrol with CDs or nanosponge complexes *vs* free
532 resveratrol (Table 3). For example, Pushpalatha et al. (2018) noted IC_{50} values for the *in vitro*
533 cytotoxicity of resveratrol carbonyl-β-CD or resveratrol carboxylate-β-CD nanosponges, 65% lower
534 (IC_{50}= 110.70 μM and 117.34 μM) than those of the unloaded compound (IC_{50}=169.98 μM) on MCF-7
535 human breast cancer cells. A reduced IC_{50} value of 20 μM was observed upon resveratrol inclusion
536 with HP-β-CD for inhibiting the proliferation of 7,12-dimethylbenz[a]anthracene-induced oral cancer
537 cells (HCPC-1 oral squamous cell carcinoma) compared to resveratrol alone (45 μM) (Berta et al.,
538 2010). Moreover, a spectacular regression of exophytic lesions displaying oral squamous cell
539 carcinoma characters was recorded in hamster cheek pouches following topical applications of
540 resveratrol-CD complexes *vs* free resveratrol (Berta et al., 2010). A significantly higher inhibition of
541 cell viability was also reported for oxyresveratrol (-75%) and resveratrol (-70%) loaded on carbonyl
542 nanosponges at the 100 μM concentration on DU-145 prostate cancer cells compared to the free
543 compounds (-60 and -50%, respectively) (Dhakar et al., 2019) (Table 3). At the same 100 μM
544 concentration, a 1.5 fold-increase (40 to 60%), a 4 fold-increase (20 to 80%) and a 6 fold-increase (10
545 to 60%) were observed in the inhibition of cell viability (from unloaded resveratrol to resveratrol
546 nanosponges) for one prostate cancer line (PC-3) and two colon cancer lines (HT-29 and HCT-116),
547 respectively (Matencio et al., 2020). Reduction in the viability of HT-29 colon cancer cells also shifted
548 from 15% with plain resveratrol to 40% with dual liposome-CD-resveratrol encapsulation complexes
549 at a dose of 100 μM (Soo et al., 2016).
550 Very marked effects of resveratrol-HP-β-CD or resveratrol-β-CD complexes have been
551 reported regarding the cell viability decrease of HeLa cervical carcinoma cells (-40%) and Hep3B
552 hepatocellular liver cancer cells (-43 to -46%) compared to the only 5% recorded with unloaded
553 resveratrol (Lu et al., 2012). Extensive alterations of the cellular morphology including membrane
554 collapse were also observed with CDs loaded with resveratrol though no such alterations were seen
555 with free resveratrol (Lu et al., 2012). Similar reduction of cell viability (> 90%) was reported upon
556 resveratrol inclusion with other types of CDs such as RAMEB-β-CD *vs* resveratrol (70%) in Caco-2
557 human epithelial colorectal adenocarcinoma cells (Duarte et al., 2015) or sulfobutylether-β-CDs

558 (65%) in the MCF-7 breast cancer line than with resveratrol alone (55%) (Venuti et al., 2014). In this
559 latter case, the slight difference observed in the reduction of the cell viability of those cancer cells
560 was attributed to a high binding constant between resveratrol and CDs thus limiting resveratrol
561 release efficiency. Resveratrol-sulfobutylether-β-CDs encapsulated in poly (lactic-co-glycolic acid)
562 nanoparticles, which have been proposed as an inhalable system for resveratrol delivery, displayed a
563 remarkable inhibition of the cell viability of non-small cell lung cancer cells, reducing by respectively
564 15.39 and 50-fold the IC_{50} against the A549 and H358 cell lines compared to plain resveratrol (Wang
565 et al., 2020).
566 Glutathione (GSH)-responsive nanosponges were used to selectively target cancer cells with
567 elevated contents of GSH such as some ovarian and breast tumorigenic cell lines (Palminteri et al.,
568 2021). The 3-D mesh of these nanosponges is constituted by the CD cavities and the interstitial
569 spaces managed by the cross linkage of the CDs with pyromellitic dianhydride and disulfure bridges
570 (Fig. 6). The latter are lysed by endocellular enzymes of the thioredoxin family in the presence of high
571 amounts of GSH thus facilitating release of resveratrol in the cell. Nanosponges are internalized in
572 the cells through different endocytosis pathways (Palminteri et al., 2021). At resveratrol
573 concentrations from 100 to 200 μM, a 50-80% inhibition of the cell viability of the OVCAR-3 ovarian
574 cancer cell line and the MDA-MB-231 breast cancer cell line was reported with the resveratrol
575 nanosponges, while a lower reduction in cell viability (-15%) was noted with the resveratrol
576 nanosponges on normal human fibroblasts, the human mammary epithelial cell line MCF-10A or the
577 SK-OV-3 human ovarian malignant cells, demonstrating the selective toxicity of these nanosponges
578 (Palminteri et al., 2021).
579
580 *8.3. Applications of stilbene-cyclodextrin inclusion complexes in vivo*
581 Stilbene inclusion in CDs and its recognized benefits to increasing the solubility, release and
582 bioavailability of these compounds has received some interesting applications in nanomedicine. For
583 example, Vectisol® formulation of resveratrol, *i.e.* its encapsulation in a monopropane diamino-β-CD,
584 turned out to allow the early recovery of proximal tubular function and glomerular filtration as well
585 as a slowdown of loss of the renal functions in a kidney transplantation preclinical study in pigs
586 thanks to the resveratrol antioxidant properties (Soussi et al., 2019). By reducing oxidative stress in
587 the right ventricle of rats displaying monocrotaline-induced pulmonary hypertension in a *cor*
588 *pulmonale* model, inclusion of pterostilbene with HP-β-CDs ameliorates the systolic function of the
589 ventricle as well as prevents it from structural alterations such as hypertrophy through an increase of
590 pterostilbene bioavailability (Lacerda et al., 2017). Likewise, pterostilbene encapsulation with HP-β-
591 CDs was shown to preserve *via* a decrease of lipid peroxidation and the regulation of some
592 antioxidant mechanisms, the function of the left ventricle following induced myocardial infarction in
593 rats (Lacerda et al., 2018). Additionally, inclusion of stilbenes in CDs may also have a positive effect
594 by increasing their antimicrobial capabilities. These compounds are indeed known for possessing
595 various antifungal and antimicrobial activities (Vestergaard and Ingmer, 2019). Complexation of
596 pterostilbene with HP-β-CDs, which is reputed to display higher fungitoxicity than its non-methylated
597 counterpart resveratrol, was reported to diminish by 7.5-fold the minimum inhibiting concentration
598 and by 4-fold the minimum bactericidal concentration on growth of *Fusobacterium nucleatum*, a

599 bacterial pathogen associated with periodontitis, compared to unloaded pterostilbene dissolved in
600 DMSO (Lim et al., 2020).
601 Numerous works have provided a large piece of evidence that stilbene compounds, mainly
602 resveratrol (Aziz et al., 2005; Boo, 2019; Costa et al., 2016, Lin et al. 2021; Osmond et al., 2012) or
603 pterostilbene (Sirerol et al., 2015) are efficient in preventing ultraviolet-B induced damages of skin,
604 treating cutaneous herpes (Docherty et al., 2004), psoriasis (Kjaer et al., 2015), modulating skin
605 cancer mechanisms or improving melanoma treatment with potential applications in onco-
606 dermatology. CDs have been shown to constitute interesting agents as good vehicles for stilbene
607 delivery and for ensuring high levels of compound penetration as well as safety of the tissues for the
608 treatment of skin or mucosal cancers (Ansari et al, 2011b; Berta et al., 2010; Sapino et al., 2009).
609 Experiments with various matrices including rabbit mucosa (Ansari et al., 2011b), porcine skin
610 (Sapino et al., 2009) and porcine ear skin (Pushpalatha et al., 2019), revealed an increased *ex vivo*
611 skin penetration of resveratrol with resveratrol CD or nanosponge formulations. Resveratrol-
612 nanosponges accumulated at a two-fold higher rate (600 $\mu g/cm^2$) than the plain compound (300
613 $\mu g/cm^2$) in porcine ear skin (Pushpalatha et al., 2019). A similar trend was reported with resveratrol-
614 HP-β-CDs in porcine skin (Sapino et al., 2009) and resveratrol-carbonyl nanosponges in rabbit mucosa
615 (Ansari et al., 2011b).
616
617 **9. Implication of cyclodextrins for the green synthesis of stilbene glucosides**
618 Glucosylation of stilbene compounds not only increases their aqueous solubility for potential uses in
619 cosmetic and onco-dermatology but substitution by a glucosyl group at the 4'-position of stilbenes
620 also protects them from oxidation by polyphenol-oxidases such as tyrosinases (Regev-Shoshani et al.,
621 2003). A lot of stilbene β-D-glucosides have been identified so far in plants, namely the 3-*O*-β-D-
622 glucosyl-resveratrol (piceid or polydatin), the 4'-*O*-β-D-glucosyl-resveratrol (resveratroloside) and the
623 4'-*O*-β-D-glucosyl-piceatannol (Fig. 1) (Jeandet et al., 2020). Research has moved over the past few
624 years toward the synthesis of their α-anomeric counterparts whose aqueous solubility and surfactant
625 properties are superior (Gonzalez-Alfonso et al., 2018; Marié et al., 2018; Ioannou et al., 2021;
626 Shimoda et al., 2015).
627 The major drawback in the green synthesis of stilbene glucosides is the compatibility of the
628 solvent employed for both the glucose acceptor (here the starting stilbenes) and the enzyme used for
629 glucosylation. For this reason, oftentimes, a compromise between enzyme stability and stilbene
630 solubility is necessary (Jeandet et al., 2020). Making use of green solvents could be the right answer
631 to this paradox. The green synthesis of 3-*O*-α-D-glucosyl resveratrol with sucrose and not CDs as a
632 glucose donor, has already been performed under the catalytic action of a phosphorylase from
633 *Bifidobacterium adolescentis* using a combination of an ionic liquid and a buffer, which considerably
634 increases resveratrol solubility (De Winter et al., 2013). Several works have reported achievement of
635 stilbene *O*-glucosylation with cyclodextrin glucosyl-(glucano)-transferases (CGTases) from various
636 sources as biocatalysts utilizing starch or CDs as glucose donors (Gonzalez-Alfonso et al., 2018;
637 Ioannou et al., 2021; Marié et al., 2018; Mathew et al., 2012; Shimoda et al., 2015; Torres et al.,
638 2011) (Table 4). CGTases have indeed often been employed for the biosynthesis of various
639 polyphenolic glucoside derivatives: epicatechin glucosides (Aramsangtienchai et al., 2011),

640 kaempferol glucoside (Choung et al., 2017), genistein diglucoside (Han et al., 2017), flavonol and
641 flavanone glucosides (Lee et al., 2017), pinoresinol glucoside (Khummanee et al., 2019) or α-arbutin
642 (Mathew et al., 2013). Torres et al. (2011) have described the use of a monophasic solvent system
643 constituted of a mixture of one organic solvent (DMSO) and acetate buffer for the synthesis of a
644 series of glucoside derivatives of resveratrol. In this synthesis, starch was employed as the primary
645 glucose donor, glucosylation being ensured by the CGTases of *Thermoanaerobacter* or *Bacillus*
646 *macerens*. Under these conditions, various glucosides of resveratrol were obtained with quite good
647 50% glucosylation yield, suggesting that CDs arising from the partially hydrolyzed starch were directly
648 implicated in the transfer of the glucosyl moiety to stilbene acceptors. In a similar manner, the
649 enzymatic production of a 4'-*O*-α-glucoside of pterostilbene whose solubility is lower than that of
650 hydroxystilbenes, was described in a monophasic solvent system constituted by DMSO and buffer
651 with the CGTase of *Thermoanaerobacter* and starch as the primary source for glucosyl groups
652 (Gonzalez-Alfonso et al., 2018). However, the high proportion of DMSO in the solvent mixture
653 renders this synthetic route unsuitable for the green production of stilbene glucosides.
654 As aforementioned, CDs allow the increasing of the internalization rate of compounds poorly
655 soluble in water such as stilbene aglycones. Their use is thus particularly conducive to the green
656 synthesis of stilbene glucoside derivatives (Ioannou et al., 2021; Jeandet et al., 2020; Marié et al.,
657 2018). The transfer of an α-glucoside group or more groups from the donor (the cyclodextrin) to the
658 acceptor (the stilbene) may proceed through coupling of the cyclodextrin and the stilbene, which
659 randomly attach to the active site of the CGTase (Lim et al., 2021; Mathew et al., 2012). A plausible
660 mechanism for the formation of a series of piceid (referred as $picG_1$) derivatives considerably varying
661 in the number of the glucosyl groups, has been deciphered under the action of the CGTase of *B.*
662 *macerans* (Mathew et al., 2012) (Fig. 8). A primary nucleophilic attack of the 4'-hydroxyphenyl group
663 of piceid ($picG_1$) on the Carbon 1 at the reducing end of an opened α-CD, α-maltohexaose, results in
664 an α-(1,4) linkage between piceid and the maltohexaose leading to the release of an initial coupling
665 product called $picG_7$. Following successive disproportionation reactions of $picG_7$, various glucoside
666 derivatives of $picG_1$ like $picG_2$, $picG_3$, etc…are then obtained (Mathew et al., 2012). This mechanism
667 may explain not only the recovery of monoglucosides but also of di and tri-glucosides during
668 resveratrol glucosylation in the presence of CGTases (see below) (Ioannou et al., 2021; Marié et al.,
669 2018, Torres et al., 2011). Polyglucosylated derivatives of 4'-*O*-β-resveratrol-glucoside like 4'-*O*-β-
670 maltoside, 4'-*O*-β-maltotrioside, 4'-*O*-β-maltotetraoside and 4'-*O*-β-maltopentaoside acting as
671 potent inhibitors of phosphodiesterase activity and displaying possible neuroprotective properties,
672 were obtained through a synthetic route including α-CD and a plant CGTase in a medium totally free
673 from organic solvent (Shimoda et al., 2015). One may pay attention to the fact that in this case, only
674 the β-anomeric forms were obtained instead of the commonly recovered α-glucosides (Table 4).
675 The CGTase-catalyzed synthesis of hundred milligrams of α-*O*-D- mono and diglucosides of
676 resveratrol (3 and 4'-α-*O*-D-glucosyl resveratrol as well as 3 and 4'-α-*O*-D-maltosyl resveratrol) was
677 performed more recently at the 2-L bioreactor scale in water (MES buffer) with the CGTase from
678 *Thermoanaerobacter* sp. (*Toruzyme*) and β-CD as a glucose donor (Marié et al., 2018) (Fig. 9).
679 Maximization of the glucosylation transfer was achieved *via* the optimization of multiple factors such
680 as pH, temperature, enzyme and donor amount as well as the resveratrol:CD ratio, performing a 35%

681 yield based on molar concentrations. This yield increases up to 50% when a 1 kDa cut-off membrane
682 is coupled to the enzymatic reactor thus allowing retention of the resveratrol β-CD inclusion complex
683 in the medium and increasing the transfer rate of the glucoside derivatives formed in the permeate
684 such that they are protected from further hydrolysis (Ioannou et al., 2021). The production rates of
685 the 3 and the 4'-*O*-α-glucosides of resveratrol were almost similar indicating the absence of any
686 regioselectivity in the glucosylation process on the stilbene moiety (Marié et al., 2018) (Table 4).
687 Glucosylation of stilbenes increases their water-solubility making them utilizable for topical
688 applications in case of cutaneous disorders for cosmetics and onco-dermatology (Intagliata et al.,
689 2019). Torres et al. (2011) indeed noted a 67-fold increase in the solubility of resveratrol-α-
690 glucosides compared to resveratrol. Likewise, pterostilbene, which is an almost insoluble compound
691 in water, has its solubility reaching 0.1 g per liter upon glucosylation (Gonzalez-Alfonso et al., 2018).
692 Except the study of Shimoda et al. (2015) reporting an increase in the inhibition of
693 phosphodiesterase activity with resveratrol glucosides that suggests their potential for the treatment
694 of neurodegenerative diseases, other works conducted on the biological activity of stilbene
695 glucosides tend to show paradoxically a decrease in their antioxidant and cytotoxic effects with
696 regards to the aglycones (Table 4). By taking resveratrol as the reference compound with an
697 antioxidant activity of 100%, the relative activities of the 3 and the 4'-*O*-α-glucosides of resveratrol
698 were respectively of only 40 and 70% (Marié et al., 2018; Torres et al., 2011) as confirmation that
699 glucosylation on the 4'-position of stilbenes is less detrimental to their biological activity (Regev-
700 Shoshani et al., 2003). Similarly, Gonzalez-Alfonso et al. (2018) reported a near 40% decrease in the
701 antioxidant activity of 4'-*O*-α-glucoside of pterostilbene as well as a significantly lower toxicity on HT-
702 29 colon cancer cells compared to the aglycone.
703 Apart from the synthesis of stilbene glucosides, use of RAMEB-β–CDs was also found to
704 facilitate hydroxylation of the stilbene core with engineered cytochrome P450 leading to various di-
705 and trihydroxystilbenes and limiting the use of organic solvents to a few percents (Ruhlmann et al.,
706 2017).
707
708 **10. Cyclodextrins for the induction of stilbene production in plant cell systems**
709 As aforementioned, one major feature of CDs is their ability to form inclusion complexes with poor
710 water-soluble organic molecules due to the hydrophobic character of their central cavity, which thus
711 serve as nano-sized carriers for these molecules in aqueous solutions. In addition to such a
712 remarkable property, CDs are able to interact with plant cells in which they can trigger a defense
713 response. This makes them useful tools to study plant biochemistry and physiology as well as
714 biotechnology aspects. The first evidence for a CD-plant cell interaction arose from experiments run
715 with grapevine cell cultures treated with the phytoalexin resveratrol, either unloaded or complexed
716 with the dimethyl-β-CD (DM-β-CD) in order to evaluate its efficacy as a protecting agent against the
717 phytopathogen *Xylophylus ampelinus*. Although unloaded resveratrol completely disappeared within
718 48 h, resveratrol loaded on DM-β-CD remained stable in the medium. Unexpectedly, controls treated
719 only with DM-β-CD exhibited an accumulation of resveratrol evidencing for the first time that CDs
720 may act as inducers of *de novo* resveratrol synthesis in grapevine cells (Morales et al., 1998).

721 As seen before, CDs display a high chemical diversity, including CDs of natural origin with free
722 hydroxyl groups, and the ones of synthetic origin with chemical groups attached to the glucosidic OH
723 groups (Bonnet et al., 2015). The capability of a limited number of β-CDs to induce resveratrol
724 bioproduction was first evaluated in grapevine cell cultures (Bru et al., 2003; Bru et al., 2006). Only
725 chemically modified CDs, *e.g.* methyl- or hydroxypropyl-CDs, induced a strong resveratrol production
726 unlike the natural CDs, which yielded a very weak response. However, sulfated β-CDs, which are
727 frequently used as carriers in pharmaceutical formulations (Stella and Rajewski, 2020), brought about
728 a hypersensitive response in grapevine cells. Bru group's study thus highlighted the importance of
729 the chemical nature of CD-linked groups to raise a cellular response and suggested that one plausible
730 reason for the reported elicitor activity of CDs is their structural similarity to the oligosaccharidic
731 elicitors released from plant cell walls upon plant-fungal interactions. Dimethylated-β-CDs also well-
732 known as DIMEB thus became the gold standard in subsequent research works. Another piece of
733 evidence that CDs differentially interact with plant cells is the species- and genotype-dependent cell
734 resveratrol production observed as a response to a particular cyclodextrin type (Zamboni et al.,
735 2006).
736 CDs are almost non-toxic for cell cultures and display a superior eliciting activity than other
737 oligosaccharides like chitosan, a major component of fungal cell walls (Ferri et al., 2009). Among the
738 elicitors used to induce stilbene biosynthesis by plant cell or tissue systems, CDs lead to the highest
739 production yields (in the g/L range) (Bru et al., 2003; Bru et al., 2006; Nivelle et al., 2017) compared
740 to other common eliciting molecules derived from jasmonate, like methyljasmonate (MeJA) with
741 reported production levels of only milligrams per liter (Krisa et al., 1999; Tassoni et al., 2005;
742 Santamaria et al. 2010). Further works have shown empirically that combinatory elicitation with CDs
743 and MeJA and, to a lesser extent, CDs plus coronatine, the jasmonate-Ile analog, synergize the effects
744 of each elicitor increasing the production of resveratrol by 5 to 8-fold in grapevine cell suspensions
745 (Almagro et al., 2015; Belchí-Navarro et al., 2012; Lijavetzky et al., 2008; Oilva et al., 2018).
746 Spectroscopic approaches for understanding the synergistic mechanisms existing between CDs and
747 MeJA have reported that resveratrol, CDs and MeJA together in solution formed binary complexes,
748 respectively CD-resveratrol and CD-MeJA but no ternary inclusion complexes (Oliva et al., 2018). CDs
749 were demonstrated to improve the aqueous solubility of the reputed hydrophobic molecule, MeJA,
750 resulting in an increase of resveratrol production by grapevine cells.
751 Cost is a key issue in biotechnology and the utilization of elicitors like DIMEB and coronatine
752 could turn out to be quite expensive for large scale applications in bioreactors. Attempts to reduce
753 the production costs incurred by CDs have led to a new strategy, such as the use of CD polymers
754 coated with magnetic nanoparticles for the easy recover and reutilization of the elicitor in plant cell
755 cultures for optimizing resveratrol production (Almagro et al., 2020). The obtained results are
756 promising as HP-β-CD coated polymers can be reused up to three times yielding resveratrol levels
757 ranging from 0.3 and 0.5 g/L.
758 Stilbene production based on the use of CDs has also been accomplished in plant tissue
759 systems like the hairy roots of *Arachis hypogaea*, *Vitis rotundifolia* and *V. vinifera* leading to the
760 accumulation of tens of mg/g dry weight (DW) of resveratrol, piceid and resveratrol dimers in the
761 elicited tissues of grapevine or peanut (Medina-Bolivar et al., 2007; Nopo-Olazabal et al., 2013;

762 Tisserant et al., 2016). Elicitation resulted in a successful strategy to both enhance the production
763 level of those stilbenes and promote their extracellular accumulation, which is particularly useful for
764 facilitating their extraction from the culture medium. Use of DIMEB was also reported to induce the
765 production as well as modifying the profiles of some isoprenylated stilbenes belonging to the
766 arachidin family (Fig. 1) in the hairy roots of *A. Hypogaea* (Yang et al., 2015; Fang et al., 2020).
767 Once the feasibility of producing a natural compound or drug by tissue or cell cultures has
768 been demonstrated, the problem arises of transferring the results obtained from the laboratory scale
769 to the industrial production in bioreactors (Donnez et al., 2009; Jeandet et al., 2014; Jeandet et al.,
770 2016). The high stilbene levels recovered in plant cell systems as a response to elicitation with CDs,
771 particularly in grapevine cell cultures, have led to scale up the cultures from shaken flasks to
772 bioreactors. Most grapevine cell cultures well tolerate the typical shear stress of the bioreactor
773 environment, even with a stirred tank (Aumont et al., 2004; Lambert et al., 2019; Nivelle et al., 2017;
774 Vera-Urbina et al., 2013), although some genotypes seem to be more sensitive (Donnez et al., 2011;
775 Ferri et al., 2011). Both bubble column (Vera-Urbina et al., 2013) and disposable bag wave
776 bioreactors (Eibl and Eibl, 2008) are suitable for this purpose. Elicitation of stilbene production with
777 DM-β-CD was successfully performed in bioreactors using the *V. vinifera* and *V. labrusca* cell lines.
778 Recovered stilbene amounts well correlated with the respective achievements in shaken flasks
779 though being slightly higher in bioreactors, most likely due to a better mass transfer. When using
780 DM-β-CD alone, accomplished resveratrol yields were 2.2 and 3 mg/g fresh weight (FW) for *V.*
781 *vinifera* cv Gamay cultures in V-shaped bubble columns and in stirred tank bioreactors, respectively.
782 Resveratrol amounts rose to 13.5 mg/g FW in each bioreactor (Vera-Urbina et al., 2013) and even
783 reached 14.3 mg/g FW in a 20-litre stirred tank bioreactor upon combinatory elicitation with DM-β-
784 CD and MeJA (Lambert et al., 2019), which further confirms the synergistic effect already mentioned
785 in shaken flasks (Lijavetzky et al., 2008).
786 Elicitation with cyclodextrins combined with plant metabolic engineering has been disclosed
787 as a successful strategy to diversify the profile of stilbenes and other specialized metabolites
788 produced by cell suspension cultures. For instance, grapevine cells transformed with the *human*
789 *hydroxylase CYP1B1* (Martinez-Marquez et al., 2016) or the *Rosa hybrida orcinol*-O-*methyltransferase*
790 (Martinez-Marquez et al., 2018) produced significant levels of resveratrol derivatives like piceatannol
791 and pterostilbene, respectively, in addition to resveratrol upon elicitation. Likewise, the
792 transformation of *Sylibum marianum* cultures with the *grapevine stilbene synthase 3* yielded 12 mg/L
793 resveratrol upon elicitation with DM-β-CD, in addition to the accumulation of silymarin and coniferyl
794 alcohol as in the wild lines (Hidalgo et al., 2017).
795
796 **11. Mechanisms of induction of stilbene production by cyclodextrins**
797 Although CDs, and particularly DM-β-CDs, are known to induce a phytoalexin response in grapevine
798 cells ending up in both the production and the extracellular accumulation of various stilbenes, the
799 understanding of the cellular and molecular mechanisms involved in this response is far from being
800 elucidated. Such events obviously include perception of CDs or their hydrolyzing products at the
801 membrane level and induction of the related signaling pathways, followed by regulation of the key
802 enzymes of stilbene biosynthesis, gene transcription changes as well as modifications of some

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

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

820 Transcription factors are major components in the regulation of cellular metabolic events
821 fine-tuning the control of numerous biosynthetic routes including the resveratrol one comprising for
822 example, the *Vitis vinifera* transcription factors VvWRKY24 and VvMyB14 being able to up-regulate
823 *STS* gene expression on one hand, and the negative regulator VvWRKY8 of *STS* gene expression on
824 the other (Fig. 10) (Duan et al., 2016; Jeandet et al., 2019; Jiang et al., 2019; Vanozzi et al., 2018;
825 Wong and Matus, 2017). Transcription factors like MYB15 which activates the transcription of
826 stilbene synthase (STS) (Höll et al., 2013) and the NAC-type which promotes the biosynthesis of
827 phenylpropanoids and monolignols (Mitsuda et al., 2007), are up-regulated by DM-β-CD and further
828 enhanced by DM-β-CD + MeJA (Fig. 10) (Almagro et al., 2014). Numerous biosynthetic enzymes from
829 the connected pathways of shikimate, phenylalanine, phenylpropanoid (PAL, C4H, 4CL), malonyl CoA
830 and stilbene (STS) biosynthesis are up-regulated by DM-β-CD, and DM-β-CD + MeJA to allow a
831 marked carbon flow toward resveratrol biosynthesis (Almagro et al., 2014). Omics analyses
832 conducted on grapevine cell cultures offered an overall picture of the major metabolic events
833 following combined DM-β-CD and MeJA elicitation (Almagro et al., 2014; Martinez-Esteso et al.,
834 2011; Martinez-Marquez et al., 2017). Proteomic changes strongly correlate with transcriptional
835 events, particularly during changes in the activity of the enzymes catalyzing the late resveratrol
836 biosynthetic steps (PAL, STS) (Martinez-Esteso et al., 2011). Taken altogether, it would seem that CDs
837 and combinatory elicitation with CDs and MeJA orchestrate resveratrol accumulation by two
838 strategic actions: (i) activation of *STS* genes transcription; (ii) increase of the precursor supply taking
839 into account that all the precursors of resveratrol biosynthesis are also shared by major competing
840 pathways; *i.e.* monolignol and flavonoid routes. These omic studies also revealed the co-expression
841 of certain glutathione-*S*-transferase isoforms at both the transcript and protein levels. Interestingly,
842 overexpression of a tau class glutathione-*S*-transferase (VvGST U10a) possibly implicated in the
843 transport of resveratrol was observed in grapevine cells upon elicitation with DM-β-CD or DM-β-CD +

844 MeJA (Martinez-Marquez et al., 2017). Otherwise, combinatory elicitation with DIMEB and MeJA in
845 peanut hairy roots, led to the up-regulation of stilbene dimethylallyltransferases, which are
846 implicated in the transfer of a dimethylallyl pyrophosphate group to various stilbenic compounds, in
847 addition to STS (Yang et al. 2018). This confirms the accumulation of prenylated stilbenes at levels
848 similar with those of resveratrol (Fig. 10) (Yang et al. 2015). Combinatory elicitation is thus also able
849 to activate metabolic steps downstream resveratrol biosynthesis to diversify stilbene profiles.
850

851 **12. Conclusions and future prospects**

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

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

874 Stilbene vectorization using CDs is now moving towards the production of more specific
875 systems such as bioresponsive-cyclodextrin nanosponges targeting particular cell types or
876 microenvironments. Trotta's group recently described the inexpensive synthesis of a GSH-responsive
877 CD nanosponge capable of selectively targeting certain types of cancer cells. The crosslinking in this
878 nanosystem contains disulfide bridges whose lysis in the presence of endogenous GSH and
879 endocellular enzymes facilitates drug release. These nanosponges have successfully been studied
880 using the anticancer drug, doxorubicin during *in vitro* experiments (Trotta et al., 2016b). The method
881 was transposed very recently to the design of GSH-bioresponsive nanosponges dedicated to the
882 transport of resveratrol (Palminteri et al., 2021). This type of resveratrol-nanosponges preferentially
883 targets certain models of cancer cells *in vitro* (ovarian, breast and lung cancer cells), which contain
884 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.

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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)

962
963 **Figure 10: Regulation of stilbene biosynthesis through combinatory elicitation with dimethyl-β-CD**
964 **(DIMEB) and MeJA elicitors in grapevine cells**. Stilbene biosynthesis involves the production of the
965 early precursors erythrose 4-P (E4P) and phosphenolpyruvate (PEP) from a carbon source through
966 central carbohydrate pathways. The two direct precursors of resveratrol are produced through two
967 diferent pathways: *p-coumaroyl CoA* is a final product of the two early precursors processed *via* the
968 shikimate/aromatic aminoacid biosynthesis/phenylpropanoid serial pathways, and *Malonyl CoA*
969 comes from a parallel processing of PEP through three enzymatic steps. The first stilbene,
970 resveratrol, may undergo derivatization reactions out of which only two have been well
971 characterized to date: methylation by resveratrol-*O*-methyltransferases in grapevine (VvROMT), and
972 prenylation by resveratrol dimethylallyl transferases in peanut (AhR4/3'DT). Resveratrol and
973 prenylated derivatives are found in the extracelular médium, as well. In grapevine cell cultures upon
974 elicitation with DIMEB and DIMEB + MeJA, a tau class glutathione *S*-transferase (VvGSTU2) is
975 putatively involved in the extracelular accumulation of resveratrol as free form or complexed with
976 CDs. Elicitors such as DIMEB and MeJA trigger early signaling events starting from Ca^{2+} income from
977 the apoplastic space that ends up in transcriptional regulation through a only partly established
978 pathway where production of NO, H_2O_2 and participation of protein tyrosine phosphatases (TyrPase)
979 and MAPK is involved. In *Vitis quinquangularis,* a MAPKKK38 transcription factor has been described
980 to enhance the trancription of *STS* genes likely *via* the transcriptional activation of MYB14. In *V.*
981 *amurensis,* Ca-dependent protein kinases activate the transcription of specific *STS* paralogs. In *V.*
982 *vinífera,* the best characterized transcriptional activators of *STS* genes are MYB14/15 TFs, that are
983 also able to activate the transcription of shikimate pathway key genes as well as those of *PAL* and
984 *ROMT*. MYB14, WRKY8 and resveratrol are components of a regulatory loop in which MYB14
985 promotes the production of resveratrol; resveratrol activates the transcription of WRKY8, likely
986 through undisclosed effector proteins, and WRKY8 interacts with MYB14 to block it, thus down-
987 regulating resveratrol levels. Such a negative loop was discovered upon UV light irradiation which
988 activates the transcription of MYB14. Other steps of the phenylpropanoid pathway have also specific
989 transcriptional activators such as WRKY2 and MYB5a, and NAC TFs which are active up-regulators of
990 some key steps of the shikimate pathway. Regulatory entities described in relation with combinatory
991 elicitation with DIMEB and MeJA are shown in orange colour. Blue arrows indicate possible hierarchy
992 between early signaling events. Green and red arrows stand for transcriptional up- and down-
993 regulation respectively; solid lines indicate that the evidence has been validated in targeted
994 experiments while slashed lines means the evidence only comes from omics analysis. Genes
995 encoding for TFs have been labelled in their promoter regions according to the stimulus they
996 respond: elicitor responding (ERE), hormone responding (HRE), UV light responding (UVRE) and
997 resveratrol responding (RRE). DIMEB are symbolized by small troncated structures

998
999

1000 **References**

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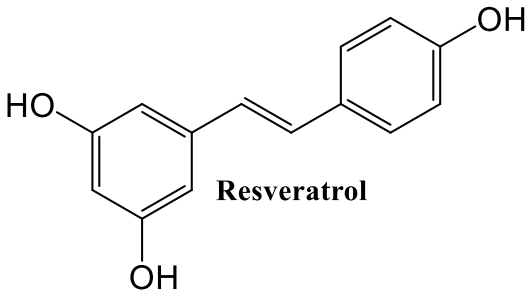
1002

1003



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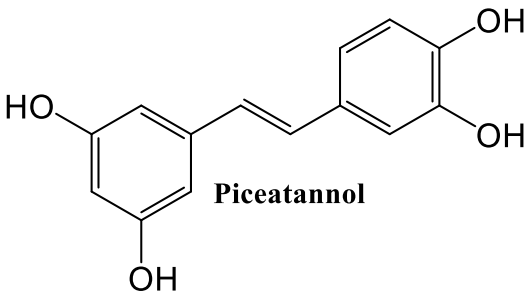

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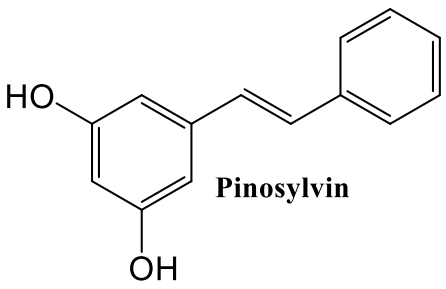

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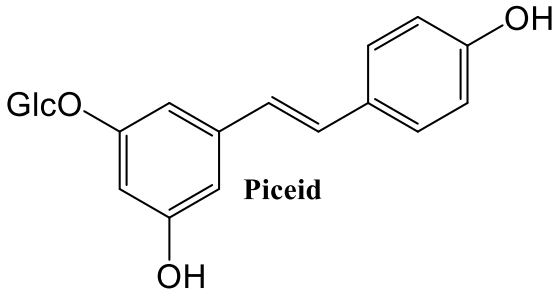
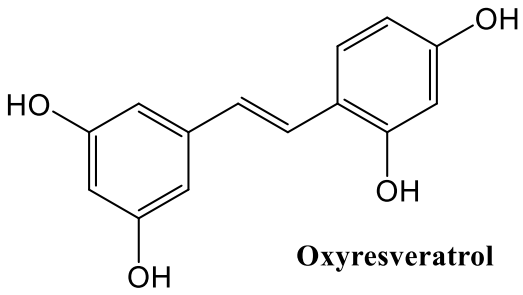


Piceid



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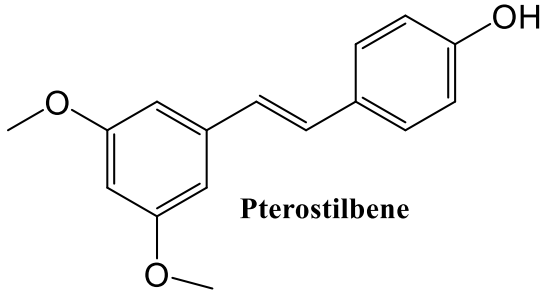

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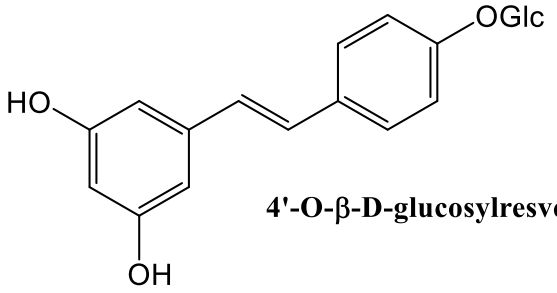

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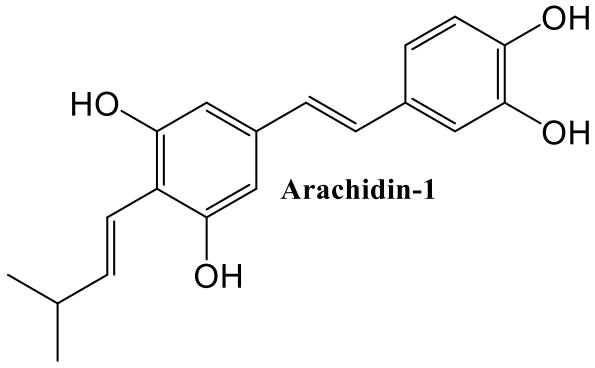

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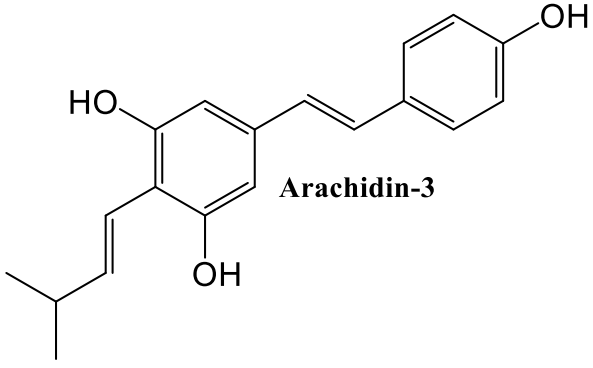

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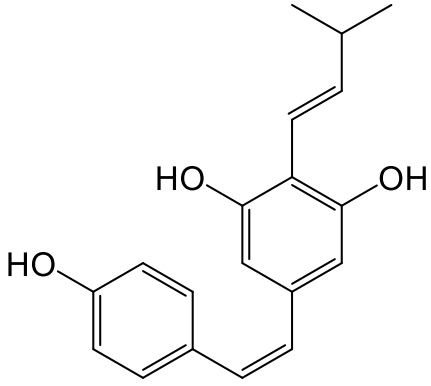

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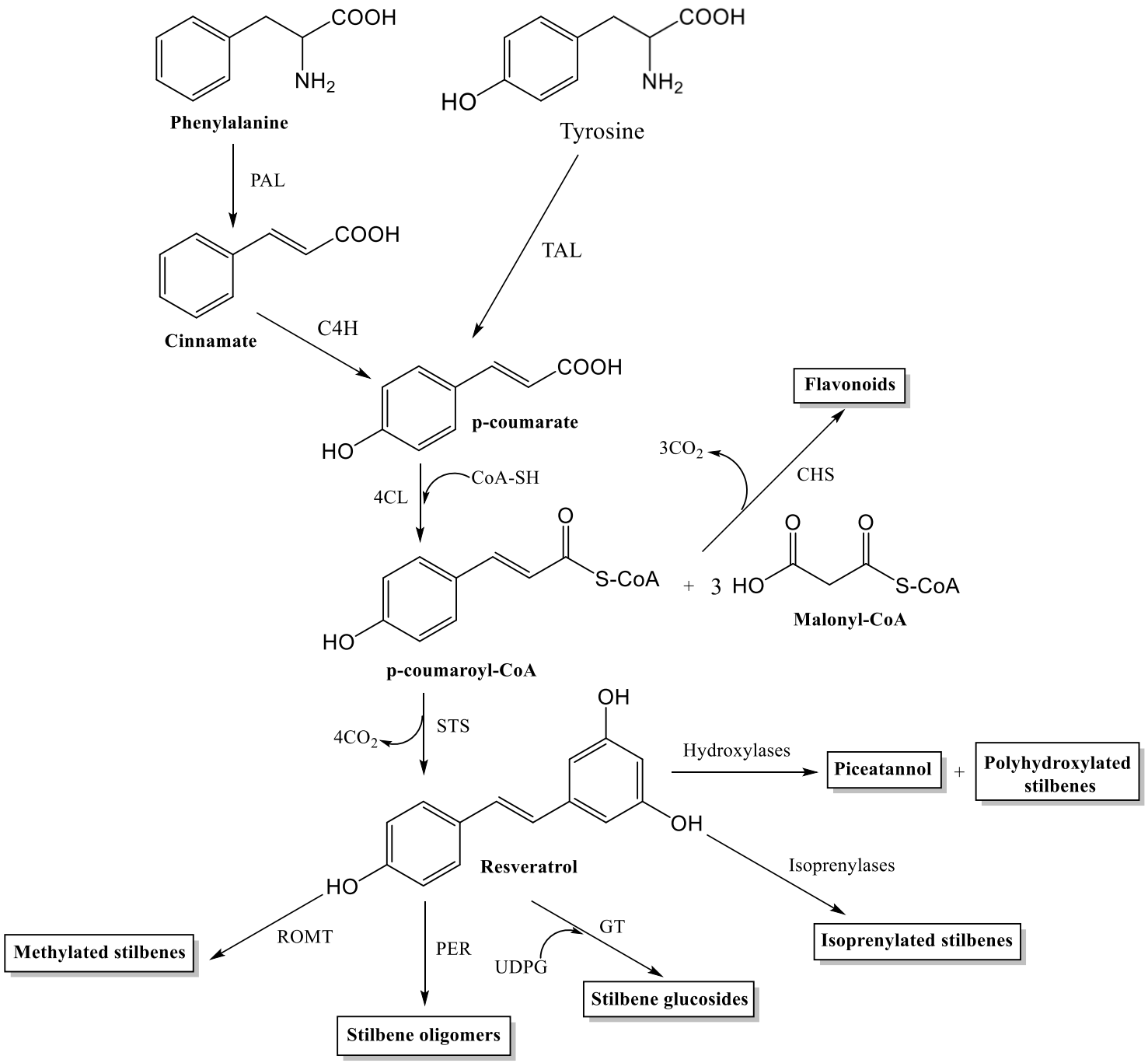
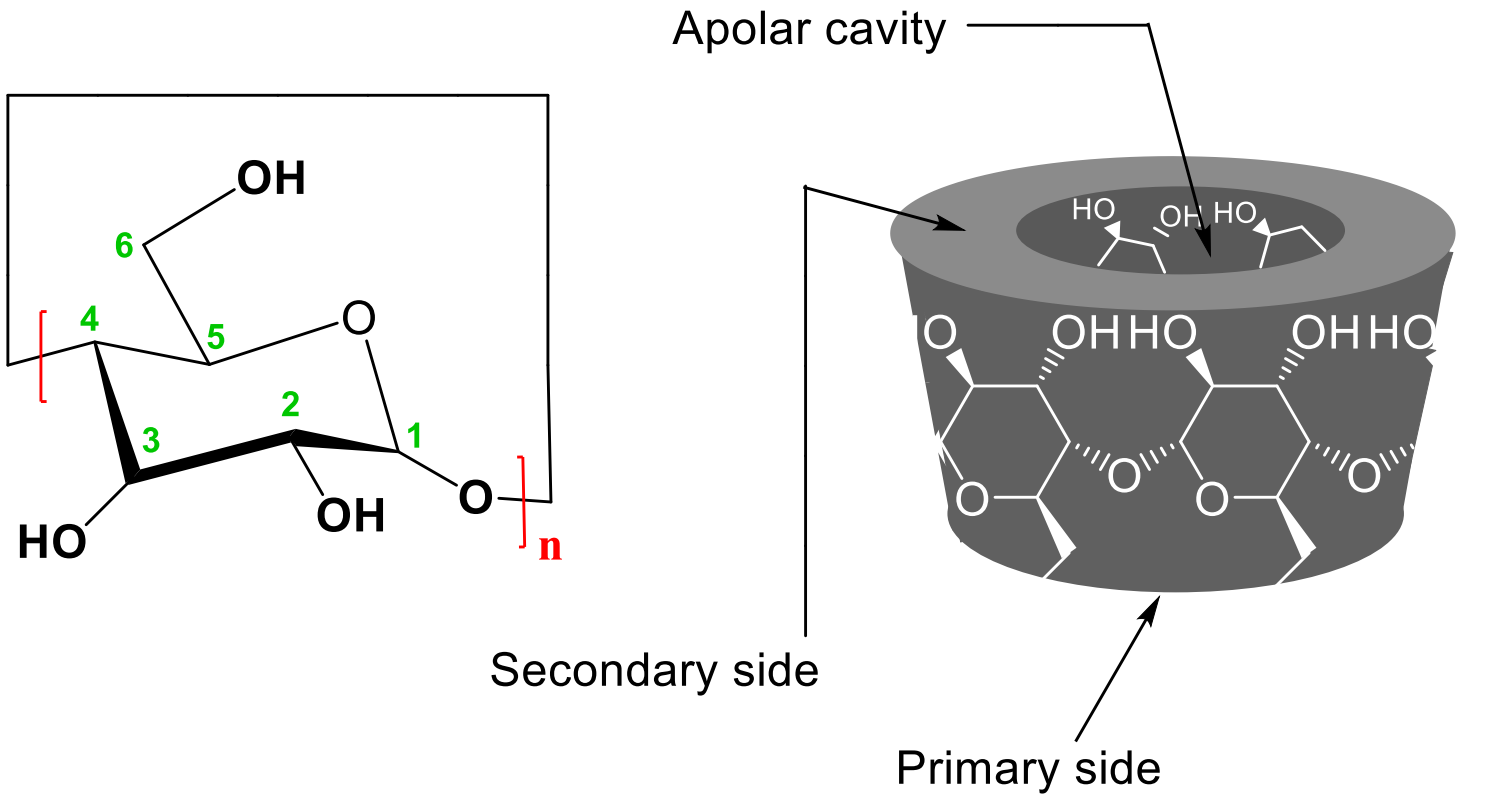
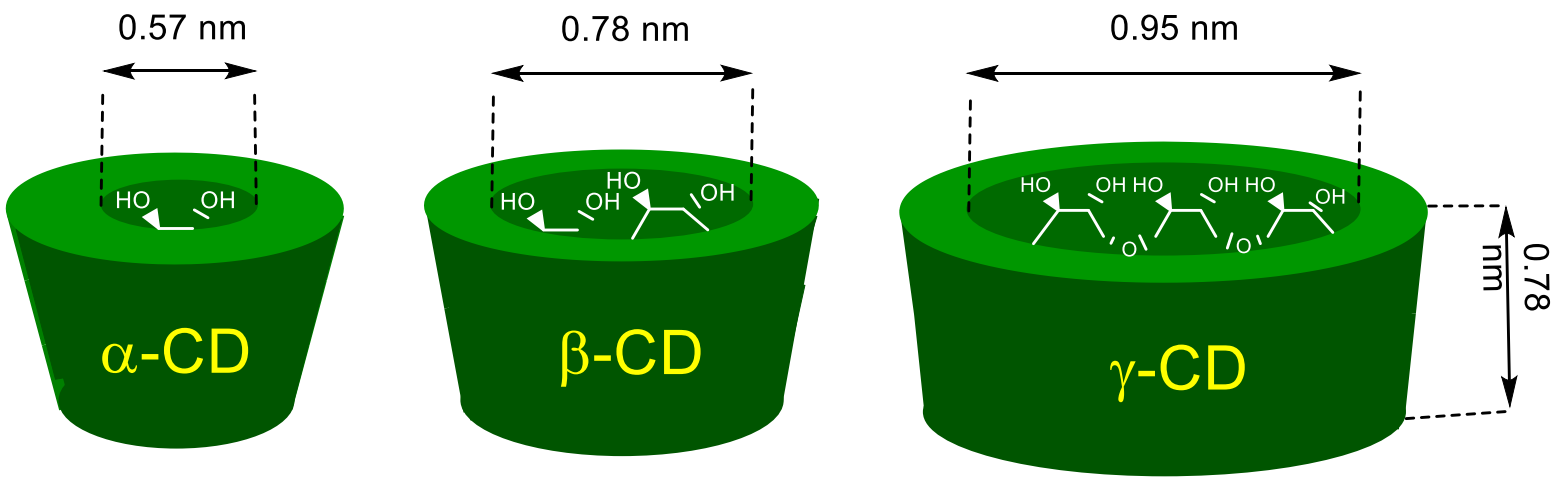
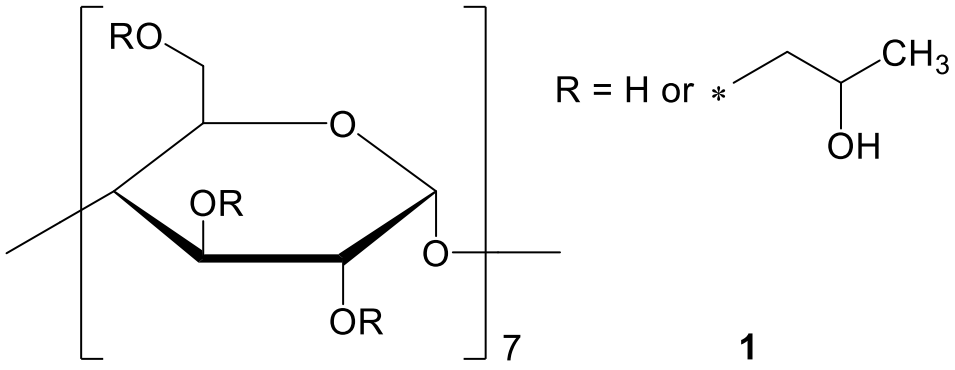
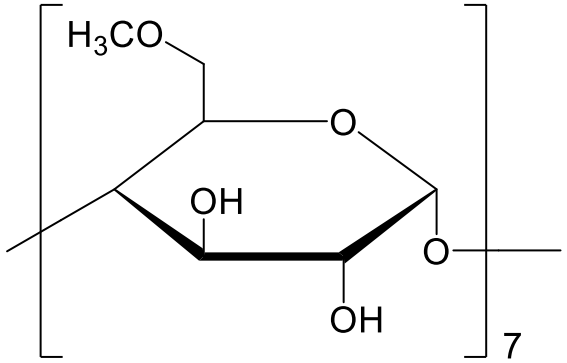

COOH
NH2
Phenylalanine
COOH
NH2
HO
Tyrosine
PAL
TAL
COOH
Cinnamate
C4H
COOH
p-coumarate
HO
4CL
CoA-SH
O
S-CoA
HO
p-coumaroyl-CoA
+ 3 HO
O
O
S-CoA
Malonyl-CoA
3CO2
CHS
Flavonoids
4CO2
STS
OH
OH
HO
Resveratrol
Hydroxylases
Piceatannol
+
Polyhydroxylated stilbenes
Isoprenylases
Isoprenylated stilbenes
ROMT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


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

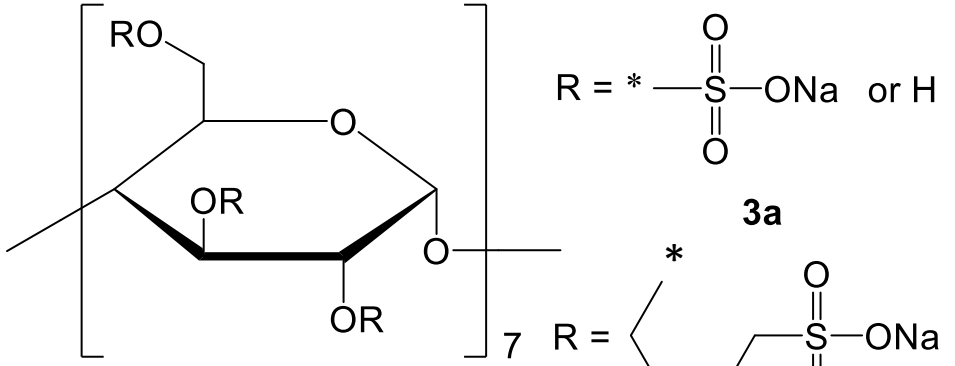

0.57 nm
0.78 nm
0.95 nm
HO
OH
α-CD
β-CD
γ-CD
0.78 nm


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

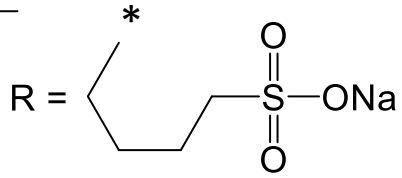
1


H3CO
O
OH
O
OH
7

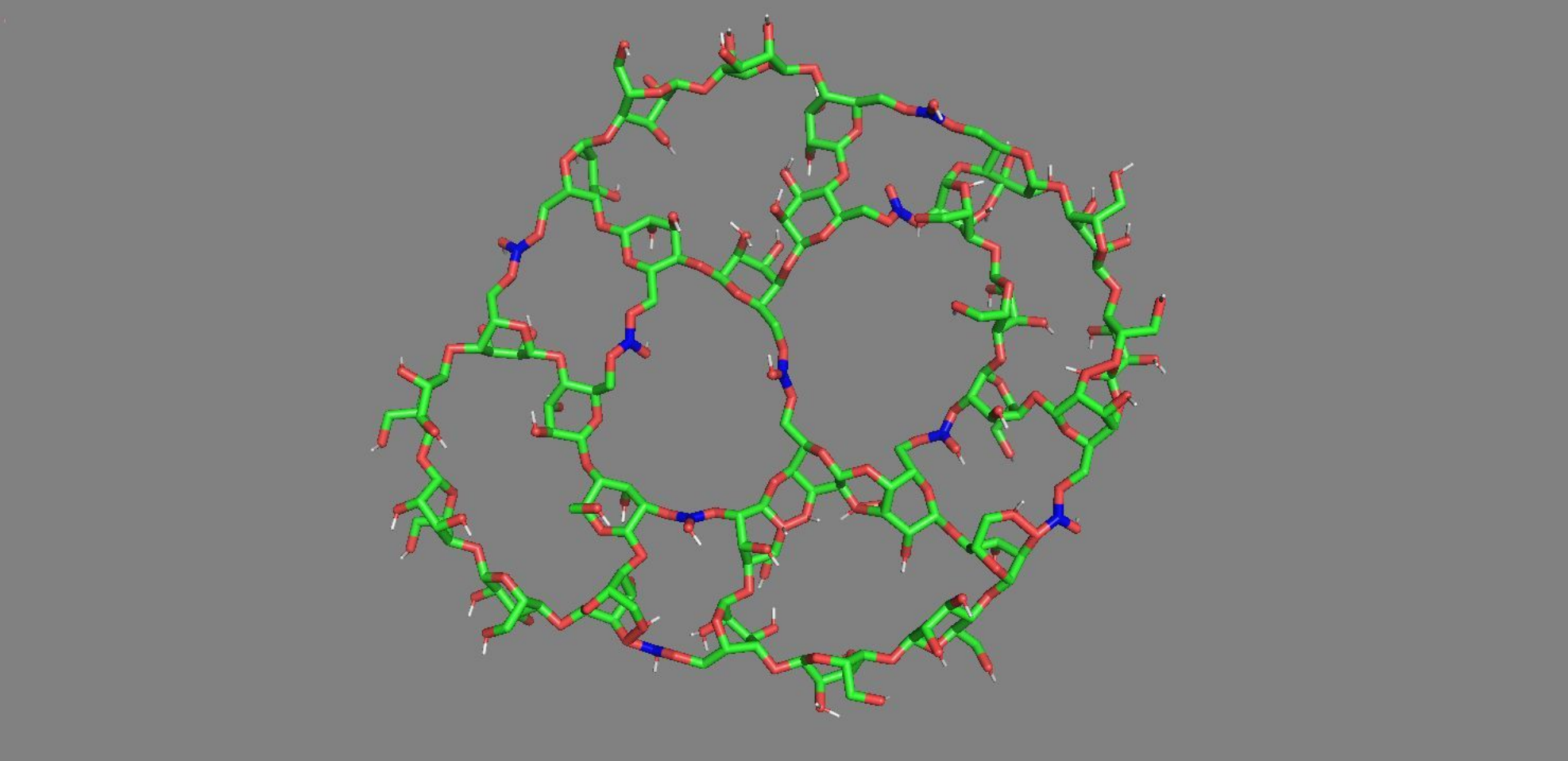
2

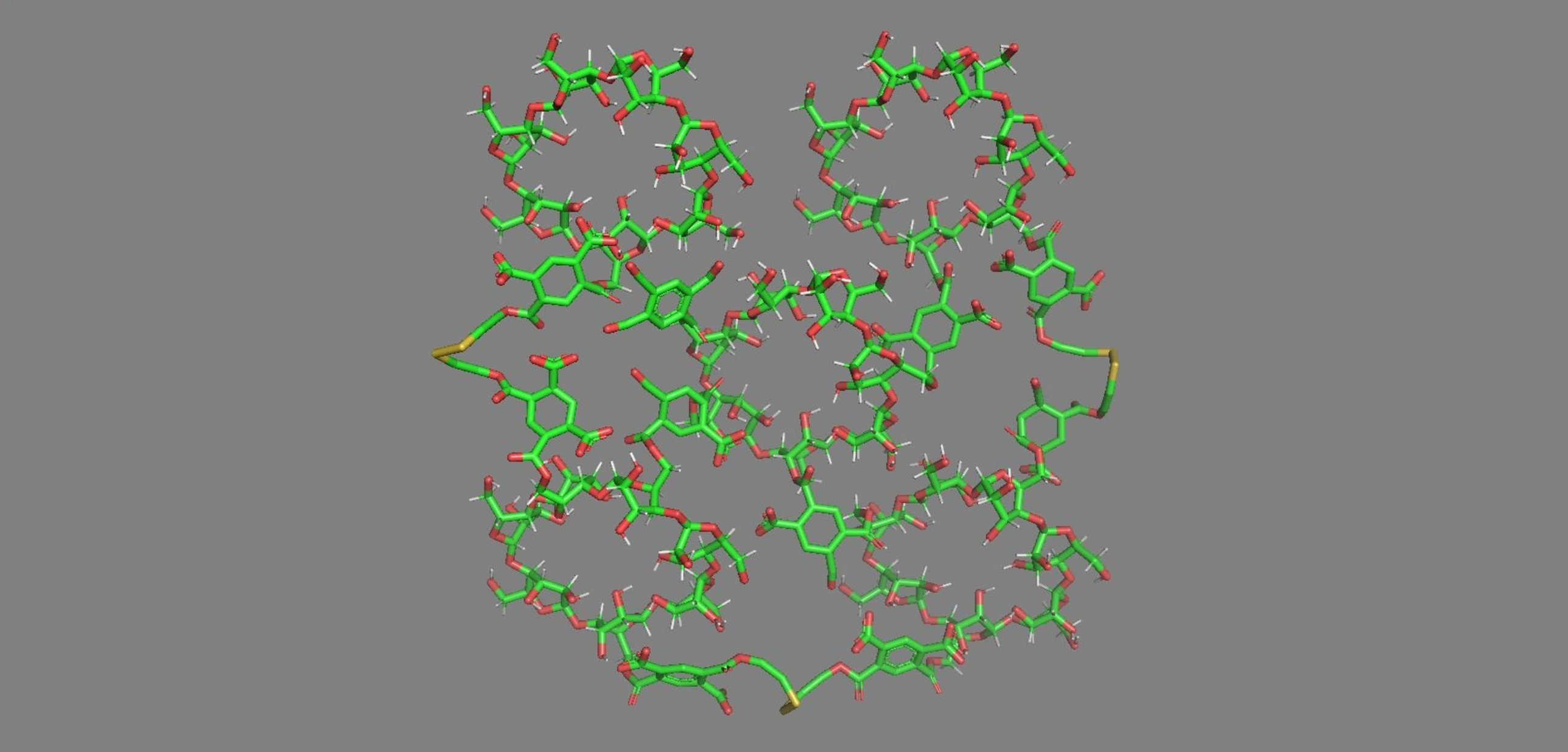

RO
O
OR
O
OR
7
R = *
S
O
O
ONa
or H

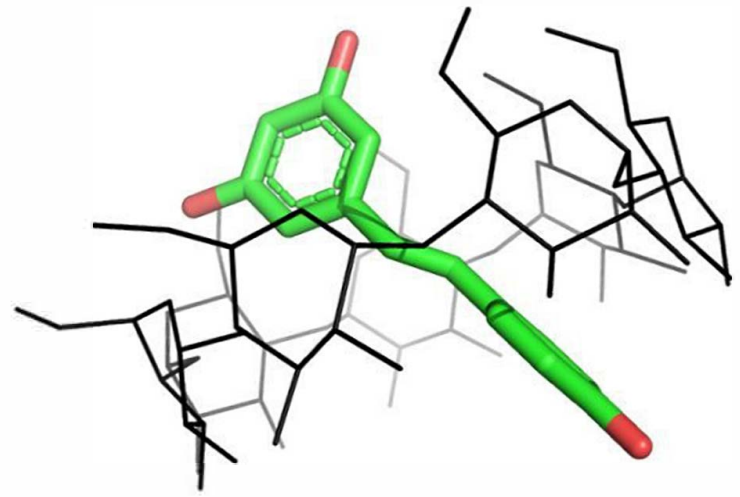
3a

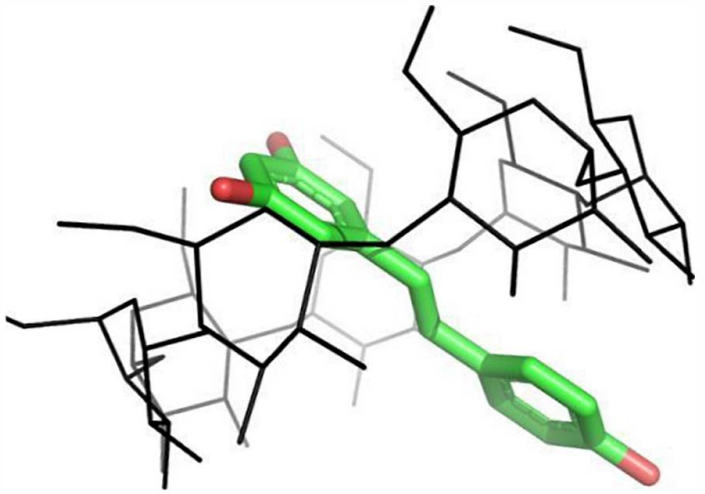

*
R =
S
O
O
ONa

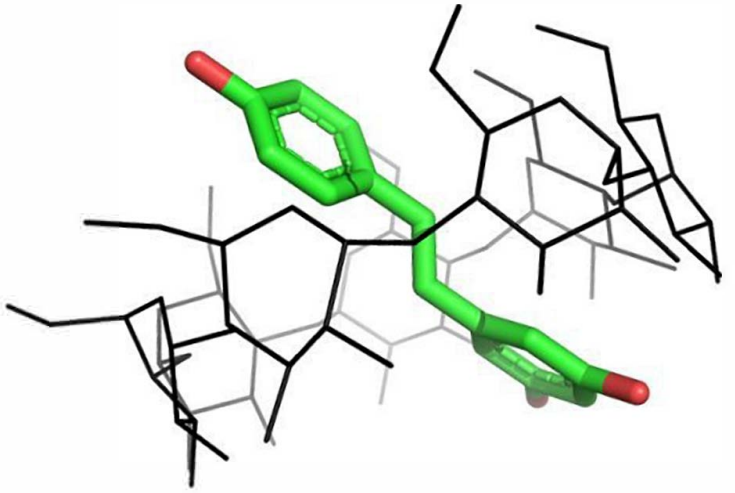
3b

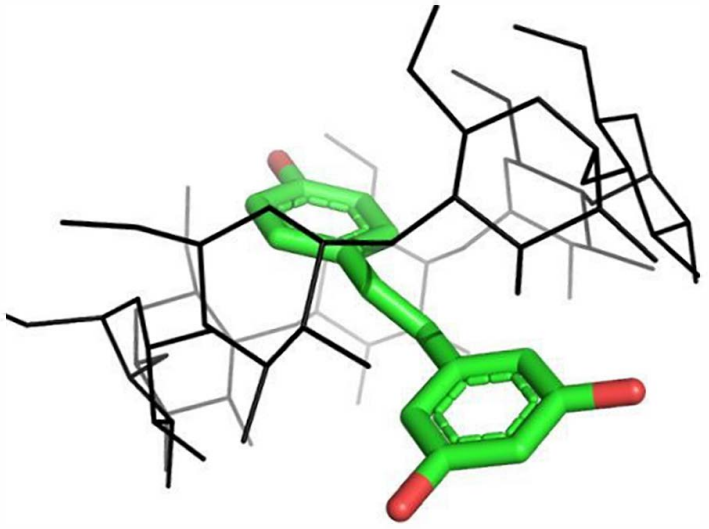


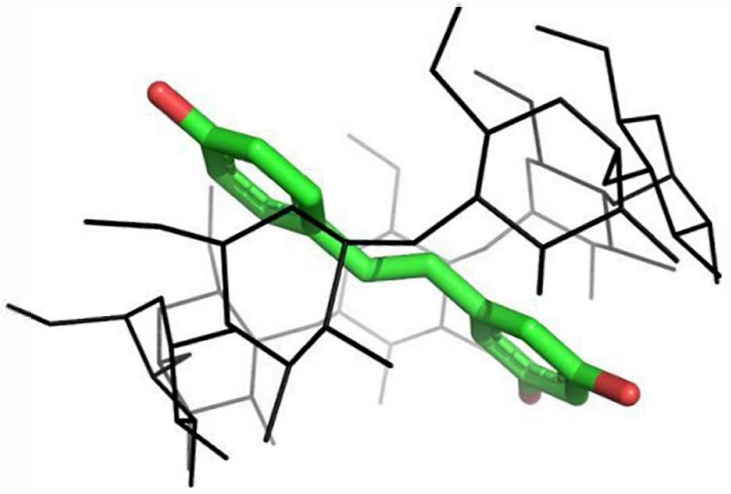


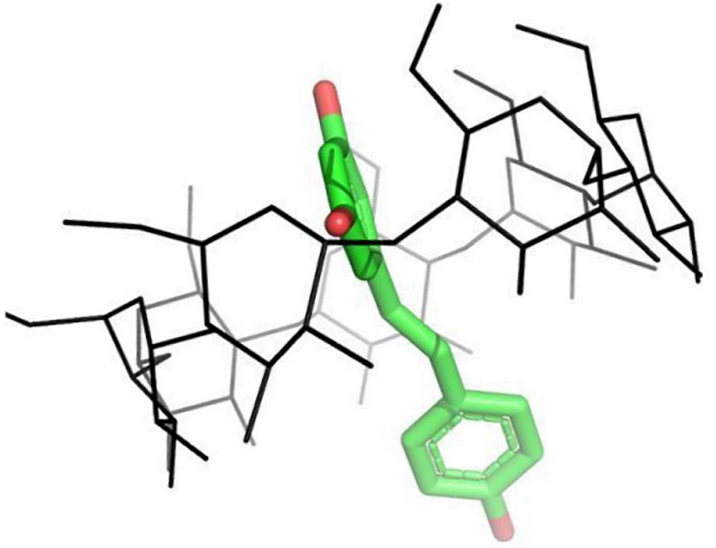


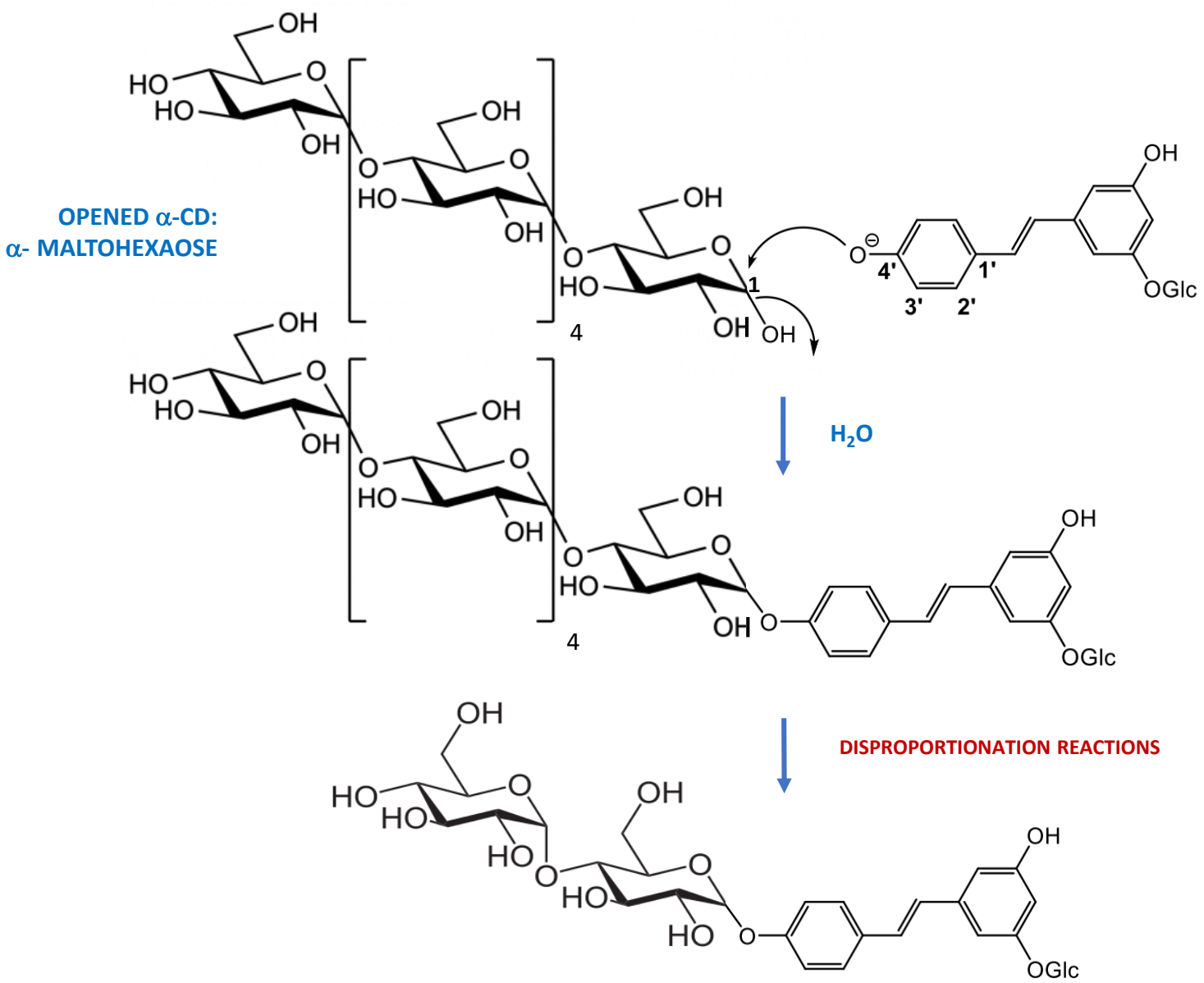


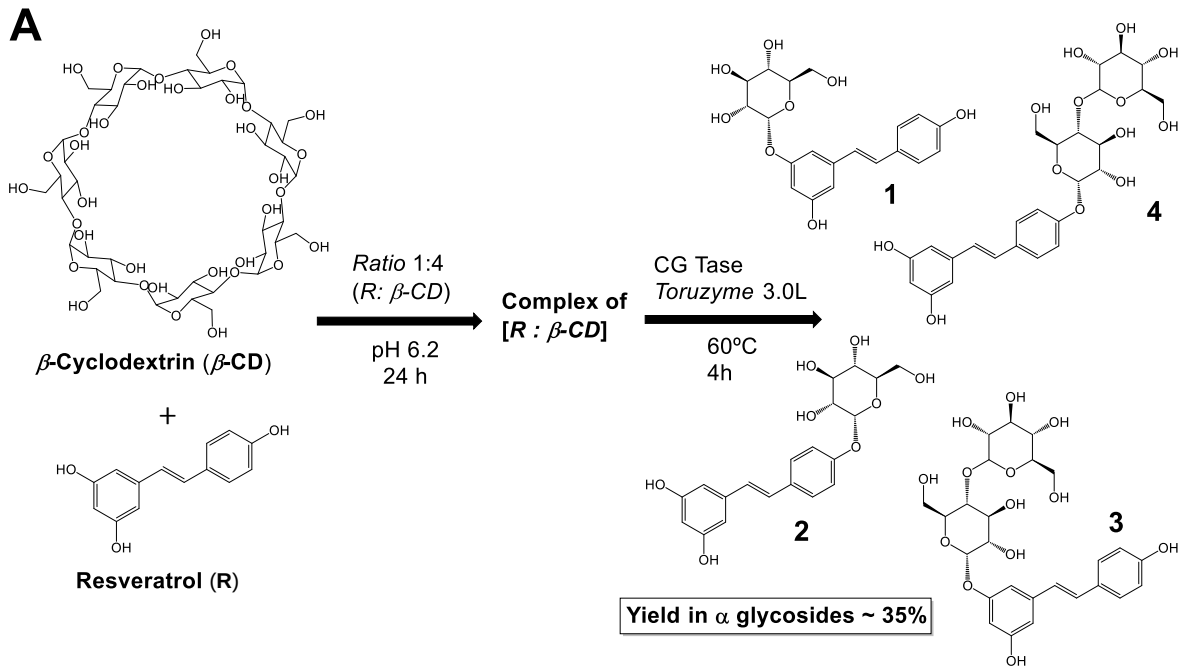


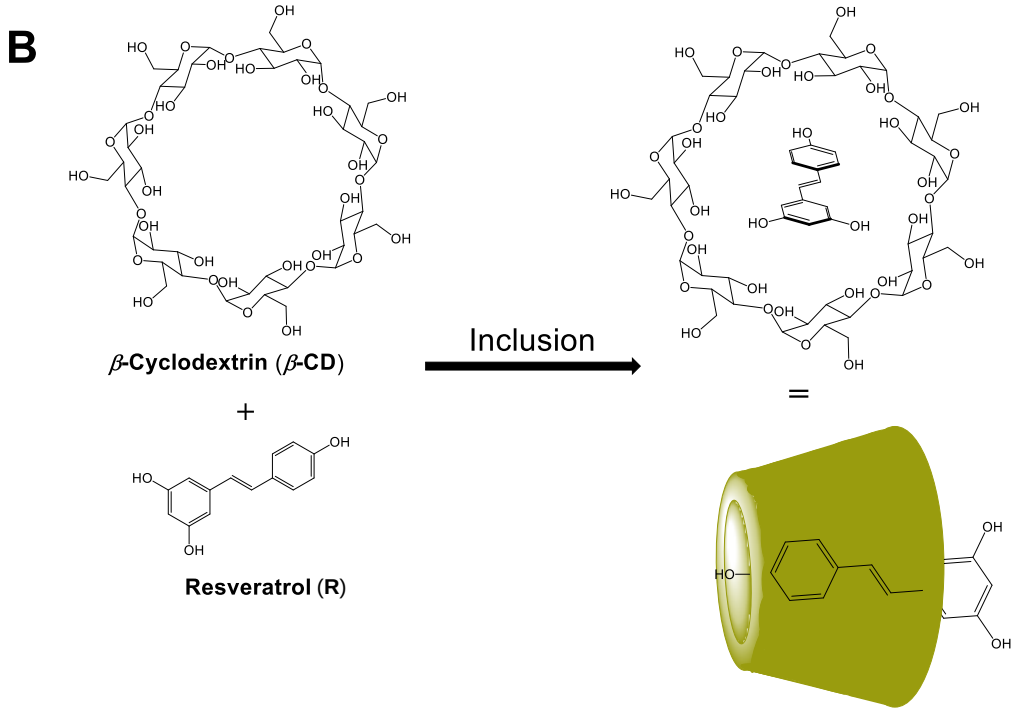







OPENED α-CD:
α- MALTOHEXAOSE
H2O
DISPROPORTIONATION REACTIONS
PicG3 + various glucosides


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
=

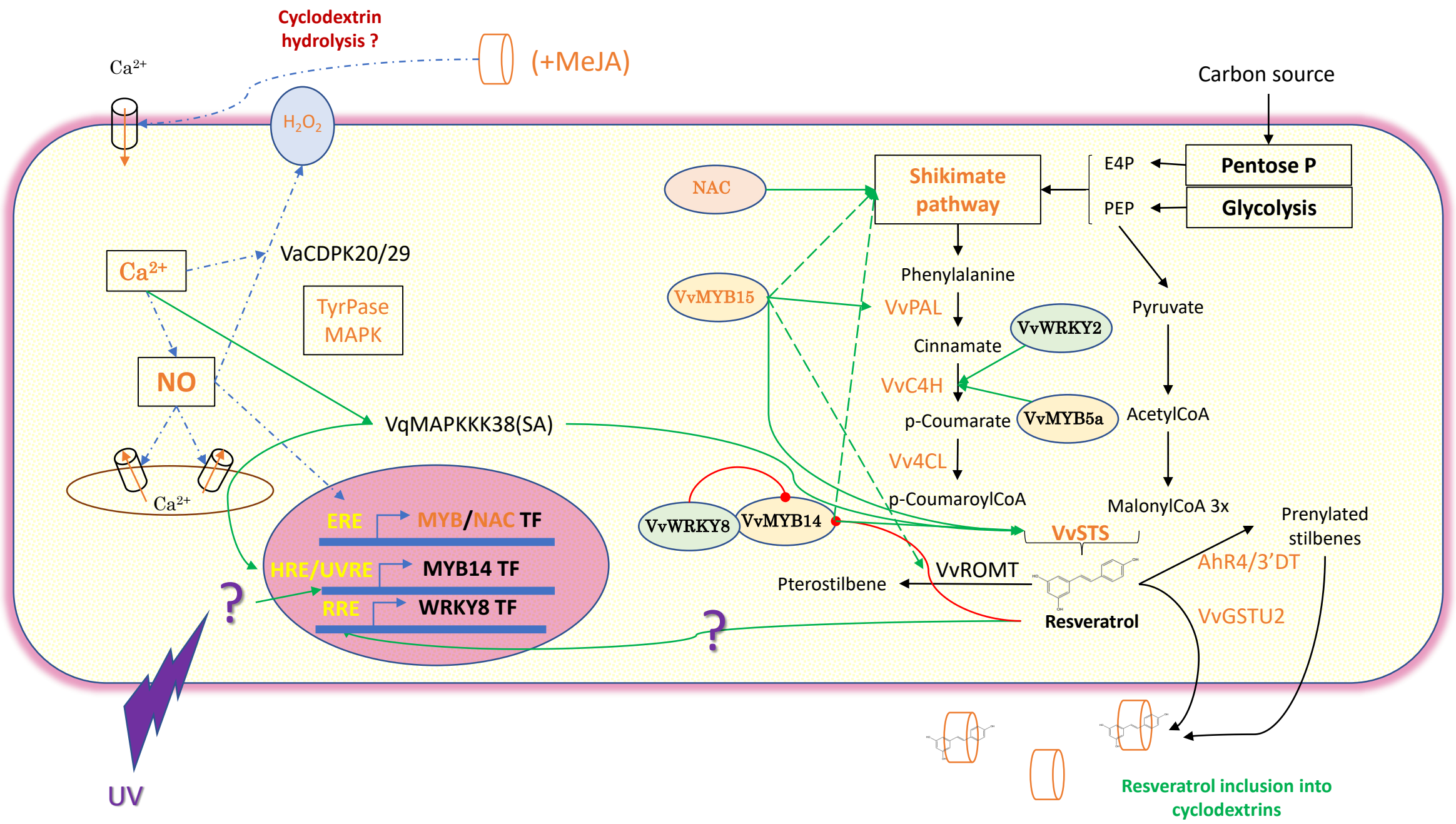

Cyclodextrin hydrolysis ?
(+MeJA)
Ca2+
H2O2
Carbon source
Pentose P
Glycolysis
E4P
PEP
Shikimate pathway
NAC
VaCDPK20/29
Ca2+
TyrPase
MAPK
NO
VvMYB15
Phenylalanine
VvPAL
Cinnamate
VvWRKY2
VvC4H
p-Coumarate
VvMYB5a
Pyruvate
AcetylCoA
VqMAPKKK38(SA)
Ca2+
Vv4CL
p-CoumaroylCoA
MalonylCoA 3x
ERE
MYB/NAC TF
HRE/UVRE
MYB14 TF
RRE
WRKY8 TF
VvWRKY8
VvMYB14
VvSTS
Prenylated stilbenes
AhR4/3'DT
VvROMT
Pterostilbene
Resveratrol
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)	$AUC_{0\to t}$ (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)