Stilbenols – A class of privileged structures

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The name "privileged structures" was originally suggested for benzodiazepines but now generally applied for structures of "class of compounds that bind to several protein-receptor surfaces"(1). This article will examine whether this appellation of privileged structures will fit the stilbenols, represented by their prominent member Resveratrol and its analogs. Plants biosynthesize their secondary metabolites, more often than not, for specific reasons. Resveratrol is a phytoalexin, a substance produced under response to a biotic or abiotic threat to the plant. One anticipates such structure should have a natural potential to bind several classes of protein structures to elicit a variety of responses.

RESVERATROL (2)

The accumulation of Resveratrol in plant cells increases in response to fungal infections (biotic stress) or other physical stresses such as UV radiation, ultrasound, wounding such as slicing as well as in response to invasion of chemicals such as hydrogen peroxide, paraquat etc (3). Resveratrol is *trans*-stilbene that undergoes isomerization under UV radiation. It is the *trans* form of Resveratrol that has been shown to display a much broader spectrum of pharmacological activity than its *cis* isomer. It is the early observation that Resveratrol is the substance behind "French Paradox" that shot this chemical into broader limelight. The Southern French have a low mortality rate due to coronary heart disease despite having high-fat diet and smoking habits. This so-called "French Paradox" has been attributed to wine consumption (4) thought to be responsible for the cardiovascular benefits and protection. The occurrence of Resveratrol and its glycoside in red wine as well as studies that led to the relation of the cardioprotective role of Resveratrol established the beneficial effects of this stilbenol.

Since then various pharmacological activities have been associated with this compound, and its close analogs have been the subject of numerous studies.

The cardioprotective effects of Resveratrol encompass inhibition of LDL oxidation, suppression of platelet aggregation, reduction in myocardial damage during ischemia-reperfusion (I-R) and modulation of vascular cell functions (5). The cardioprotective effects of Resveratrol in I-R rata was correlated with its antioxidant activity (6) and NO production (7).

Caloric restriction has been associated with increased longevity. In turn increased longevity is associated with reduced rates of incidence of cancer, diabetes, inflammation and cardiovascular malfunctions. There is a strong relationship between the activation of enzyme SIRT1 and caloric restriction that has led to many exciting results. Resveratrol has been demonstrated to activate SIRT1, mimicking caloric restriction and Resveratrol was shown to extend the life span in multiple organisms (8). This has stirred enormous interest in stilbenols in general. Experimental investigations have demonstrated that food supplementation

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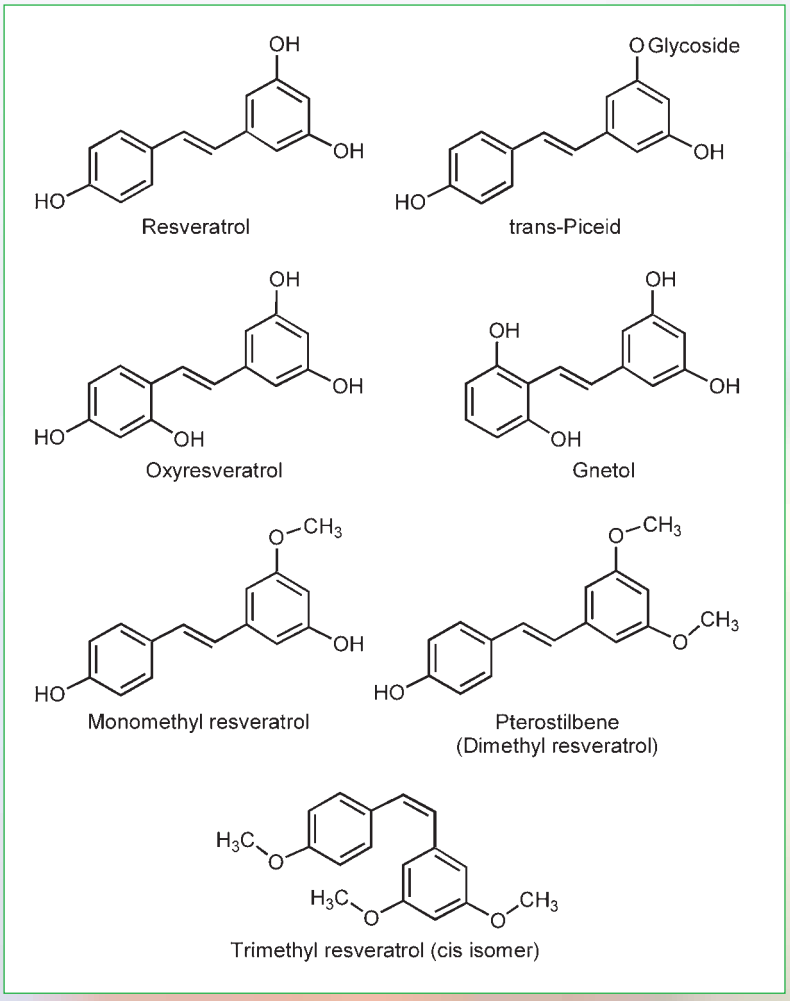
with Resveratrol prolongs life span and retards the expression of age-dependent traits in short-lived vertebrates (9).

Resveratrol exhibits cancer chemopreventive activity (10). It was found to have chemopreventive activity in assays representing three major stages of carcinogenesis: anti-initiation activity, anti-promotion activity, and anti-progression activity. It also inhibited the development of pre-neoplastic lesions in carcinogen-treated mouse mammary glands in culture and inhibited tumorogenesis in a mouse skin cancer model.

The extensive mechanistic studies done on the anti-cancer activity of Resveratrol has led to its status as an experimental chemopreventive and chemotherapeutic agent. Its status as an anti-cancer nutrient has been discussed in detail (11).



Structures of stilbenols and their methylated analogs

The antioxidant activity, free radical scavenging activity as wells as its ability to activate SIRT-1 enzyme has led to the expectation that Resveratrol will be able to slow-down and prevent neuronal degeneration. Its potential for fighting neuronal diseases such as Alzheimer's Disease has been suggested (12). Neuroprotective effect of Resveratrol has been studied in cerebral ischemia-induced neuron damage and was attributed to the free radical scavenging role of Resveratrol as well as its ability to increase cerebral blood elevation due to nitric oxide release (13).

The anti-inflammatory properties of Resveratrol have also been described. The anti-inflammatory property has been attributed to the inhibition of cyclooxygenase-2 transcription and inhibition of cyclooxygenase-1 activity via a peroxide mediated mechanism. Other mechanisms have also been discussed (14).

A treatment that combines antimicrobial activity and anti-inflammatory actions may be desirable for alleviating many skin conditions that range in severity. The studies have led to the conclusion that Resveratrol can combat human fungal pathogens. It may also have promising potential for diabetic wounds (15). The activity of Resveratrol against *Propionibacterium acnes* has also been reported (16). Inhibitory effect of Resveratrol on Influenza virus A is also known (17).

OXYRESVERATROL

An isomer of hydroxylated resveratrol, Oxyresveratrol, is an excellent inhibitor of the enzyme tyrosinase. Tyrosinase is the enzyme responsible for coloring of skin, hair, eyes in animals and also for the browning of fruits and vegetables. Oxyresveratrol showed potent inhibitory activity of tyrosinase with IC_{50} value of 1.2 μM on mushroom tyrosinase activity which is many times stronger than kojic acid, a depigmenting agent used as a cosmetic material with skin-whitening effect and the medical agent for hyper-pigmentation disorders (18).

Neuroprotective effect of Oxyresveratrol in cultured rat cortical neurons has been studied (19).

The Oxyresveratrol range of product are available from Sabinsa under the trade name Oxyresvenox®.

GNETOL

Gnetol is a positional isomer of Oxyresveratrol. Gnetol has also been found to have tyrosinase inhibition. Gnetol (IC_{50}, 4.5 μM) was found to be a stronger inhibitor of murine tyrosinase activity than a standard inhibitor, kojic acid (IC_{50}, 139 μM). Moreover gnetol suppressed significantly melanin biosynthesis in murine B16 melanoma cells. The authors proposed (20) that Gnetol is a promising pharmacological or cosmetic agent. Gnetol also occurs naturally in *Gnetum*, a special group of gymospermous plants.

PTEROSTILBENE (DIMETHYL RESVERATROL)

Pterostilbene, naturally occurring in *Pterocarpus marsupium,* has anti-diabetic activity. Pterostilbene significantly reduced the plasma glucose levels of the streptozotocin-induced hyperglycemic rats, and the effect was comparable to metformin. The standardized products are available from Sabinsa under the tradename Silbenol® (21).

Pterostilbene is a dimethylated analog of Resveratrol.

MONOMETHYL RESVERATROL

Monomethyl resveratrol was found to occur in *Muscari comosum*, a popular plant in Southern Italy used in gastronomy (22). This compound exhibits an apoptosis-inducing activity against sensitive and resistant leukemia cells and acts as an antioxidant.

TRIMETHYL RESVERATROL

The *cis* isomer of permethylated Resvertarol (Trimethylated) is found to occur in more than five different plants. This compound is found to exhibit anticancer property in experimental systems. It especially inhibits Ornithine decarboxylase, an enzyme involved in the rate-determining step in the synthesis of polyamines.

Sabinsa has developed and patented chemical processes that lead to the various stilbenols and their derivatives

exhibiting a wide range of useful and interesting pharmacological activities.

CONCLUSION

Future research will lead to more number and variety of pharmacologically useful novel compounds based on the molecular skeleton of stilbenols, definitely a privileged structural class.

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