Stilbenes: a review of their physicochemical properties, biological activities, molecular encapsulation and structural modifications

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Abstract

Stilbenes are secondary metabolites produced by some plant species like grapes, peanuts or mulberries as a defense mechanism against biotic and abiotic stress conditions (fungal infections, UV radiation, etc.). These compounds are produced through the shikimic acid pathway and they share the 1,2-diphenylethylene structure with different substituents. These substituents are responsible for the vast variety of stilbenes that we know (resveratrol, piceatannol, pterostilbene, gnetol, pinosylvin, piceid, etc.), as well as responsible for their different physicochemical properties (solubility, polarity, stability, fluorescence and spectrophotometric features, among others) and their different biological activities (anticancer, antifungal, antioxidant, cardioprotective, antiobesity, etc.). Resveratrol is the most studied stilbene, but recently there is a growing interest for other stilbenes (both natural and synthetic) with better properties due to their structure.

However, these beneficial properties that stilbenes have are accompanied by some pharmacokinetic and physicochemical drawbacks that have to be solved to use them in cosmetic, food and pharmaceutical industries. Among these problems, the most important is the low water solubility of stilbenes (they are highly hydrophobic) and their fast degradation because of pH, temperature, oxidation or radiation. Moreover, the good bioactive results showed in *in vitro* studies do not correspond with those seen in the *in vivo* ones, probably because of the low bioavailability of stilbenes and their fast metabolization. To overcome these issues, 2 possible solutions have been proposed: the molecular encapsulation of stilbenes in cyclodextrins and the structural modification of native stilbenes.

The molecular encapsulation of stilbenes can be performed with liposomes, cyclodextrins or nanosponges, among other encapsulating agents. All of them have hydrophobic regions where stilbenes can be included, enhancing their water solubility and protecting them from degradation. On the other hand, the stilbene derivatization with different functional groups (hydroxyl, methoxyl, glycosyl, etc.) frequently improve the physicochemical properties and/or biological activities of native stilbenes.

Introduction

Stilbenes are plant secondary metabolites produced by some species like *Vitis vinifera* in response to different stress conditions. They are very interesting in food, pharmaceutical and cosmetic industries due to their multiple applications [1]. These molecules share the same scaffold structure (1,2-diphenylethylene) with different substituents like hydroxyl, methoxyl or glycosil groups, which give rise to the vast variety of stilbenes (resveratrol, piceatannol, rhapontigenin, piceid, etc.) *(Fig. 1)*. Stilbenes posses numerous biological activities (*Fig.* 2), and there are many studies testing their effects *in vitro*. However, the information about the *in vivo* effects of stilbenes is still scarce due to some physicochemical and pharmacokinetic issues that have to be overcome to be able to use them in therapy, in functional foods or in cosmetics, like their low water solubility, low stability and low bioavailability [2]. To solve these problems, there are several strategies like the encapsulation of stilbenes in different agents and their structural modification to obtain new products with enhanced properties. This review highlights the main pros and cons of stilbenes as bioactive ingredients, providing interesting solutions to the problems that currently limit their potential applications [3].

Sources of stilbenes

There are different plant families like *Vitaceae* (grapes), *Pinaceae* (pines) or *Fabaceae* (peanuts) that are able to synthesize stilbenes. The enzyme that plays a key role in the biosynthetic pathway of these compounds is the stilbene synthase (STS). Besides natural extraction of stilbenes from these plants, there are some alternative sources, for example, cell cultures in bioreactors. There are suspension cultured cells of *Vitis vinifera* or *Arachis* hypogaea roots treated with different elicitors. Finally, stilbenes can also be synthesized by chemical reactions like the Heck, Perkin or Witting reactions [3].

Physicochemical characterization of stilbenes

- **Solubility:** stilbenes have a very low water solubility. Depending on the number and the nature of the substituents, their hydrophobicity can be even lower. For instance, gnetol solubility (0.31 mg/mL) is higher than resveratrol (0.03 mg/mL) but lower than oxyresveratrol (0.75 mg/mL). The solubility of these compounds is higher in some organic solvents like methanol, ethanol and DMSO [3].
- **Absorbance:** the maximum absorbance of stilbenes is given in the UV region, near the 300-330 nm. The maximum absorbance is different depending on the isomeric form of the stilbene *(trans* or *cis*), which enables their identification.
- **Fluorescence:** stilbenes are fluorescent molecules due to their phenolic structure. They are excited by radiation within the UV region and they usually emit fluorescence at 370-400 nm.
- **Acid dissociation constants (pK_as):** the majority of stilbenes have free hydroxyl groups. These groups can be deprotonated or not depending on the environmental pH, so the charge of the molecule can change. Every stilbene has as many pK_as as free hydroxyl groups. For example, resveratrol pKas were determined at pH 8.8, 9.8 and 11.4 [3].
- **Stability and degradation:** *Trans*-stilbenes are very sensitive to degradation, especially when exposing them to UV/Vis light. They isomerise to *cis*-stilbene, a non-bioactive degradation intermediate, and then they are transformed into a phenantrenoid degradation product. Besides, high temperature or pH can also degrade stilbenes.

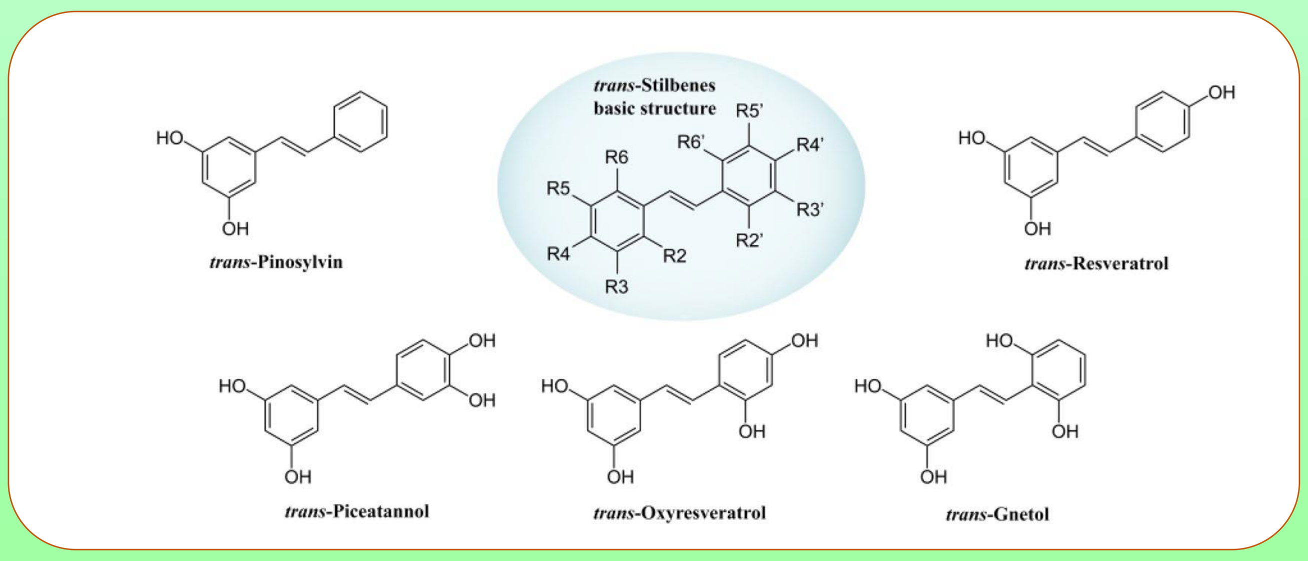

Fig. 1: variety of stilbenes and their main chemical substituents.

Promising approaches: molecular encapsulation and structural modification

There are some strategies to overcome the physicochemical and pharmacokinetic problems of stilbenes, for example, the molecular encapsulation in different encapsulating agents: liposomes, cyclodextrins and polymeric nanoparticles like nanosponges [4] *(Fig. 3)*. The molecular encapsulation of stilbenes protects them from degradation. For example, **liposomes** can avoid resveratrol degradation under UV radiation and they also enhance their bioactivity as anti-cancer drug. **Cyclodextrins** and polymeric nanoparticles (**nanosponges**) also protect stilbenes from degradation as well as enhancing their water solubility, promoting their use as potential drugs and bioactive ingredients in functional foods and cosmetics [3].

Besides encapsulation, there are other strategies like the structural modification of stilbenes. Thus, with **hydroxylation** it is possible to enhance the water solubility of stilbenes and their anti-oxidant capacity. **Methoxylation** is another structural modification that can increase the bioavailability of stilbenes (allowing them to cross the cell membranes) and some biological activities (cytotoxic effects in cancer cells, antifungal activity, etc.). **Glycosylation** increases the water solubility of stilbenes, but sometimes with a loss of their antioxidant activity. In some cases the glycosylation also inhibits the enzymatic oxidation of stilbenes. **Halogenation** can enhance some biological properties like the anti-cancer and antimicrobial activities. Finally, **acylation** is a structural modification that can increase the bioavailability and stability of stilbenes while maintaining their bioactive properties (anti-inflammatory, anti-cancer, etc.) but sometimes with a loss of their native antioxidant capacity.

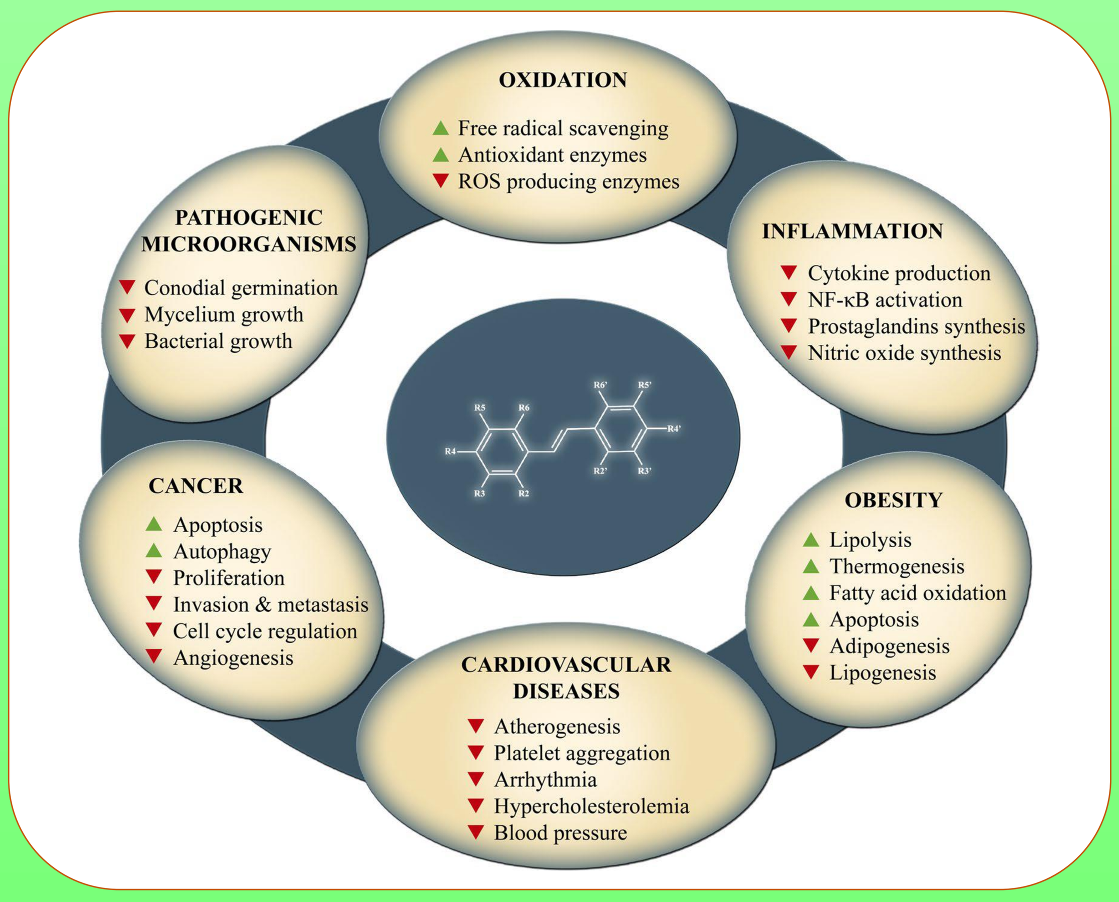

Fig. 2: biological activities of stilbenes.

Conclusions

- Stilbenes are very interesting compounds with antioxidant, anticancer, cardioprotective and antiobesity effects, among others.
- The bioactivity of stilbenes is related to their chemical structure, as well as their physicochemical properties.
- There are several physicochemical and pharmacokinetic problems that have to be overcome to use these compounds in food and pharma industries (low water solubility, poor bioavailability and high instability). Fortunatelyn these issues can be solved through molecular encapsulation (cyclodextrins, liposomes and polymers) and structural modifications (hydroxylation, methoxylation…).

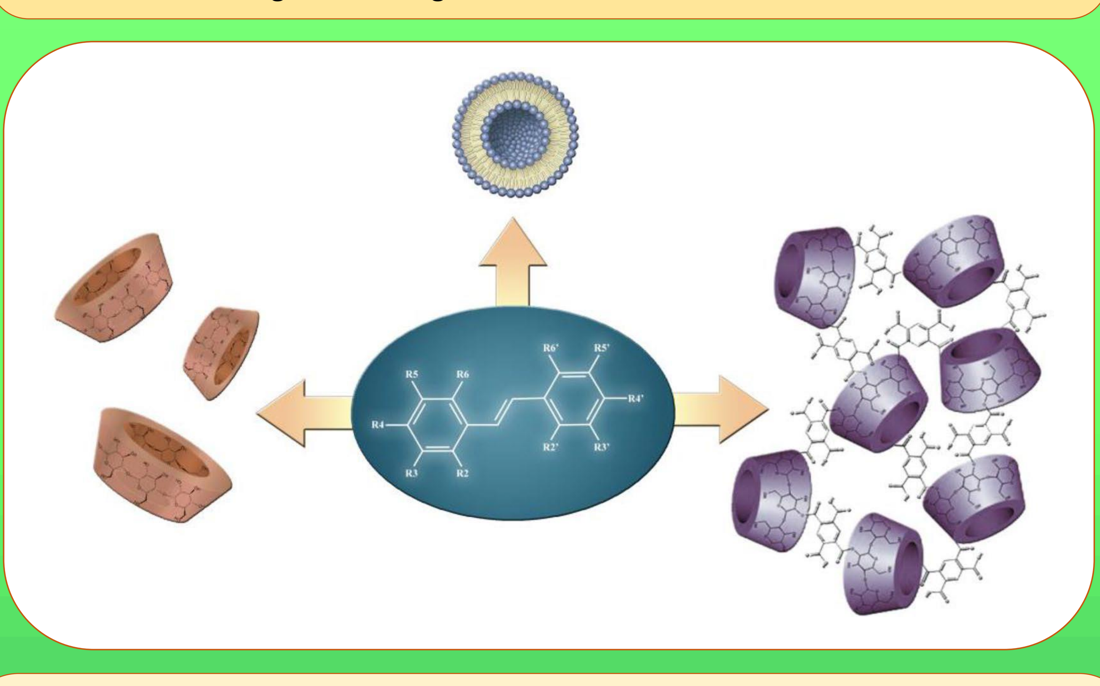

Fig. 3: different encapsulating agents to protect stilbenes (cyclodextrins, liposomes and polymeric cyclodextrin nanosponges).

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