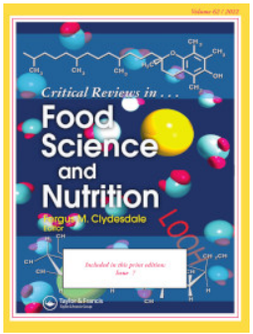

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REVIEW

Stilbenes: Characterization, bioactivity, encapsulation and structural modifications. A review of their current limitations and promising approaches

Silvia Navarro-Orcajada[a], Irene Conesa[a], Francisco José Vidal-Sánchez[a], Adrián Matencio[b], Lorena Albaladejo-Maricó[a], Francisco García-Carmona[a], and José Manuel López-Nicolás[a]

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ABSTRACT

Stilbenes are phenolic compounds naturally synthesized as secondary metabolites by the shikimate pathway in plants. Research on them has increased in recent years due to their therapeutic potential as antioxidant, antimicrobial, anti-inflammatory, anticancer, cardioprotective and anti-obesity agents. Amongst them, resveratrol has attracted the most attention, although there are other natural and synthesized stilbenes with enhanced properties. However, stilbenes have some physicochemical and pharmacokinetic problems that need to be overcome before considering their applications. Human clinical evidence of their bioactivity is still controversial due to this fact and hence, exhaustive basis science on stilbenes is needed before applied science. This review gathers the main physicochemical and biological properties of natural stilbenes, establishes structure-activity relationships among them, emphasizing the current problems that limit their applications and presenting some promising approaches to overcome these issues: the encapsulation in different agents and the structural modification to obtain novel stilbenes with better features. The bioactivity of stilbenes should move from promising to evident.

KEYWORDS

Stilbenes; synthesis; physicochemical; activity; encapsulation; structure

1. Introduction

Stilbenes are phenolic compounds which belong to the stilbenoid group along with oligostilbenes, bibenzyls, bisbibenzyls and phenanthrenes. They are the most researched stilbenoids and are characterized by a basic 1,2-diphenylethylene skeleton with different substituents (Shen et al. 2013) (Figure 1). Stilbenes are secondary metabolites produced *de novo* to protect plants from biotic and abiotic stress. In natural sources, they may be found as aglycones or conjugated as glycosides. The beneficial effects on human health that stilbenes may possess have been subject of much research in recent years, and it is mainly related to their chemical structure.

Among them, resveratrol has received the most attention since the *French paradox* was postulated, reaching a total of 2321 publications in WOS in 2020, compared to 127 publications for pterostilbene or 98 for piceatannol. However, the number of natural and synthesized stilbenes being discovered and tested is constantly increasing and other lesser-known stilbenes are gaining prominence over resveratrol (Pecyna et al. 2020; Likhitwitayawuid 2021; Szekeres et al. 2010; de Vries, Strydom, and Steenkamp 2021).

Besides resveratrol (Tian and Liu 2020), reviews that compare stilbenes are less abundant and are mainly focused on their occurrence, biological activity, or pharmacokinetics (El Khawand et al. 2018; Oh, Gao, and Shahidi 2021; Akinwumi, Bordun, and Anderson 2018). In fact, information about the physicochemical characterization and limitations of these molecules are very scarce when searching for stilbenes other than resveratrol. This should encourage researchers to conduct exhaustive basic research prior to applied research in order to make progress. Physicochemical problems of stilbenes need to be solved before even considering their potential applications. Otherwise, the in vivo effectiveness of these bioactive compounds could be compromised. For this reason, this review puts together the most relevant information on the physicochemical and biological properties of stilbenes, establishing structure-activity relationships among them and highlighting some of the strategies that could help to overcome their limitations when applied in the food, cosmetic or pharmaceutical industry.

2. Natural sources of stilbenes

Stilbenes can be isolated from phylogenetically distant botanical plant families, some common examples are Pinaceae (pine), Vitaceae (grapes), Poaceae (sorghum), Fabaceae (peanut) and Ericaceae (blueberry). They are usually located in the roots, rhizomes leaves and barks (Chong, Poutaraud,

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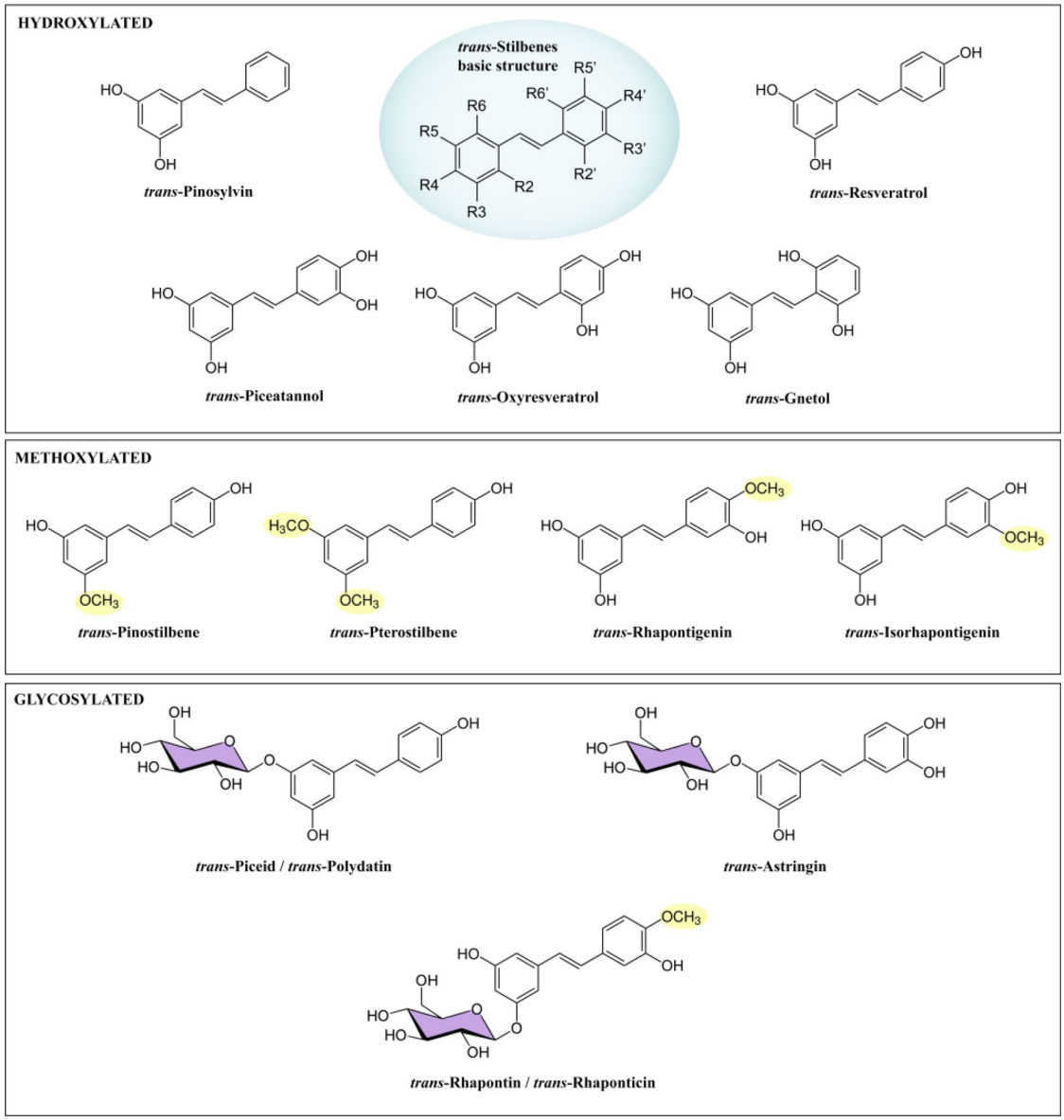

Figure 1. Chemical structure of some natural *trans*-stilbenes.

and Hugueney 2009; Dubrovina and Kiselev 2017; Cassidy, Hanley, and Lamuela-Raventos 2000).

The enzyme stilbene synthase plays a key role in this irregular taxonomic distribution of stilbenes in plants, since this enzyme is only found in some taxa. This protein is paramount in the synthesis of stilbenes since it acts in the last step of the route. The presence of stilbene synthase in different taxa could be explained by a chemical evolution convergence (Grayer, Chase, and Simmonds 1999). It could be also explained by a differential gene expression. Some species may have lost or "turned off" the stilbene synthase gene because of the presence of better defense mechanisms (Rivière, Pawlus, and Mérillon 2012).

2.1. Biosynthesis pathway in plants

Stilbenes are synthesized in plants through the shikimate pathway (Figure 2). The metabolic route starts with a molecule of cinnamic acid or *p*-coumaric acid, previously synthesized by phenylalanine ammonia lyase (PAL) or tyrosine ammonia lyase (TAL) from L-phenylalanine or L-tyrosine, respectively. Moreover, cinnamic acid can be transformed in *p*-coumaric acid by the enzyme cinnamate 4-hydroxylase (C4H). Next, the enzyme coumarate CoA ligase (CL) can transform these two molecules in cinnamoyl-CoA or *p*-coumaryl-CoA, respectively.

Then, stilbene synthase (STS) utilizes three malonyl-CoA units and one cinnamoyl-CoA or *p*-coumaryl-CoA to produce a polyketide intermediate. After that, STS acts again on the intermediate and catalyzes the aldol condensation reaction to produce stilbene-2-carboxylic acid. This molecule is used as a decarboxylated starter skeleton to produce different stilbenoids, like *trans*-resveratrol. Later, the stilbenes can be modified (glycosylated, methylated or prenylated) by different enzymes (Rivière, Pawlus, and Mérillon 2012; Dubrovina and Kiselev 2017).

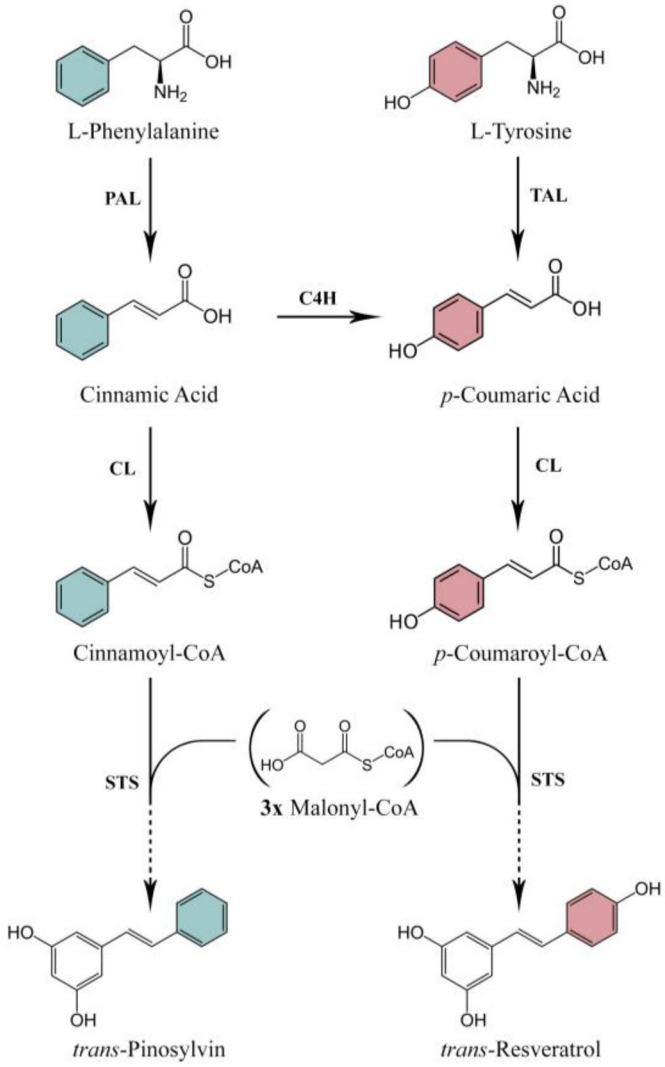

Figure 2. Biosynthesis pathway of stilbenes in plants. PAL = Phenylalanine Ammonia Lyase, TAL = Tyrosine Ammonia Lyase, C4H = Cinnamate 4-Hydroxylase, CL = Coumarate-CoA Ligase, STS = Stilbene Synthase.

On the other hand, CL catalyzes the formation of caffeoyl-CoA, using caffeic acid as a substrate. It has been hypothesized that STS could use the molecule of caffeoyl-CoA to produce piceatannol (Dubrovina and Kiselev 2017).

The substrates of STS are also used by the chalcone synthase (CHS), although in this case they are used to produce flavonoids. These enzymes are similar and show a great homology in their amino acid sequences. In fact, STS and CHS of *Arachis hypogea* only differ in 35 residues throughout their protein sequences and share up to 70% (Jeandet et al. 2010; Shomura et al. 2005).

2.2. Stilbenes in diet

In plants, polyphenol production in general is higher than that of stilbenes specifically. There are many plant sources rich in stilbenes, but they are not usually consumed as food. Moreover, these molecules are sometimes in non-edible tissues. For example, *Polygonum cuspidatum* and *Veratrum formosanum,* which are used in traditional Chinese medicine, are rich in these bioactive compounds but are not consumed as food. In fact, the latter is a poisonous plant (Cassidy, Hanley, and Lamuela-Raventos 2000; El Khawand et al. 2018).

It should be noticed that the consumption of stilbenes is different depending on the country and its culture. For example, the extraction of resveratrol from the *Polygonum cuspidatum* roots are used in Europe as a food complement, while in Asia they are used as traditional medicine and food. In Europe the main dietary sources of stilbenes are grapes, red wine and peanuts. There are studies that report the presence of resveratrol and piceid (the glycoside of resveratrol) in several fruits and vegetables like plum, apple, pear, peach, and blueberries (Dubrovina and Kiselev 2017; G. Li et al. 2013).

2.3. Alternative sources of stilbenes

Traditionally, stilbenes have been isolated from different parts of naturally producing stilbenes plants, but it is hard to obtain commercially profitable yield due to the multiple steps of extraction and isolation as well as seasonal dependence (Thapa et al. 2019).

For this reason, multiple investigations are being carried out with the goal of finding new production methods. For instance, suspension cultured cells and roots, among which should be mentioned the culture of *Vitis vinifera* treated with several elicitors (cyclodextrins, methyl jasmonate, UV rays, etc.) in order to increase stilbene production (Laura et al. 2007; Z. Cai et al. 2013; Hosseini et al. 2017; Sák et al. 2021). Another alternative is the use of genetically modified plants (Hain and Grimmig 2000; Giovinazzo et al. 2005) and microorganisms (Beekwilder et al. 2006; C. G. Lim et al. 2011; Shrestha et al. 2018; Kallscheuer et al. 2016) transformed via genetic engineering with the genes implied in the stilbene synthesis route. Chemically, stilbenes can be synthesized by Heck, Perkin or Witting reactions, among others (Tian and Liu 2020).

3. Physicochemical characterization of stilbenes

Stilbenes have two natural isomeric forms: *trans*-stilbenes (E-stilbenes) and *cis*-stilbenes (Z-stilbenes). *Trans*-stilbenes are the most interesting forms of stilbenes because of their well-known properties. In fact, *cis*-stilbenes are a degradation product formed after the photo-oxidation of *trans*-stilbenes (Tian and Liu 2020). In general, when the isomerization is not specified for a stilbene, we refer to the *trans*-form since it is the most common.

The stilbene molecule can have substituents such as sugars and hydroxyl and methoxy groups in different positions. These substituents are responsible of the variety of stilbenes (resveratrol, oxyresveratrol, gnetol, piceatannol, pinosylvin, pterostilbene, piceid, astringin, etc.) with different physicochemical properties: solubility, polarity, lipophilicity, spectrophotometric and spectrofluorimetric features, dissociation constants, aggregation states and stability.

3.1. Solubility, polarity and lipophilicity

When working with stilbenes, one of the biggest problems is their low aqueous solubility and bioavailability as they are highly hydrophobic compounds. For example, the aqueous solubility of resveratrol is in the range of 3 mg/100 mL (Kershaw and Kim 2017), one of the most hydrophobic stilbenes as well as pterostilbene, this one with an aqueous solubility of 2,1 mg/100 mL (Bethune, Schultheiss, and Henck 2011). Stilbenes with more hydroxyl groups have higher solubility values, like the ones of piceatannol (50 mg/100 mL) (Kershaw and Kim 2017), gnetol (31 mg/100 mL) (Navarro-Orcajada et al. 2022) and oxyresveratrol (75 mg/100 mL) (Suzuki et al. 2019).

However, there are other solvents more suitable for solubilizing these stilbenes, like ethanol, methanol and dimethyl sulfoxide (DMSO). Thus, the solubility of resveratrol is 50 g/L in ethanol and higher than 16 g/L in DMSO at room temperature (Kershaw and Kim 2017). Piceatannol is also more soluble in ethanol and DMSO (10 g/L in both cases) (Kershaw and Kim 2017).

These values are strongly dependent of the environment and can suffer important variations at different levels of pH and temperature (Zupančič, Lavrič, and Kristl 2015).

In Table 1, the values of aqueous solubility of different stilbenes can be seen when there is information about it, as well as the topological polar surface area (TPSA) and lipophilicity expressed as the partition coefficient (LogP) of these compounds. In general, the polar surface area is higher in glycosylated stilbenes, while among aglycones, the greater number of hydroxyl groups increases this value with almost no variation with the presence of methoxy groups. By contrast, lipophilicity is inversely proportional to the number of hydroxyl groups, and much lower in the case of the glycosylated derivatives.

3.2. Spectrophotometric features

Stilbenes have its maximum peak in the UV region, in the range of 300–330 nm, especially the *trans*-stilbenes. For example, *trans*-resveratrol has its maximum absorbance peak at a wavelength (λ_{max}) of 304–308 nm, whereas *cis*-resveratrol absorbs at a λ_{max} of 286 nm (Trela and Waterhouse 1996). *Trans*-piceid, the glycoside of resveratrol, has λ_{max} of 318.4 nm, unlike its *cis*- isomer which has λ_{max} of 284.4 nm (Giorcelli et al. 2004). This is very relevant when separating both isomers using an HPLC system, as most of them have a UV-Vis detector. Besides, a relationship between *cis*- and *trans*- oxyresveratrol can be calculated with the quotient of the absorbance at 290 and 310 nm (secondary peaks in the spectrum) to determine the degradation level of the molecule (Matencio et al. 2020d).

In Table 1, the maximum absorbance peaks for some stilbenes and their glycosylated derivatives are presented, as well as the value of the molar extinction coefficient (ε) if it is determined. There are different data of molar attenuation coefficient in bibliography for *cis*- and *trans*-stilbenes. In the case of resveratrol and according to Trela and Waterhouse (1996) results (Trela and Waterhouse 1996), for *trans*-resveratrol ε is 31,800 $M^{-1}cm^{-1}$ at its maximum of absorbance (306 nm), whereas for *cis*-resveratrol ε has a value of 13,100 $M^{-1}cm^{-1}$ at 286 nm, the maximum for this isomer. These values were measured with resveratrol in an aqueous solution with 10% ethanol (v/v). Besides, Džeba, Pedzinski, and Mihaljević (2015) characterized resveratrol excited states and determined spectra and molar attenuation coefficients for the radical cation of resveratrol and deprotonated form (Džeba, Pedzinski, and Mihaljević 2015).

The addition of an extra hydroxyl group in R3', gave a similar molar attenuation coefficient although different λ_{max}. At a wavelength of 326 nm, the ε of piceatannol was 33,100 $M^{-1}cm^{-1}$, dissolved in pure ethanol (Rhayem et al. 2008). There are other values of ε for different λ; for example, the molar extinction coefficient of piceatannol at 304 nm (a shoulder on its spectrum) is 26,350 $M^{-1}cm^{-1}$. By contrast, rhapontigenin, a methoxylated analogue of piceatannol had an ε of 36,824 $M^{-1}cm^{-1}$ at 325 nm in 50% methanol. The glycosylation of this stilbene (rhapontin) maintained the λ_{max} despite increasing ε to 43,894 $M^{-1}cm^{-1}$ (Hui, Li, and Chen 2011).

In general, the available data of the ε of the main natural stilbenes is in the range of 33,000–44,000 $M^{-1}cm^{-1}$, with some variations depending on the solvent.

3.3. Spectrofluorimetric features

The stilbene structure with two aromatic rings joined with a methylene brigde makes them fluorescent compounds when they are irradiated with UV light. Indeed, the name stilbene was derived from the Greek word "στίλβω," which means shining. Table 1 shows that the majority of natural stilbenes emit fluorescence at a λ_{em} near 370–400 nm. For example, *trans*-resveratrol emits at 389 nm when exciting the molecule at 300–330 nm and *cis*-resveratrol at 400 nm after exciting it at 260 nm (Vitrac et al. 2002).

The addition of another hydroxyl group in different positions slightly changes these values. In the case of *trans*-piceatannol (hydroxyls at R3', R4', R3 and R5), its maximum emission is also recorded in the range of 400 nm (Y. Shi et al. 2020; C. Cai et al. 2019) exciting the molecule at 321 nm. Oxyresveratrol (hydroxyls at R2', R4', R3 and R5) is another stilbene which has its λ_{em} in the range of 400 nm (He et al. 2017) when it is excited at 288 nm. By contrast, gnetol (hydroxyls at R2', R6', R3 and R5) has a different emission spectrum with a main peak in the range of 503 nm and a secondary peak at 390 nm (Navarro-Orcajada et al. 2022), after excitation at 280 nm. Other stilbenes with fewer hydroxyl groups, like pinosylvin (hydroxyls at R3 and R5) and pterostilbene (hydroxyl at R4'), were reported to emit at a lower wavelength (both at 374 nm) (López-Nicolás, Rodríguez-Bonilla, and García-Carmona 2009; López-Nicolás et al. 2009).

The knowledge of these fluorescence values (especially the emission) is very important as fluorescence can be detected in a Liquid Chromatography (LC) system, being

Table 1. Physicochemical characterization of natural *trans*-stilbenes.

Stilbene	Substituents	Molecular formula	MW (g/mol)	Water solubility (mg/100mL)	pK_a	**LogP**[a]	**TPSA**[a]**(Å^2)**	ε ($M^{-1}cm^{-1}$)	λ_{max} (nm)	λ_{ex} (nm)	λ_{em} (nm)	References
Pinosylvin	2x -OH	$C_{14}H_{12}O_2$	212.24	–	7.7; 10.3	3.5	40.5	–	312	330	374	(López-Nicolás, Rodríguez-Bonilla, and García-Carmona 2009; Stojanović and Brede 2002)
Resveratrol	3x -OH	$C_{14}H_{12}O_3$	228.24	3	8.8; 9.8; 11.4	3.1	60.7	31,800[b]	306	334	389	(Kershaw and Kim 2017; Trela and Waterhouse 1996; Vitrac et al. 2002; López-Nicolás and García-Carmona 2008)
Piceatannol	4x -OH	$C_{14}H_{12}O_4$	244.24	50	–	2.9	80.9	33,100[c]	323	321	402	(Kershaw and Kim 2017; Rhayem et al. 2008; Y. Shi et al. 2020; C. Cai et al. 2019)
Oxyresveratrol	4x -OH	$C_{14}H_{12}O_4$	244.24	75	–	2.8	80.9	–	328	288	400	(Suzuki et al. 2019; He et al. 2017; Matencio, García-Carmona, and López-Nicolás 2017a)
Gnetol	4x -OH	$C_{14}H_{12}O_4$	244.24	31	–	2.8	80.9	40,003[c]	310	280	503	(Navarro-Orcajada et al. 2022)
Pterostilbene	1x -OH 2x -O-CH_3	$C_{16}H_{16}O_3$	256.30	2.1	9.4	3.8	38.7	–	315	330	374	(Bethune, Schultheiss, and Henck 2011; Orgován, Gonda, and Noszál 2017; López-Nicolás et al. 2009)
Pinostilbene	2x -OH 1x -O-CH_3	$C_{15}H_{14}O_3$	242.27	–	9.1; 9.9	3.5	49.7	35,481[c]	307	–	–	(Orgován, Gonda, and Noszál 2017; Tyukavkina et al. 1972)
Rhapontigenin	3x -OH 1x -O-CH_3	$C_{15}H_{14}O_4$	258.27	–	–	3.1	69.9	36,824[d]	324.5	–	–	(Hui, Li, and Chen 2011)
Isorhapontigenin	3x -OH 1x -O-CH_3	$C_{15}H_{14}O_4$	258.27	–	–	3.2	69.9	–	325	–	–	(Fernández-Marín et al. 2012)
Piceid / Polydatin	2x -OH 1x -O-Gluc	$C_{20}H_{22}O_8$	390.40	–	–	1.7	140	–	318.4	–	–	(Giorcelli et al. 2004)
Astringin	3x -OH 1x -O-Gluc	$C_{20}H_{22}O_9$	406.40	–	–	0.7	160	–	325	298	400	(Toscano Underwood and Pearce 1991; Carando et al. 1999)
Rhapontin	2x -OH 1x -O-CH_3 1x -O-Gluc	$C_{21}H_{24}O_9$	420.40	–	6.39	0.5	149	43,894[d]	325	355	390	(Hui, Li, and Chen 2011; Liu et al. 2019)

O-Gluc = O-glucosyde (O-$C_6H_{11}O_5$); MW = molecular weight; TPSA = topological surface area; LogP = lipophilicity index.
[a]PubChem database.
[b]Measured in 10% ethanol (*v/v*).
[c]Measured in ethanol.
[d]Measured in 50% methanol (*v/v*).

more sensitive than absorbance to quantify the concentration of a stilbene within a sample.

3.4. Acid dissociation constants (pK_a)

Protonation states of stilbenes are crucial for their biological activity, for instance, radical scavenging activity is highly dependent on the ability to transfer hydrogen atoms. As resveratrol has 3 hydroxyl groups, there are 3 different pK_as for the molecule: pK_{a1} is at a pH of 8.8, pK_{a2} at a pH of 9.8 and pK_{a3} is at a pH of 11.4. The most unstable hydroxyl group has been reported to be at R4', so the first pK_a is associated to the deprotonation of 4′-OH. It remains unclear whether the second pK_a indicates the deprotonation of 3-OH or 5-OH, and the same for the third pK_a, as both are located nearby (López-Nicolás and García-Carmona 2008). Other authors suggested that the protonation of the three phenolates occurs in an overlapping pH range (Orgován, Gonda, and Noszál 2017).

Stojanović and Brede (2002) established that the protonation constants for pinosylvin, an analogue of resveratrol without the hydroxyl at R4', were at pH 7.7 and 10.3 (Stojanović and Brede 2002). Methoxylated stilbenes such as pinostilbene, a 3-methoxy analogue of resveratrol, has been described to have its dissociation constants at pH 9.1 and 9.9, while pterostilbene, a 3,5-dimethoxy analogue, at pH 9.4 (Orgován, Gonda, and Noszál 2017). Besides, the acid dissociation constant for rhapontin, the glycoside of rhapontigenin, was reported at pH 6.39 (Liu et al. 2019). The *cis*- form of resveratrol, pinostilbene and pterostilbene slightly increase these values of pK_as (Orgován, Gonda, and Noszál 2017).

3.5. Aggregation states

Information about pK_as of stilbenes is also relevant because the aggregation state is strongly dependent of pH, as it was confirmed by López-Nicolás and García-Carmona (2008) by fluorescence spectroscopy and UV-visible absorption (López-Nicolás and García-Carmona 2008). Thereby, at an acid pH (5.5), the critical concentration of resveratrol before the molecule aggregates is 12.5 µM. Above this concentration, a bathochromic displacement can be seen in a fluorescence study, as the maximum excitation and emission wavelengths are higher. The maximum fluorescence emission wavelength changes from 376 to 393 nm.

If the same study is performed at a basic pH (10.5), the critical concentration of resveratrol is quite higher (37 µM). Above this concentration, resveratrol forms aggregates (López-Nicolás and García-Carmona 2008).

3.6. Stability and degradation mechanism

Stilbenes, and particularly *trans*-stilbenes, are very sensitive to light, which transforms the *trans*- into the *cis*- isomer, a less bioactive form and a degradation product of the molecule. In the case of resveratrol, this isomerization occurs after several hours of sunlight exposure or when the molecule is irradiated with ultraviolet light. However, this photocatalytic degradation is bigger when *trans*-resveratrol is exposed to UV-Vis light than only to UV or visible light (Silva et al. 2013; Francioso et al. 2014). *Trans*-resveratrol is more stable in vitro than *cis*-resveratrol, and *cis*-resveratrol can give rise to 4a,4b-dihydrophenantrene (DHP) and other phenantrenoids like trihydroxydihydrophenantrene (THDHP) as a result of the photocatalytic degradation (Francioso et al. 2014).

Trans-piceatannol is also very sensitive to light and the degradation mechanism is very similar to that of resveratrol. When piceatannol is irradiated with a λ of 366 nm, *trans*-piceatannol isomerizes to the *cis*- isoform. Afterwards, the *cis*- stilbene loses 2 hydrogens and forms a phenanthrenoid ring (Latva-Mäenpää et al. 2021). This degradation mechanism is also the same for other stilbenes like isorhapontigenin, isorhapontin and astringin.

Although the mechanism is the same, there are remarkable differences in the time that each stilbene remains stable. Tang, Xie, et al. (2017) studied how much time was required to degrade 50% of different *trans*-stilbenes in vitro, that is, the half-life of each compound (F. Tang, Xie, et al. 2017). This study showed that some stilbenes were very stable, like pinosylvin or pterostilbene (above 180 minutes), followed by resveratrol, gnetol and oxyresveratrol (109.35, 66.51 and 65.43 minutes, respectively); whereas others like piceatannol or isorhapontigenin were much more unstable, with a half-life of 14.38 and 27.89 minutes, respectively. *Trans*-piceid and other glycosides such as *trans*-astringin and *trans*-rhapontin are more sensitive to light than their aglycones (*trans*-resveratrol, *trans*-piceatannol and *trans*-rhapontigenin), which are more susceptible to *cis* isomerization and, subsequently, to the formation of a phenanthrenoid ring (Latva-Mäenpää et al. 2021). Tang, Xie, et al. (2017) also studied the stability of these glycosides: astringin had a half-life of 42.05 minutes and piceid of more than 180 minutes (F. Tang, Xie, et al. 2017).

Apart from their photosensitivity, there are other parameters that play a role in the stability of stilbenes, like pH or temperature. Resveratrol is more stable at low levels of pH and temperature, remaining stable even for months within low pH buffers. However, when pH is above 6.8, the stability of *trans*-resveratrol decreases dramatically. In fact, at pH 10, the half-life for *trans*-resveratrol is about 1.6 hours (Francioso et al. 2014). This is because the basic pH causes the deprotonation of resveratrol on the R4' and, subsequently, the formation of a quinonoid radical. At neutral pH, temperatures above 25 °C can completely degrade resveratrol in days, meanwhile storage at 4 °C and −22 °C can preserve it for months (Zupančič, Lavrič, and Kristl 2015). This information should be considered in experiments in physiological conditions.

4. Biological activity of stilbenes

The structure of stilbenes allows them to have certain biological properties such as antioxidant, antimicrobial and anti-inflammatory agents. In addition, a growing number of studies show that these molecules also play a protective

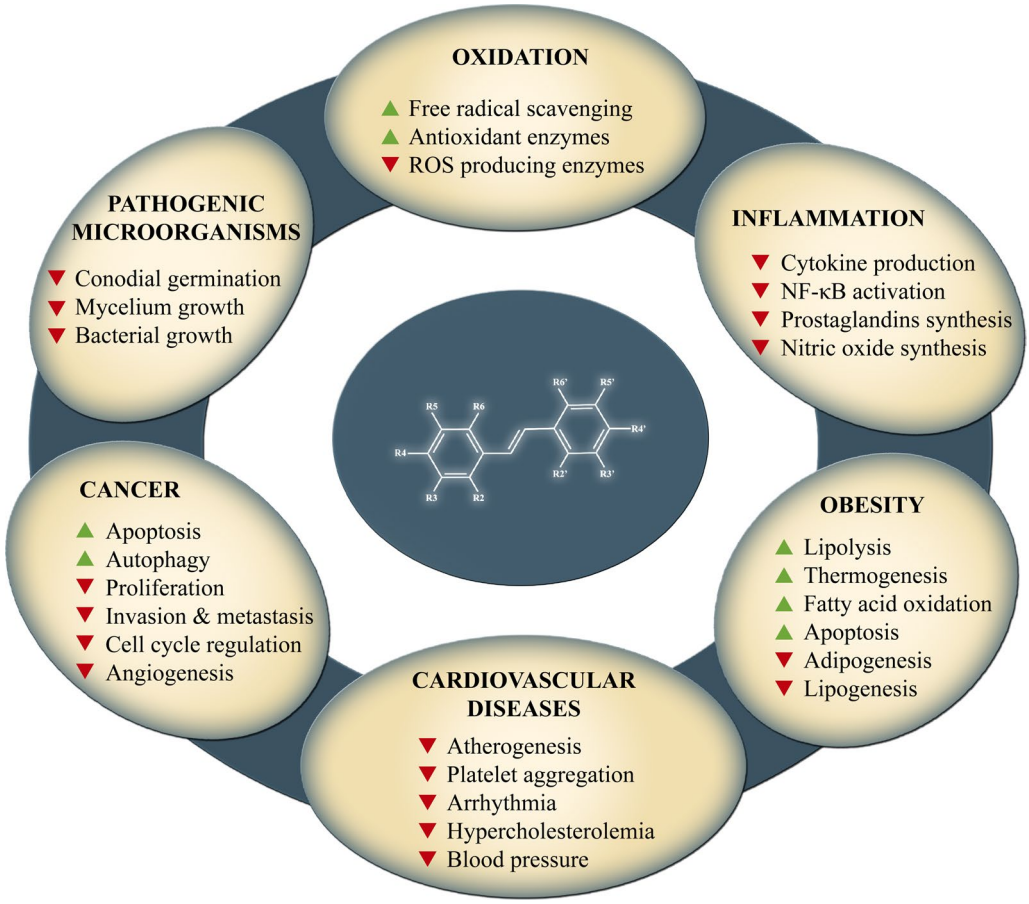

Figure 3. Stilbenes activity against harmful biological processes, pathogens and diseases. Upward triangles indicate activation or increase, while downward triangles mean inhibition or decrease.

role against health problems such as cardiovascular, cancer and obesity, among others (Figure 3). In this section, the different biological activities of stilbenes are discussed, establishing structure-activity relationships among them.

4.1. Antioxidant activity

The antioxidant activity of stilbenes prevents the formation of the reactive oxygen and nitrogen species (ROS and RNS) that play important roles in several diseases. As there is no official standardized method, it is recommended to evaluate the activity in a variety of oxidation conditions and using different measurement methods.

The antioxidant activity measured by ABTS and FRAP assays has proved that piceatannol has higher activity than gnetol and oxyresveratrol, resveratrol, pinosylvin and finally pterostilbene (Rodríguez-Bonilla et al. 2017; Navarro-Orcajada et al. 2022). By DPPH method, a similar order was observed when more stilbenes were tested: piceatannol > gnetol > oxyresveratrol > astringin > isorhapontigenin > resveratrol > pterostilbene > pinosylvin > pinostilbene > piceid (F. Tang, Xie, et al. 2017). By contrast, in the ORAC assay, the greatest antioxidant activity was shown by resveratrol, followed by oxyresveratrol, pterostilbene and pinosylvin (Rodríguez-Bonilla et al. 2017); and glycosylation of stilbenes decreased their antioxidant activity (Uesugi et al. 2017).

In general, the more hydroxyl groups the molecule has, the better antioxidant activity. However, the position of these groups and the presence of other substituents on the aromatic rings can affect the activity. For instance, glycosylation or methylation of hydroxyl groups can decrease the antioxidant activity of stilbenes, especially in R4'. It has been described that the hydrogen abstraction from R4' in resveratrol is more favorable than R3 or R5 because it generates a stable semiquinone radical with electrons delocalization over the whole molecule and not only one ring (Papuc et al. 2017). In addition, the *orto*-position of hydroxyl groups in piceatannol makes it more efficient than resveratrol, because the abstraction from R4' is easier and the resulting semiquinone radical more stable (Rossi et al. 2008). Moreover, the pH of the medium also has some influence on this capacity because it changes the protonation state of the molecule (Rodríguez-Bonilla et al. 2017).

Besides, stilbenes have been proved to regulate the production of some endogenous enzymes with antioxidant activity such as catalase, superoxide dismutase (SOD), NADPH quinone oxidoreductase (NQO), glutathione peroxidase (GPx) and glutathione-S-transferase (GST) (Rubiolo, Mithieux, and Vega 2008). In vivo, the antioxidant activity of stilbenes has been attributed to this gene regulation capacity more than its intrinsic scavenging activity (Xia et al. 2017). For instance, resveratrol was able to up regulate

catalase, GPx1, SOD1 and SOD3, as well as down regulate NADPH oxidases NOX2 and NOX4 in the hearts of apolipoprotein E knockout (ApoE-KO) mice (Xia et al. 2010).

4.2. Antimicrobial activity

Large numbers of potentially pathogenic microorganisms challenge plants. Since stilbenes are phytoalexins, they are active against some bacterial or fungi pathogens.

A comparison of antibacterial potential of different stilbenes revealed that pinosylvin has the highest activity against gram-negative bacteria, followed by resveratrol. Piceatannol, oxyresveratrol and pterostilbene exhibited less activity compared to resveratrol. In the case of gram-positive bacteria, pinosylvin and pterostilbene exhibited higher activity than resveratrol (Singh et al. 2019). The fact that pterostilbene was inefficient against gram-negative bacteria but was the most active against gram-positive bacteria, emphasizes that different stilbene structures can develop different outcomes depending on the type of bacteria.

In addition, resveratrol, pterostilbene, pinosylvin and piceatannol exhibited inhibitory activity against filamentous fungi. Pterostilbene was found to be 5-fold more active than resveratrol in inhibiting conidial germination and in vitro mycelium growth, indicating that methylation of hydroxyl groups could benefit antifungal activity. Furthermore, the higher hydrophobicity of pterostilbene has been suggested to play a positive role in its ability to diffuse through the cytoplasmic membrane compared to resveratrol (Mattio et al. 2021).

4.3. Anti-inflammatory activity

Inflammation is a response to pathogens and tissue injury in which immune cells release various inflammatory mediators, such as cytokines, histamine, nitric oxide, leukotrienes or prostaglandins, and ROS are generated. Likewise, prolonged oxidative and inflammatory reactions lead to chronic inflammation which could result in some diseases, such as asthma, arthritis, inflammatory bowel diseases, liver fibrosis, cardiovascular diseases, neurodegenerative disorders and cancer. Due to their anti-inflammatory properties, stilbenes have been used in folk medicine as treatment of some inflammatory diseases (Dvorakova and Landa 2017).

Stilbenes can act and inhibit in different points of the inflammatory process. It has been proved that resveratrol inhibits cyclooxygenase enzymes COX-1 and COX-2, the prostaglandins producers (Dvorakova and Landa 2017). In vitro studies determined that resveratrol caused dose-dependent suppression of prostaglandin synthesis by inhibiting COX-2 gene expression and enzyme activity (Willenberg et al. 2015). COX-2 was also inhibited by piceatannol (Q. Tang, Xie, et al. 2017), pterostilbene (Dvorakova and Landa 2017), pinosylvin (Teplova et al. 2018), desoxyrhapontigenin and rhapontigenin (Dvorakova and Landa 2017). Meanwhile, oxyresveratrol (Wongwat et al. 2020) and piceatannol (H. J. Lee et al. 2019) significantly inhibited the production of nitrite and inducible nitric oxide synthase (iNOS) and reduced prostaglandins synthesis. Pterostilbene, pinosylvin and desoxyrhapontigenin down regulated iNOS gene and protein expression.

Moreover, resveratrol (Dvorakova and Landa 2017), oxyresveratrol (Wongwat et al. 2020) and piceatannol (Q. Tang, Xie, et al. 2017) inhibited NF-κB activation, a transcription factor that regulates genes responsible for inflammation and other diseases. Pterostilbene has been reported to block NF-κB nuclear translocation, suppressing the production of pro-inflammatory cytokines (Dvorakova and Landa 2017).

In a comparison of anti-inflammatory effects among stilbenes, it can be observed that the activity of oxyresveratrol was generally lower than that of resveratrol, possibly attributed to its inability to form a semiquinone radical (Dvorakova and Landa 2017). By contrast, piceatannol was more efficient in inhibiting COX-2 activity, NF-κB activity and cytokine production than resveratrol (Dvorakova and Landa 2017), while pinosylvin inhibited COX-2 with a potency approximately two-fold higher than that of resveratrol (Teplova et al. 2018). Moreover, rhapontigenin was less active in inhibiting COX-1 and COX-2 than desoxyrhapontigenin, which lacks the hydroxyl group in R3' (Dvorakova and Landa 2017).

These encouraging effects in vitro have attracted the attention of several research groups with interesting applications in inflammatory-related diseases such as chronic colonic inflammation (Sánchez-Fidalgo et al. 2010) where an administration of 20 mg/kg resveratrol not only produced the above cited biochemical changes, but also attenuated clinical signs such as loss of body weight, diarrhea and rectal bleeding, these effects were studied with fatty acid related inflammation where renal damage in obese mice induced by a high-fat diet was alleviated through suppression of inflammation and oxidative stress (Cheng et al. 2019). Interestingly, in a clinical case against Takayasu arteritis, a total of 271 patients were randomized administered with 250 mg resveratrol or placebo during 3 months. The authors established two outcomes, the first was defined as the disease activity, determined using the Birmingham Vascular Activity Score (BVAS). Second, a mix of laboratory parameters, including erythrocyte sedimentation rate (ESR), plasma levels of C-reactive protein (CRP) and TNF-α were used. While the parameters of placebo remained practically unchanged, the resveratrol group exhibited a steady decline throughout the study with a strong linear correlation with the parameters studied (G. Shi et al. 2017).

4.4. Cardiovascular protection

The World Health Organization (WHO) has established that cardiovascular diseases are the leading cause of death in the world, claiming approximately 18 million lives each year, accounting for 31% of all deaths worldwide. Some of the major risk for cardiovascular diseases, such as age, genetic predisposition, diet, lifestyle like physical inactivity, tobacco and alcohol, are constant (WHO 2021). Different stilbenes

show a cardiovascular protection effect and could be useful in the treatment and prevention of these diseases.

In human vascular endothelial cells, resveratrol keeps a balance between vasodilators and vasoconstrictors that prevents atherogenesis and provides thombus-resistance, by means of an increase in the expression of endothelial nitric oxide synthase (eNOS), which synthesize the potent vasodilator nitric oxide (NO), and decreases the expression of endothelin-1 (ET-1), a vasoconstrictor. In addition, resveratrol inhibits platelet aggregation induced by collagen, epinephrine and thromboxane, and has antioxidant effects on cholesterol metabolism (Colica et al. 2018). In vivo studies confirm that resveratrol has a dose-dependent effect on blood pressure in animal models. Furthermore, resveratrol inhibits platelet aggregation in both animal and human studies (Akinwumi, Bordun, and Anderson 2018).

Numerous in vivo and in vitro studies have demonstrated that piceatannol has effect on cardiovascular diseases as well. Piceatannol can help to prevent cardiovascular diseases, including atherosclerosis and cardiac arrhythmia, through multiple mechanisms such as LDL-c in plasma, platelet aggregation, and inflammation. It also prevents hypercholesterolemia by activation of PPAR-α receptors (D. Wang et al. 2019). A study in ischemia-reperfused rat hearts proved that piceatannol is more potent than resveratrol, as it produces a bigger anti-arrhythmic efficacy (Ellermann et al. 2017).

Moreover, in vivo studies proved that pterostilbene improves cardiac function in rat models of ischemia-reperfusion, protects vascular endothelial cells against autophagy, and at high doses, reduces systolic and diastolic blood pressure in humans. Like resveratrol, pterostilbene also inhibits pellet aggregation, but not when induced by thrombin (Otręba et al. 2020).

4.5. Anticancer activity

The WHO has reported that cancer is the second main reason for death worldwide. Various factors are responsible for cancer, for instance, exposure to different physical, chemical and biological carcinogens, infections, heredity, poor dietary habits and lifestyle. Current literature displays a wide range of human cancers that can be influenced by these bioactive compounds, with resveratrol being the most studied (Rauf et al. 2018).

In vitro, resveratrol has promising therapeutic effects on different cancers, including breast, head and neck, gastric, esophageal, colorectal or liver cancer, by the activation and inhibition of different signaling pathways in cancer progression (Rauf et al. 2018; Varoni et al. 2016; Fulda 2010). It inhibited cell cycle regulation, invasion/metastasis and angiogenesis and induced apoptosis and autophagy mediated through the regulation of cell cycle associated proteins (S. M. Kim and Kim 2018). However, only a few human clinical trials have shown beneficial effects in cancer treatment, most of them have shown a neutral effect on cancer, probably due to its low bioavailability and high metabolism (Ávila-Gálvez et al. 2020; S. M. Kim and Kim 2018). Within the clinical trials completed with cancer patients that have given encouraging results on the use of pure resveratrol (not extracts) is that of Patel et al. (2010), in which a reduction of tumor cell proliferation by 5% was observed in patients with colorectal cancer after consuming 0.5 or 1 gram of resveratrol daily for eight days (n = 20) (Patel et al. 2010). In addition, Howells et al. (2011) observed an increase in cleaved caspase-3, an apoptosis marker, after administration of 5 grams daily of micronized resveratrol for fifteen days in patients also with colorectal cancer but with liver metastases (n = 9) (Howells et al. 2011). Apart from that, there are other promising studies on prostate, breast and colon cancers using plant extracts or formulations containing resveratrol, but the presence of other polyphenolic compounds prevents attributing the effects solely to this stilbene (Paller et al. 2015; Zhu et al. 2012; Nguyen et al. 2009).

Oxyresveratrol had cytotoxicity against murine leukemia and human gastric cancer cells, selective in the latter. In addition, it inhibits angiogenesis and induces caspase-independent cell death in highly chemo-resistant breast cancer cell lines (Likhitwitayawuid 2021). In a study using head and neck squamous cell carcinoma, oxyresveratrol showed a lower antiproliferative and antiangiogenic efficacy compared to that of resveratrol (Sintuyanon et al. 2017).

Piceatannol induced an intrinsic mode of apoptosis in cells. Besides, it was able to inhibit the proliferation of various tumor cells, such as leukemia, lymphoma, melanoma and cancers of breast, prostate and colon (Seyed et al. 2016). Many reports suggest that piceatannol has stronger anticancer activity than resveratrol (H. J. Lee et al. 2019). It seems that the addition of a hydroxyl group in *orto*-position to resveratrol makes it more active than in *meta*-position.

Pinosylvin regulates growth inhibition and apoptosis in cancer cells by regulating NAG-1 over-expression. In addition, pinosylvin exerted an inhibitory effect on metastatic oral cancer cells by regulating the expression and activity of MMP-2 through the ERK pathway (Chen et al. 2019). In leukemia cells, pinosylvin induces cell death through apoptosis or autophagy by AMPKα1 down-regulation (Song, Seo, and Park 2018).

Pterostilbene can regulate the cell cycle, augment apoptosis, enhance autophagy and inhibit tumor angiogenesis, invasion and metastasis by modulating signal transduction pathways which block multiple stages of cancer (Lin et al. 2020). Pterostilbene exerted more potent inhibitory actions on human colon cancer cells than resveratrol due to its higher lipophilicity (Zhang et al. 2021).

Isorhapontigenin, another methoxylated stilbene, induced cell death, cell cycle arrest, oxidative stress, and inhibited cell proliferation on breast cancer. In a comparison with resveratrol, isorhapontigenin treatment showed a higher potency for inducing cell death and growth arrest through activation of caspase-dependent cell death cascades (Subedi et al. 2019).

The glycoside stilbene piceid affected tumor cells viability mainly by cell cycle arrest, while the effect on apoptosis was minor. Cytotoxicity of piceid was weaker than that of resveratrol, probably because piceid was more difficult in being captivated by cells (Su et al. 2013).

4.6. Antiobesity activity

Some stilbenes have been reported as preventing obesity. Aguirre et al. (2014) made a throughout revision of the role of resveratrol in several metabolic pathways such as adipogenesis, apoptosis, lipogenesis, lipolysis, thermogenesis and fatty acid oxidation (Aguirre et al. 2014). The regulation of peroxisome proliferator-activated receptor gamma (PPARγ), CCAAT-enhancer-binding protein (C/EBPα), sterol regulatory element binding protein 1c (SREBP-1c), uncoupling proteins (UCPs), sirtuin-1 (SIRT1), lipoprotein lipase (LPL), fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) seems to be essential for this effect.

Piceatannol and pterostilbene have also been suggested to affect adipogenesis, lipogenesis and fatty acid oxidation through the regulation of ACC, SREBP1, PPARγ or PPARα (Yang et al. 2020; Carpéné et al. 2018; H. Kim, Seo, and Yokoyama 2020). Indeed, pterostilbene was more efficient in vivo than resveratrol at dose of 15 mg/kg/day probably due to higher bioavailability (Gómez-Zorita et al. 2014). Furthermore, a molecular docking suggested that pterostilbene can hydrogen bond to three amino acids of PPARα, while resveratrol only bonds to two amino acids (H. Kim, Seo, and Yokoyama 2020).

Overall, the structure-activity relationships established for natural stilbenes in this section and the previous one concluded that (i) the better aqueous solubility of hydroxylated and glycosylated stilbenes could facilitate their incorporation into hydrophilic matrices, although it is still low for using high concentrations, (ii) the greater lipophilicity of methoxylated stilbenes may increase bioavailability and therefore, make them more interesting for clinical trials, (iii) glycosylated stilbenes are more susceptible to isomerization than their aglycones, so more attention must be paid to preservation, and finally, (iv) *orto*-hydroxylated stilbenes may have better antioxidant, anti-inflammatory and anticancer activity than *meta*-hydroxylated stilbenes probably due to the formation of a stable semiquinone radical.

5. Limitations of stilbenes

The previously described physicochemical and biological properties of natural stilbenes denote some problems that limit their potential applications. In general, stilbenes have low solubility in water which might prevent their incorporation in a hydrophilic matrix, for example, some functional foods. Moreover, they are easily degraded by external factors such as light, oxygen, pH or temperature, which could compromise the stability of the molecule during manufacturing and storage (Zupančič, Lavrič, and Kristl 2015).

Furthermore, bioactivity of stilbenes in vitro usually differs from in vivo, and this discrepancy can be explained by a hormetic activity and poor bioavailability. It is often difficult to extrapolate doses in cells or animals to humans and to establish the correct exposure times. Dosages in preclinical and clinical trials should be set considering the hormetic curve of the stilbene. According to this concept, there is a limited range of doses in which the beneficial effect is observed, below or above this range, bioactive compounds may not be effective or may even produce adverse effects (Scapagnini et al. 2014). Most preclinical studies on stilbenes fail in this regard, and use concentrations which are too high or short-term exposure, with non-physiological concentrations or metabolites (Tome-Carneiro et al. 2013).

Besides, stilbenes have a rapid metabolism. Despite absorbing 75% by oral administration, stilbenes can suffer from phase II reactions in the liver or intestine, such as glucuronidation and sulfation, which forms more soluble derivatives that are easily disposed, mainly by urine. It has been described that the available concentration of resveratrol which arrives at target tissues in human can be lower than 1% (Walle 2011). In rats, oral bioavailability may vary from 9.13% of oxyresveratrol to 80% of pterostilbene (Akinwumi, Bordun, and Anderson 2018), which outlines the relevance of the structure in the biological activity of stilbenes.

All these reasons have led the European Food Safety Authority (EFSA) to reject the health claim for resveratrol (EFSA 2010), although it has accepted synthetic resveratrol as a safe novel food (EFSA 2016). Despite this, food supplements with health claims containing resveratrol are currently being marketed and consumed. However, these claims never refer to resveratrol itself, but to other minerals or vitamins in the formula that do have accepted health claims. This marketing strategy, even if legally permitted, is still questionable. To achieve an EFSA-authorized health claim for stilbenes, a different approach to their study is needed. It would be necessary to solve their physicochemical problems before applying them in vivo.

Some strategies have been proposed to overcome the physicochemical and bioavailability problems of stilbenes (de Vries, Strydom, and Steenkamp 2021; López-Nicolás, Rodríguez-Bonilla, and García-Carmona 2014). Below, two different approaches that have been proved to be effective in solving some of these issues are detailed: the encapsulation of stilbenes in different agents and their structural modification to generate novel stilbenes with better features.

6. Promising approaches

6.1. Encapsulation of stilbenes in different agents

As mentioned above, stilbenes present a wide range of bioactivities although with poor stability and water solubility. Different strategies are being proposed to achieve higher dosage of active stilbene, encapsulation of stilbenes in a carrier is one of the most promising strategies (Figure 4). Encapsulation occurs when the stilbene is introduced in a matrix which carries and protects the molecule. This is a dynamic equilibrium displaced to form the complex or to release depending on different factors such as composition, temperature, etc. At this point, a selection of different strategies will be explained.

6.1.1. Liposomes

Liposomes consist generally of an aqueous core enclosed within a phospholipid bilayer, although different molecules

such as cholesterol may be added to increase the stability of the vesicle (S.-C. Lee et al. 2005). These particles have a good way to carry hydrophilic drugs in the aqueous core, and lipophilic within the bilayer. For example, Coimbra et al. (2011) found that the chemical stability of *trans*-resveratrol was improved in liposomes; after 16 min of UV exposure, 70% remained stable in contrast to 10% of the free sample (Coimbra et al. 2011). Indeed, the liposome stability depends on the proportion of *cis*- and *trans*-resveratrol, while *trans*-resveratrol does not affect the stability of the bilayer, the *cis*-isomer may have caused the molecule to destabilize the liposomes (Detoni et al. 2012). According to their capacities, the liposome structure is quite good for cell uptake, which increases the efficacy of the drug: for example, the resveratrol cytotoxicity against HeLa cervical carcinoma and Hep 2 hepatocellular carcinoma cells were improved being complexed in polyPEG2000 or standard liposomes (X.-Y. Lu et al. 2012). The conjugation of some molecules to the liposomes may increase the targeting activity of the formulations. As example an immunoliposome containing resveratrol and curcumin was successfully developed to target the Human epidermal growth factor receptor (HER2) which improved the selectivity of this codelivery (Catania et al. 2013). Although a similar behavior with other stilbenes is expected, no works were found.

6.1.2. Cyclodextrins

Cyclodextrins (CDs) are well-known members of the science community for their uses to solubilize poor-soluble drugs and enhance their activities (Jansook, Ogawa, and Loftsson 2018; Matencio et al. 2021). Chemically, CDs are truncated cone-shaped oligosaccharides made up of α-(1,4) linked glucose units, obtained by the degradation of starch by the enzyme cyclodextrin glucosyltransferase (CGTAse). The most common CDs are the natural α, β and γ-CD, which contain six, seven and eight glucose units, respectively. The CD ring is a conical cylinder of an amphiphilic nature, with a hydrophilic outer layer (formed by the hydroxyl groups) and a lipophilic cavity (Kurkov and Loftsson 2013; Matencio et al. 2020e). Moreover, CD presents intrinsic bioactivity to manage some diseases such as atherosclerosis or Niemann Pick type C (Matencio et al. 2020a, 2020f).

Several stilbenes have been complexed with CDs to increase their solubility or stability such as resveratrol (López-Nicolás et al. 2006; Lucas-Abellán et al. 2007; López-Nicolás and García-Carmona 2010), pinosylvin (López-Nicolás, Rodríguez-Bonilla, and García-Carmona 2009), pterostilbene (López-Nicolás et al. 2009), *trans*-α-methylstilbene (Matencio et al. 2017b), piceatannol (Matencio, García-Carmona, and López-Nicolás 2016; Messiad, Amira-Guebailia, and Houache 2013), gnetol (Navarro-Orcajada et al. 2022) or oxyresveratrol (He et al. 2017; Matencio, García-Carmona, and López-Nicolás 2017a; Rodríguez-Bonilla, López-Nicolás, and García-Carmona 2010). In fact, a recent publication reviews the most relevant applications of resveratrol and cyclodextrin (Jeandet et al. 2021). Moreover, the different bioactivities of the stilbenes were affected by complexation by the increase of its stability or concentration (Matencio et al. 2021). As examples, in a study, the effect of the naturally occurring β-CD was tested in juice and milk *food models*, in these matrixes, the complexation not only improved storage but also antimicrobial activity of the stilbene (Matencio et al. 2020d). Similar behavior of the antimicrobial, anticancer or antioxidant capacities were found with resveratrol (Duarte et al. 2015; Hao et al. 2021; Z. Lu et al. 2009). Pterostilbene was able to increase its antimicrobial and anti-inflammatory bioactivities encapsulated in hydroxypropyl-β-CD (Y. R. I. Lim et al. 2020; Appleton et al. 2021).

6.1.3. Polymeric nanoparticles

Several authors studied the effect of different polymers. A polymer based on polyethylene glycol–polylactic acid was used to complex resveratrol. The polymer increased the stability and improved the release of resveratrol; even with

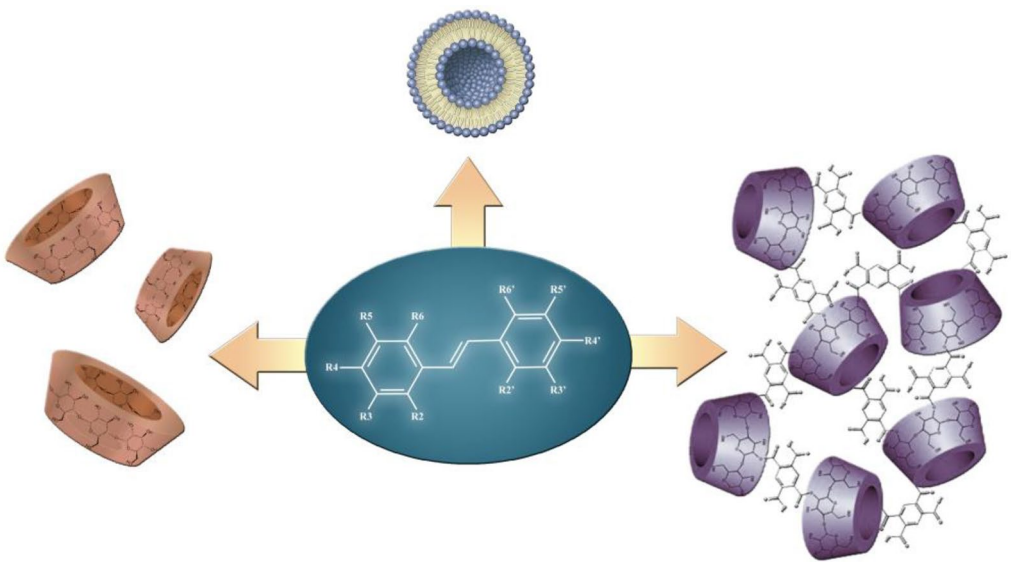

Figure 4. Encapsulation of stilbenes in different agents.

better anticancer activity in vitro and the same in vivo (Jung et al. 2015). Recently, a PGLA polymer (polyethylene glycol–polylactic acid) polymer was used to carry resveratrol for age-related macular degeneration. The formulation showed good stability, compatibility and the cells were able to uptake resveratrol successfully, decreasing the VEGF expression more than free resveratrol (Bhatt et al. 2020). Other polymers such as chitosan can complex stilbenes; and used for resveratrol delivery, in one study, chitosan nanoparticles modified with biotin and avidin were prepared to target hepatic carcinoma, with an improved delivery (Bu et al. 2013). Other stilbenes are also being studied; for example, (i) oxyresveratrol can inhibit inflammatory mediators when embedded in PLGA nanoparticles, which are released by human dendritic cells (Gaglio et al. 2021), or (ii) piceatannol in chitosan/poly (lactic acid) nanoparticles improve the in vitro apoptosis activity on liver, lung and breast cancer cell lines (Dhanapal and Ravindrran 2018). The polymerization of CDs is an interesting alternative to improve their qualities, creating some materials such as the so-called "nanosponge" (Krabicová et al. 2020). In this way, resveratrol and oxyresveratrol were complexed with different nanosponges, increasing their stability and anticancer activity (Dhakar et al. 2019; Matencio et al. 2020b) or their anti-aging activity (Matencio et al. 2020c).

6.2. Structural modifications to generate novel stilbenes

Another strategy to overcome the limitations and improve the properties of this family of phenolic compounds is the chemical modification of their structure. In this regard, current literature displays some examples of stilbenes that after the addition or modification of functional groups improve their physical, chemical and/or biological properties. For example, Fulda (2010) reviewed the anticancer activity of resveratrol and analogue derivatives (Fulda 2010).

This section highlights studies that not only synthesize novel stilbenes but also test them. For clarity, the structural modifications have been classified into the following groups: hydroxylation (-OH), methoxylation (-O-CH_3), glycosylation or glucosylation (-O-$C_6H_{11}O_5$), halogenation (-F, -Br, etc.) and acylation (-CO-R), according to the radicals that have been added to the basic stilbene structure, although authors may have followed different synthesis processes. A summary of the main effects produced by these structural changes can be observed in Table 2.

6.2.1. Hydroxylation

As stated in Sec. 3. *Physicochemical characterization of stilbenes*, some natural hydroxylated analogues of resveratrol have improved water solubility, which would be of great interest in the formulation of functional foods enriched with stilbenes. This is because hydroxyl groups increase the interaction with water molecules, by forming hydrogen bonds.

Apart from that, hydroxyls are the main groups responsible for some biological properties such as free radical scavenging. Thus, stilbenes derivatives with more hydroxyl radicals are expected to have more antioxidant activity. This fact along with the influence of the radical position was analyzed by measuring the antioxidant activity of di-, tri-, tetra- and penta- hydroxylated stilbenes (M. Wang, Jin, and Ho 1999). Moreover, the *ortho*-dihydroxy structure in the aromatic ring has been reported to enhance antioxidant activity (Fulda 2010).

Besides, the antiproliferative effect of stilbenes in cancer has been suggested to be closely related to the presence of hydroxyl groups in the R4 or R4' position of *trans*-stilbenes. In this sense, *trans*-4,4′-dihydroxystilbene was found to be more antioxidant and cytotoxic than resveratrol (Fulda 2010).

Murias et al. (2005) synthesized novel tetra-, penta- and hexa- hydroxylated analogues of resveratrol with additional hydroxyl groups on R4, R3' and/or R5', and found out that those with pyrogallol and catecol groups (including the natural piceatannol) had higher antioxidant and anticancer (leukemia cell line) in vitro activities than those with resorcinol groups (including resveratrol itself) (Murias et al. 2005). Moreover, these derivatives showed stronger inhibition of COX-2 than resveratrol, which pointed to better anti-inflammatory activity (Murias et al. 2004). All these compounds showed a lower lipophilicity index and higher molar refractivity, topological surface area and atom polarizability (Murias et al. 2004). Among them, the authors highlight the potential of *trans*-3,3′,4,4′,5,5′-hexahydroxystilbene (named as M8), which also demonstrated effect against melanoma, breast cancer and colon tumor cell lines (Szekeres et al. 2010).

Li et al. (2006) developed and tested several stilbenes against SARS-COV-1 in Vero E6 cells (Y.-Q. Li et al. 2006). The tetrahydroxystilbene substituted in R3, R5, R2' and R5' was effective in the inhibition of the replication of SARS virus, as well as another derivative with hydroxyl groups in R3, R6, R2' and R5' and pyridine ring instead of benzene ring.

6.2.2. Methoxylation

Natural pterostilbene with two methoxy groups in R3 and R5 has improved oral bioavailability compared to resveratrol due to its more lipophilic and metabolically stable structure (Pecyna et al. 2020). In contrast with hydroxyl, these groups cannot undergo the glucuronidation and sulfation reactions that decrease oral bioavailability.

Cardile et al. (2007) synthesized novel di- and trimethoxy analogues of *trans*- and *cis*- resveratrol modified in R3, R4, R5 or R4' and test them for anticancer activity in vitro in prostate tumors (androgen responsive and not responsive), melanoma and mouth epidermoid carcinoma (Cardile et al. 2007). Most derivatives had higher cytoxicity than resveratrol, but the authors highlight the effect of the *cis*-3,4′,5-trimethoxystilbene.

Likhitwitayawuid et al. (2006) developed mono-, di-, and tetra- methoxylated derivatives of oxyresveratrol and found an increase in cytotoxicity against lymphoma, cervical carcinoma and lung cancer cell lines, which depended on the number of O-methyl groups and isomerization, the *cis*-isomer with four

Table 2. Effect of common structural modifications on the physicochemical and biological properties of stilbenes.

Modification	Physicochemical effect	Biological effect	References
Hydroxylation (-OH)	↑ MR ↑ APOL ↑ TPSA ↓ logP	↑ Anticancer ↑ Antioxidant ↑ Anti-inflammatory ↑ Antiviral	(Szekeres et al. 2010; Y.-Q. Li et al. 2006)
Methoxylation (-O-CH_3)	↑ MR ↑ APOL	↑↓ Anticancer ↑↓ Anti-inflammatory ↓ Inhibition of tyrosinase ↑ Antimicrobial	(Szekeres et al. 2010; Cardile et al. 2007; Likhitwitayawuid et al. 2006; Hu et al. 2017)
Glycosylation (-O-Gluc)	↑ Water solubility	↓ Antioxidant ↓ Enzymatic oxidation	(Regev-Shoshani et al. 2003; Torres et al. 2011; Lepak et al. 2015)
Halogenation (-F, -Br, etc.)	–	Antimicrobial ↑↓ Anticancer	(Albert et al. 2011)
Acylation (-CO-R)	↑ LogP ↓ Oxidative discoloration	↓~ Anticancer ↓ Antioxidant ↓ Anti-inflammatory ~Antimelanogenic	(Park et al. 2014; Oh and Shahidi 2017; Oh and Shahidi 2018)

The symbols ↑, ↓ and ~ means increase, decrease or similar activity compared to resveratrol; O-Gluc = O-glucosyde (-O-$C_6H_{11}O_5$); MR = molar refractivity; APOL = atom polarizability; TPSA = topological surface area; LogP = lipophilicity index.

substituted radicals was the most active (Likhitwitayawuid et al. 2006; Likhitwitayawuid 2021). These modifications also caused a loss in tyrosinase inhibitory activity.

In a different study, the methoxylation of resveratrol was described to protect it from the enzymatic oxidation by tyrosinase, especially when R4' was the modified radical (Regev-Shoshani et al. 2003).

Fulda (2010) reviewed the effect of tri-, tetra- and penta-methoxystilbenes in cancer (Fulda 2010). Overall, these compounds showed a more potent inhibition of cell growth than resveratrol and some of them were selective with transformed cells.

Hu et al. (2017) analyzed the structure-activity relationship of pterostilbene and analogues against *Candida albicans* biofilms and concluded that the presence of methoxy groups might enhance the antifungal activity of stilbenes (Hu et al. 2017). They emphasized the *meta*-dimethoxy structure, since previous studies affirmed that trimethoxy compounds were less active.

Antiviral activity was evaluated for stilbene methyl ethers in R3, R5, R2' and R5' and they showed lower inhibition of SARS-COV-1 than their corresponding hydroxylated derivatives. The same was observed for those modified in R3, R6, R2' and R5' with a pyridine ring instead of a benzene ring (Y.-Q. Li et al. 2006).

Murias et al. (2004) produced tri-, tetra-, penta- and hexa- methoxylated stilbenes, however, this modification led to lower anti-inflammatory activity compared to hydroxylation (Murias et al. 2004). These molecules were poor inhibitors of COX enzymes and had low selectivity for COX-2, although inhibition of COX-2 was stronger than resveratrol with the hexa- and penta- methoxylstilbenes and tetramethoxylstilbene modified in R3, R5, R3' and R4'. All the methoxylated derivatives had higher molar refractivity and atom polarizability than resveratrol.

The addition of methyl ether groups in R2', R5' and/or R4 in resveratrol improved its antioxidant activity as well as decreased its genotoxicity (Fukuhara et al. 2008). An increase in antioxidant and anticancer activity was also observed when every radical in resveratrol was methoxylated and an additional hydroxyl group incorporated in R2 position (Basini et al. 2010). It is important to note that these two studies include both methoxy and hydroxyl radicals in the stilbene structure.

6.2.3. Glycosylation or glucosylation

It has been described above that natural stilbene glycosides are more sensitive to isomerization than their aglycones. However, glycosylation could provide some benefits to stilbenes, for instance, an enhancement in water solubility. In this sense, Torres et al. (2011) produced glycosylated derivatives of resveratrol in R3 and/or R4' and observed that they were at least 65 and 5-fold more water soluble than natural resveratrol and piceid (Torres et al. 2011). Since they have surfactant activity, critical micelle concentration (c.m.c.) was established. However, this modification also caused a loss in antioxidant activity, especially in 3-O-glucosylstilbenes.

Lepak et al. (2015) synthesized and compared the properties of glycosylated analogues of resveratrol and discovered that the solubility of the derivative modified in R3 and R5 was about 1700-fold higher than that of resveratrol (Lepak et al. 2015). Despite losing antioxidant activity in comparison with resveratrol or piceid, its activity was better than resveratroloside activity (glycosylated in R4').

Moreover, the enzymatic oxidation of resveratrol by tyrosinase enzyme was completely inhibited after glycosylation (Regev-Shoshani et al. 2003).

6.2.4. Halogenation

Moran et al. (2009) developed fluorinated analogues of resveratrol with or without acetyl, ethyl or methyl ethers (Moran et al. 2009). The authors highlight the greater activity of the compound *trans*-3,5-di-fluoro-4′-acetoxystilbene than resveratrol against melanoma and lung cancer. Several fluoro-hydroxystilbenes, with and without methoxy groups, were synthesized by Albert et al. (2011) and tested for antimicrobial activity against some species of bacteria and fungi (Albert et al. 2011). The greater activity observed was for *trans*-6-fluoro-4-methoxy-2′,3,5′-trihydroxystilbene and *trans*-3-hydroxy-3′,4′,5′-trifluorostilbene. Some of these compounds had higher cytotoxicity than resveratrol in mouse embryonic fibroblasts cell line.

A previous study (Ruan et al. 2006), described that the anticancer activity in vitro of resveratrol improved after its structural modification with mono-, di- and tri-bromoethyl radicals.

6.2.5. Acylation

Acetylated derivatives of stilbenes have been reported to be more stable and bioavailable than their parent compounds. Triacetyl resveratrol was more resistant to oxidative discoloration than resveratrol and preserved its anticancer and antimelanogenic activities (Park et al. 2014; Fu et al. 2019; Duan et al. 2016). Torres et al. (2010) synthesized mono-, di- and triacetylated derivatives of resveratrol and concluded that the antioxidant activity decreased with the degree of substitution (Torres et al. 2010). Moreover, the modification in R3 caused a higher loss of activity than the modification in R4'.

Oh and Shahidi (2017) acylated resveratrol with short and long chain fatty acids. Although this modification led to a decrease in antioxidant activity in vitro by ABTS and DPPH methods (Oh and Shahidi 2017), the antioxidant activity of some esters in ground meat was higher, as well as the inhibition against copper-induced LDL oxidation and hydroxyl radical induced DNA scission (Oh and Shahidi 2018). Monoesters of resveratrol modified with propionic acid or docosahexanoic acid (DHA) were tested for anti-inflammatory and anticancer activity in liver, colon, breast and gastric cancer cell lines, however, they did not show a clear enhancement of activity compared to the unmodified resveratrol (Oh et al. 2019). Despite that, author suggested that these compounds could improve resveratrol applications in food and biological systems.

6.2.6. Others structural modifications

Some diarylacrylonitrile analogues of stilbenes and the modification of resveratrol with tyramine, morpholine or furfurylamine improved its anticancer activity (Huang et al. 2007; Madadi et al. 2015). Furthermore, antifungal activity was enhanced after the substitution of a benzene ring to a furan ring in the stilbene structure (Caruso et al. 2011). Besides, amino derivatives of stilbenes were synthesized to develop anticancer agents with better water solubility (Simoni et al. 2009).

7. Conclusions

Stilbenes have demonstrated much potential as antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective and antiobesity agents. These biological activities are of great interest for the prevention or treatment of human diseases. Moreover, their bioactivity is closely related to chemical structure, and some stilbenes have enhanced features compared to the well-known resveratrol. Still, certain physicochemical and pharmacokinetic problems that limit their applications need to be overcome. The encapsulation and structural modification of stilbenes could solve some of these issues and make stilbenes research move forward. However, more investigation is needed in this regard, especially with other stilbenes besides resveratrol.

Disclosure statement

The authors declare no conflict of interest.

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