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Resveratrol: A Molecule Whose Time Has Come? And Gone?

GEORGE J. SOLEAS,[2] ELEFTHERIOS P. DIAMANDIS,[1] and DAVID M. GOLDBERG[1]

[1]Department of Clinical Biochemistry, University of Toronto, Banting Institute, 100 College Street, Toronto, Ontario, and [2]Andres Wines Limited, Grimsby, Ontario, Canada

Objectives: Resveratrol (3,5,4′-trihydroxystilbene) is the parent compound of a family of molecules, including glucosides and polymers, existing in *cis* and *trans* configurations in a narrow range of spermatophytes of which vines, peanuts and pines are the prime representatives. Its synthesis from *p*-coumaroyl CoA and malonyl CoA is induced by stress, injury, infection or UV-irradiation, and it is classified as a phytoalexin anti-fungicide conferring disease resistance in the plant kingdom.

Results: *In vitro, ex vivo* and animal experiments have shown that it possesses many biological attributes that favour protection against atherosclerosis, including antioxidant activity, modulation of hepatic apolipoprotein and lipid synthesis, inhibition of platelet aggregation as well as the production of pro-atherogenic eicosanoids by human platelets and neutrophils. Red wine represents its main source in the human diet, and it has been proposed as a major constituent of the polyphenol fraction to which the health benefits of red wine consumption have been attributed.

Conclusions: The past several years have witnessed intense research devoted to its measurement in wine and the factors likely to promote its enrichment in this beverage. Up to the present, conclusive evidence for its absorption by human subjectsin biologically significant amounts is lacking, and it is questionable (but not yetexcluded) that its powerful and beneficial *in vitro* activities are reproduced as a consequence of sustained moderate red wine consumption.

KEY WORDS: stilbenes; viniferins; polydatin; phytoalexins; genetic engineering; fungicide; polyketide biosynthesis; chalcone synthase; resveratrol synthase; high performance liquid chromatography; gas chromatography-mass spectrometry; platelet aggregation; thromboxane; leukotriene; apolipoproteins; triglycerides; cholesterol esters; polyphenols; eicosanoid metabolism.

Corresponding Author: David M. Goldberg, Department of Clinical Biochemistry, University of Toronto, Banting Institute, 100 College Street, Toronto, Ontario, Canada, M5G 1L5.

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Introduction

Over 30 stilbenes and stilbene glycosides are known to occur naturally in a rather restricted distribution: they are found only among members of the plant kingdom classified as spermatophytes (1). The essential structural skeleton comprises two aromatic rings joined by a methylene bridge. From this relatively simple chemical notion, Mother Nature has contrived a bewildering array of compounds varying in the number and position of hydroxyl groups; the extent to which these groups become substituted with sugars, methyl, methoxy and other residues; the steric configuration of chemically identical molecules; and, their ability to enter into reactions forming dimers, trimers, or larger polymers.

The subject of this review, resveratrol, rejoices in the more dignified nomenclature of classical organic chemistry as 3,5,4′-trihydroxystilbene. In the laboratory, its synthesis can be accomplished by a Wittig reaction linking two appropriately substituted phenols through a styrene double bond as described initially by Moreno-Manas and Pleixats (2), and subsequently modified by others (3,4). In this strategy, methylated precursors are used to protect the OH groups which are subsequently removed by boron tribromide with formation of the *trans*-isomer which is virtually the only naturally occurring isomer of resveratrol. These heroic measures were rendered redundant when resveratrol became commercially available (Sigma, Cat No. R5010).

The main significance of resveratrol in plant biology lies in its role as the parent molecule of a family of polymers given the name viniferin (Figure 1). These compounds are able to inhibit the progress of fungal infection, a property which has earned their inclusion in the class of plant antibiotics known as phytoalexins. Another derivative, pterostilbene, in which the hydroxyl functions at positions 3 and 5 are methoxylated, has much greater antifungal activity than resveratrol (5,6), but it is only a minor constituent of the phytoalexin response.