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Review

Resveratrol and cardiovascular health – Promising therapeutic or hopeless illusion?

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ABSTRACT

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a natural polyphenolic compound that exists in *Polygonum cuspidatum*, grapes, peanuts and berries, as well as their manufactured products, especially red wine. Resveratrol is a pharmacologically active compound that interacts with multiple targets in a variety of cardiovascular disease models to exert protective effects or induce a reduction in cardiovascular risks parameters. This review attempts to primarily serve to summarize the current research findings regarding the putative cardioprotective effects of resveratrol and the molecular pathways underlying these effects. One intent is to hopefully provide a relatively comprehensive resource for clues that may prompt ideas for additional mechanistic studies which might further elucidate and strengthen the role of the stilbene family of compounds in cardiovascular disease and cardioprotection. Model systems that incorporate a significant functional association with tissues outside of the cardiovascular system proper, such as adipose (cell culture, obesity models) and pancreatic (diabetes) tissues, were reviewed, and the molecular pathways and/or targets related to these models and influenced by resveratrol are discussed. Because the body of work encompassing the stilbenes and other phytochemicals in the context of longevity and the ability to presumably mitigate a plethora of afflictions is replete with conflicting information and controversy, especially so with respect to the human response, we tried to remain as neutral as possible in compiling and presenting the more current data with minimal commentary, permitting the reader free reign to extract the knowledge most helpful to their own investigations.

Contents

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Introduction

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a natural polyphenolic compound that exists in *Polygonum cuspidatum* (Japanese knotweed), grapes, peanuts and berries, long used in traditional Chinese medicine as an herbal remedy [1,2]. Resveratrol exists in *cis*- and *trans*-configurations, of which *trans*-resveratrol is the principal biologically active form (Fig. 1). Resveratrol is produced in plants from malonyl CoA and coumaroyl CoA *via* the enzyme resveratrol synthase as a defense mechanism against deleterious microorganisms [3]. In addition to antimicrobial activity in plants, much work has revealed that resveratrol is a pharmacologically active compound in higher species, able to interact with multiple targets throughout the cardiovascular and other systems to confer protection against disease or injury. For instance, and as discussed below, resveratrol has been shown to exert its protective effect against cardiovascular disease, ischemia–reperfusion (IR) injury and diabetes mellitus through modulation of adipocyte/fibroblast biology, platelet activation, blood vessel function, oxidative stress, inflammation, serum glucose maintenance, cardiomyocyte biology, maintenance of cell structure, and serum lipid activity. In order to regulate many of these processes, data from numerous studies provide evidence that resveratrol interacts more often than not with one predominant member of the Sirtuin family of cellular enzymes, namely, the yeast Sir2 (Silent mating type Information Regulation 2 homolog 1) homologues Sirt1 in mouse and SIRT1 in human. Recent biophysical data indicate that resveratrol interacts with and modulates SIRT1 activity *via* an allosteric mechanism [4–9]. Sirtuins are categorized as members of the highly conserved Class III Histone Deacetylases, with SIRT1 having both Nicotinamide Adenine Dinucleotide (NAD^+)-dependent deacetylase and ADP-Ribosyltransferase activities. SIRT1 activity levels are dependent, in turn, on local concentrations of its cofactor NAD^+ (*versus* NADH), *i.e.*, the energy status of the cell, the presence of other factors that may modulate enzyme activity and the expression levels of the protein itself [10]. The Sirtuins can be found in several subcellular compartments across diverse species, and have been implicated in regulating a variety of cellular, systemic and organismal processes including energy metabolism, cell cycle regulation, stress mitigation, gene transcription, organ system protective functions and ultimately as a major contender in the anti-aging arena, albeit a relatively poorly understood one. With the ever expanding volume of literature devoted to promoting the health and longevity benefits of resveratrol-containing substances such as red wine and grapes, it is of utmost import to take note that the effects of resveratrol in humans remains unclear at best, and as discussed below and in more recent studies, little physiologically significant benefit has thus far been observed in healthy, non-obese mammals [11–16]. Furthermore, recent research has led to accumulating evidence that many effects resveratrol may have in mammals or other model systems appear to be mediated through molecular signaling cascades that bypass SIRT1 or other Sirtuin family members [17–21].

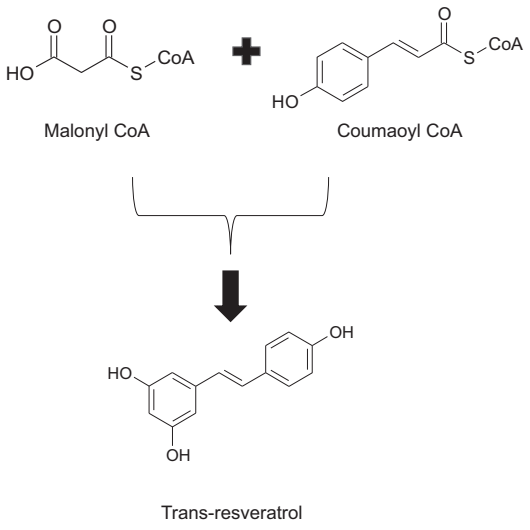

Fig. 1. Synthesis of resveratrol (3,5,4′-trihydroxy-trans-stilbene) in plant.

And so, the Collins' Dictionary defines "Illusion" as 'a perception that is not true to reality, having been altered subjectively in some way in the mind of the perceiver'. Thus, the hype in the popular media regarding resveratrol containing products promising to be the definitive "fountain of youth" may indeed turn out to be nothing more than a slight-of-hand marketing device using peer-reviewed, published, non-human research as a cover. The intent of this review is simply to distil this large volume of relevant and often conflicting information with the hope of providing a "one-stop-shopping" experience for investigators working in the field regarding the current state of affairs with respect to resveratrol and the cardiovascular system, or for those who may be interested in entering the field or incorporating resveratrol in their existing projects. We set out to objectively summarize in this review the body of recent work focused on defining the cellular and biochemical mechanisms so reported as being modulated by resveratrol in a variety of primarily *in vivo* and *in vitro* cardiovascular disease models (Table 1), including human data whenever possible. The putative targets and molecular pathways implicated in the ability of resveratrol to confer a protective function upon the cardiovascular system are organized according to the effects resveratrol imparts across a range of model systems having varying degrees of impact on cardiovascular health, with the understanding that some of the more current data presented in this review could indeed provide a useful launch point on which to embark for further exploration. One salient theme that consistently arises throughout this voluminous body of work underscores the fact that data from human studies regarding any biological effects of resveratrol is sorely lacking, despite its popularity as an over-the-counter nutritional supplement. As such, it has never been more appropriate to ask