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Resveratrol and related stilbenes: Their anti-aging and anti-angiogenic properties

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ABSTRACT

Dietary stilbenes comprise a class of natural compounds that display significant biological activities of medicinal interest. Among them, their antioxidant, anti-aging and anti-angiogenesic properties are well established and subjects of numerous research endeavors. This mini-review aspires to account and present the literature reports published on research concerning various natural and synthetic stilbenes, such as *trans*-resveratrol. Special focus was given to most recent research findings, while the mechanisms underlying their anti-aging and anti-angiogenic effects as well as the respective signaling pathways involved were also presented and discussed.

1. Introduction

Stilbenes comprise a group of bioactive compounds found in plants but only few of them are encountered in human diet, including *trans*-resveratrol (3,5,4′-trihydroxystilbene, RES) and its natural glycoside, *trans*-piceid. Their structure is characterized by two benzene rings linked via an isopropylene moiety that form a compact ring structure separated by a double bond (Fig. 1). Main focus of the present review is devoted to dietary stilbenes and includes only selected synthetic analogs of RES that display potent anti-aging and anti-angiogenic properties.

The first reported biological activity of RES attributed to its simplified but increasingly important structure– refers to the antioxidant profile of RES (Stivala et al., 2001). Despite the concomitant presence of two structural isomers of RES, only the *trans* counterpart is biologically active, displaying a significant activity as scavenger of free radicals. The latter play a major role in both physiological and pathological conditions, forcing cells to develop advanced defense systems for lessening the harmful effects when exposed to high concentration of free radicals. Deregulation of this dynamic equilibrium provokes a physiological situation known as oxidative stress. The antioxidant activity of dietary stilbenes can be rationalized considering their well-established ability to display strong antioxidant properties, acting either as direct ROS scavengers (Stagos et al., 2007) or as potent inhibitors of NADPH oxidase expression and xanthine oxidase activity (Lin et al., 2000).

During the last decades considerable ongoing research is devoted towards the exploitation of polyphenols bioactivities and resulted an enormous interest on RES (as pure compound or plant derived enriched extract), as a consequence of its application either as food supplement or as active constituent in medicinal and cosmetic preparations. The everlasting emerge for medicinal plants, in combination with the recent trend on "natural products" and the numerous reports on polyphenols bioactivities (with special focus on the broad spectrum of RES activities) provoked the publication of numerous scientific reports and patents as a reflection of their health beneficial character (Gollücke and Ribeiro, 2012). In particular, the scientific interest on RES has continually gained motion since 1997, when Jang et al. first demonstrated that RES prevents carcinogenesis in mice (Jang et al., 1997). During the intervening years the molecule of RES received considerable attention due to its anti-inflammatory, anti-tumorigenic and anti-oxidant properties, as well as its ability to increase the lifecycle in lower organisms and improve generally the health of mammals.

2. Sources of resveratrol and other stilbenes

Resveratrol (RES) is a naturally occurring phytoalexin produced by a wide variety of plants as a response to stress, injury, ultraviolet (UV) irradiation and fungal (e.g. *Botrytis cinerea*) infection. Red wine constitutes the most important dietary source of RES, a molecule suggested as one of the most important factors of "French

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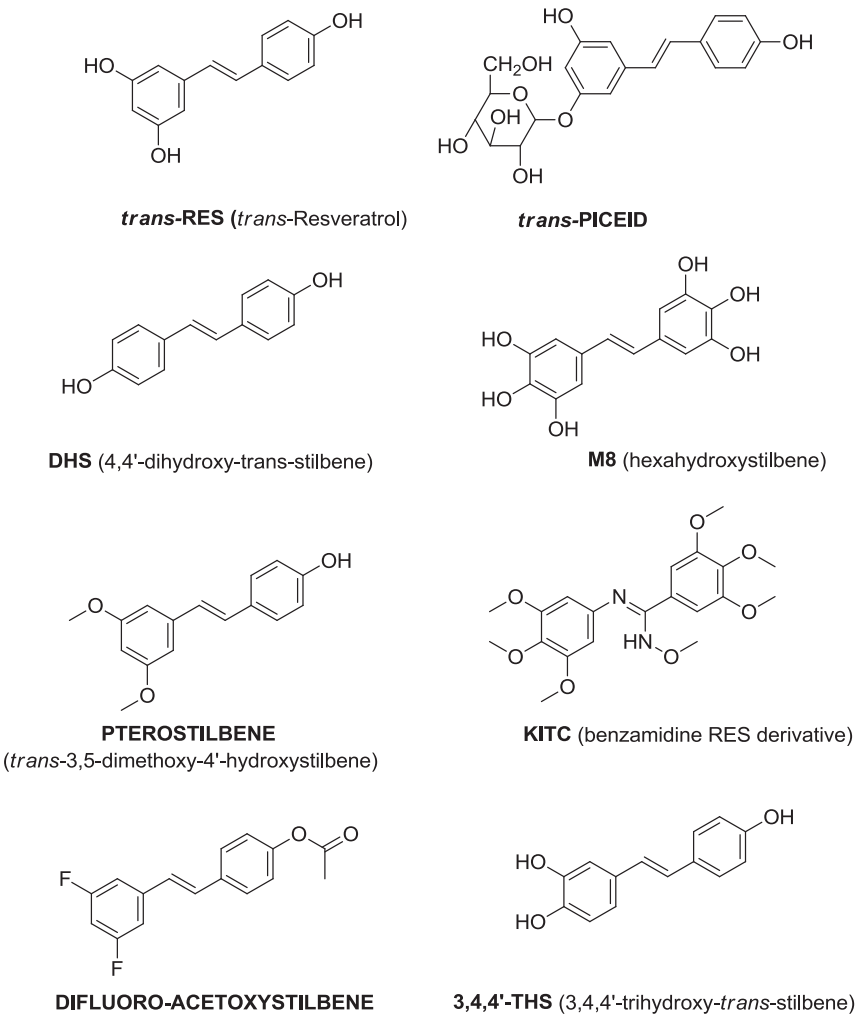

Fig. 1. Structures of RES, PICEID and other bioactive stilbenes.

Paradox". The latter describes an epidemiological finding that links the low incidences of cardiovascular diseases of French population (despite their diet high in saturated fats), with their daily consumption of moderate quantities of red wines (Kopp, 1998). RES is biosynthesized by grapevine (and several other plants) as a respond to attack by pathogens from the precursor molecules of malonyl-coenzyme A (CoA) and *p*-coumaroyl CoA, in the presence of stilbene synthase. Though the molecule of RES was firstly isolated in 1940 from the roots of white hellebore, grapes (*Vitis* spp., grapevines, leaves, and berry-skins) constitute their prevalent and most investigated source. RES and other naturally occurring stilbenes (and respective glycosides) are also found in a wide variety of plants such as peanut, *Vaccinum* spp. (including blueberry, bilberry, and cranberry), pine (*Pinus* spp.), *Morus* spp. (including mulberry), legumes (*Cassia* spp., *Pterolobium hexapetallum*), *Rheum* spp. (including rhubarb), eucalyptus and other sources. Recently, RES was also detected in plum fruits, expanding its abundance profile in nature and dietary sources in particular (Huang and Mazza, 2011; Sebastia et al., 2012).

The rising interest for compounds bearing the RES structural backbone is delineated by a vigorous ongoing research on a broad variety of related compounds, such as their hydroxylated metabolites, dimmers, trimers [indicatively see (Yao et al., 2012)], which are isolated and investigated from an increasingly number of plants.

Recently, an association between the dietary intake of RES and its health promoting effects was reported (Llorach et al., 2010) raising questions about the possible synergistic (or antagonistic) effects of polyphenols present in grapes and plants.

3. Extraction of RES and other stilbenes from plants

For decades the solvent extraction is the method of choice for the extraction–isolation of polyphenols from plant sources. Most techniques of this field refer to distillation and Soxhlet or liquid–liquid extractions (Handley, 1999). Advantage of these methods is considered their easy setup, while the need of large amounts of solvents, the prolonged extraction time and the possible heating which leads to compounds degradation account as major drawbacks. Recently, researchers have proposed the utilization of various more "sophisticated" extraction techniques that devoid the downsides mentioned. In this respect, microwave assisted extraction (MAE) constitutes a method providing effective internal and external heating of the matrix that prevents their thermal gradient (Li et al., 2011). Consecutively, polyphenols may efficiently be extracted without the chemical/structural transformations arising from increased temperature.

During the last 15 years our groups have been actively involved in research concerning the efficient extraction and analysis of polyphenols from grapes (seeds, stems etc.) and vilification products/byproducts (Anastasiadi et al., 2012). In this endeavor, the grape polyphenols were efficiently isolated using an ultrasonic-assisted extraction (UAE) procedure. The efficiency of the latter is affected