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The pharmacology of resveratrol in animals and humans ☆

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ABSTRACT

In addition to thousands of research papers related to resveratrol (RSV), approximately 300 review articles have been published. Earlier research tended to focus on pharmacological activities of RSV related to cardiovascular systems, inflammation, and carcinogenesis/cancer development. More recently, the horizon has been broadened by exploring the potential effect of RSV on the aging process, diabetes, neurological dysfunction, *etc.* Herein, we primarily focus on the *in vivo* pharmacological effects of RSV reported over the past 5 years (2009–2014). In addition, recent clinical intervention studies performed with resveratrol are summarized. Some discrepancies exist between *in vivo* studies with animals and clinical studies, or between clinical studies, which are likely due to disparate doses of RSV, experimental settings, and subject variation. Nevertheless, many positive indications have been reported with mammals, so it is reasonable to advocate for the conduct of more definitive clinical studies. Since the safety profile is pristine, an added advantage is the use of RSV as a dietary supplement. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes.

1. Introduction

Resveratrol (RSV) was first isolated in 1939 by Takaoka from *Veratrum grandiflorum* Loes. fil. (the root of the white hellebore) [1]. It is speculated that the name resveratrol was derived from the combination of its chemical structure and plant source used for isolation: a *res*orcinol derivative or polyphenol in the *res*in, occurring in *Veratrum* species which contains hydroxyl (–OH) groups (*-ol*). In addition to the most popular name, resveratrol, further nomenclature includes *trans*-resveratrol, (*E*)-resveratrol, 3,4′,5-trihydroxy-*trans*-stilbene, 3,4′,5-stilbenetriol, (*E*)-3,4′,5-trihydroxystilbene, *trans*-3,5,4′-trihydroxystilbene, 5-[(1*E*)2-(4-hydroxyphenyl)ethenyl]1,3-benzenediol, (*E*)2-(3,5-dihydroxyphenyl)1-(4-hydroxyphenyl)ethane, (*E*)5-(*p*-hydroxystyryl)resorcinol, Bioforte™, Regu®-Fade (for skin), resVida™, and SRT 501.

As a defense mechanism in plants, the production of RSV, one of the phytoalexins, can be triggered in response to fungi, rhizobacteria, UV irradiation, metallic salts, methyl jasmonate, *etc.* The main enzyme responsible for RSV biosynthesis is stilbene synthase which condenses one *p*-coumaroyl-CoA (4-coumaroyl-CoA) and three molecules of malonyl-CoA [2]. Stilbene synthase encoding genes have been identified in grapevine, pine, *Arachis hypogea*, *Parthenocissus henryana*, *Vitis riparia* cv Gloire de Montpellier, *Sorghum*, *etc.* [3].

Despite the early discovery, RSV gained little attention until an article coining the phrase 'the French paradox' was published, in which it was suggested that people of France, who consume a relatively high level of saturated fat, had a relatively low mortality from coronary heart disease, presumably as a result of wine consumption [4]. Later, RSV was touted as an active ingredient in red wine responsible for reduced serum lipids [5], but of course the concentration of RSV in wine is relatively low [6], and grapes are known to contain over 1600 phytochemicals [7]. As shown in Fig. 1, there has been an enormous upsurge of studies investigating the characteristics of RSV since 1997, undoubtedly due to the publication or our paper reporting cancer chemopreventive potential with a number of model systems [8].

Based on a search using SciFinder® [accessed July 18, 2014, using the RSV chemical structure (CAS 501-36-0)], 219 commercial sources are available and 679 reactions to yield RSV have been published. A large number of patents have been filed that are related to the effects of RSV in therapeutic, cosmetic and nutraceutical applications [9]. The response of the nutraceutical industry has been robust. Many dietary supplements containing RSV as a single component or in combination with other ingredients are on the market. Unit doses range from about 0.2 to 1000 mg (Google search, July 19, 2014). In some products RSV is encapsulated in liposomal formulations, micronized, or filled as a liquid capsule, ostensibly to improve the absorption.

In addition, a wide array of compounds and extracts are used in combination with RSV, including: *compounds* such as glucosamine, flavonoids (*e.g.*, quercetin, catechins, rutin, anthocyanins, and proanthocyanidins), stilbenoids (*e.g.*, piceid), phenolic acids (*e.g.*, ellagic acid), vitamins (*e.g.*, vitamins B6, B12 and C, folic acid, and coenzyme Q10), phosphatidylcholine, piperine, tocotrienols, lutein, lycopene, fatty acids

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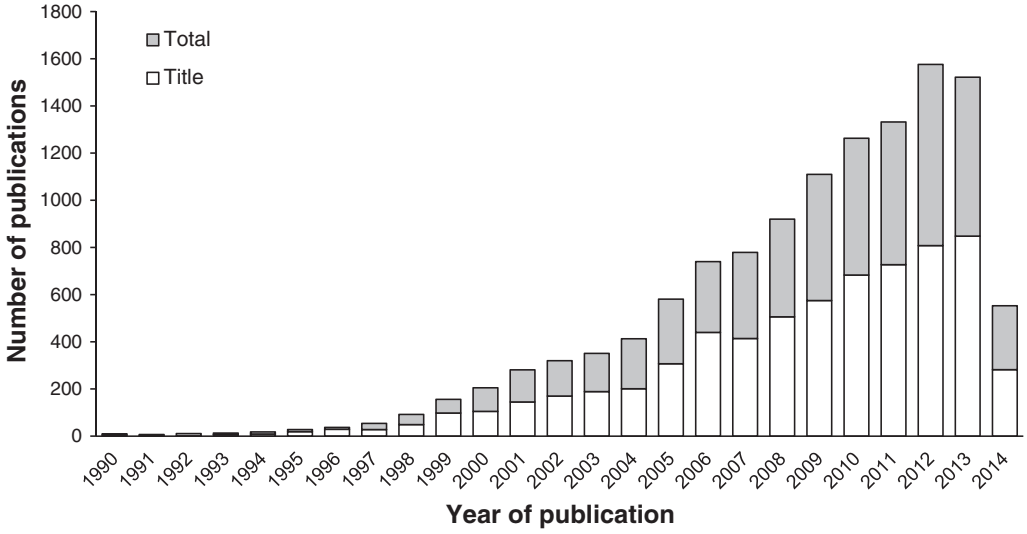

Fig. 1. Yearly publications related to RSV (1990–2014). The original search with the chemical structure of RSV (CAS number 501-36-0) followed by the removal of duplicate articles using the SciFinder® program yielded a total of 15,782 references (accessed July 18, 2014) as shown in 'total' bar (shaded). Within the 15,782 references, a total of 6664 articles include 'resveratrol' in the title ('title' bar, open).

(*e.g.*, docosahexaenoic acid, eicosapentaenoic acid), L-carnitine, and reduced L-glutathione; *extracts* from kelp, acai berry, blueberry, cherry, cranberry, pomegranate, olive, citrus fruits, melon, grape, French red wine, turmeric rhizome, black pepper fruit, potato, or calamari oil. Also, RSV has been used as an active ingredient in skin care products, with vitamin C, calcium, methylsulfonylmethane, polyphenols, or proanthocyanidins.

Although scores of *in vitro* studies have added to our understanding of the vast biological potential of RSV, it is common to use high concentrations that may not be of physiological relevance. Since RSV is known to have poor bioavailability in that it is rapidly metabolized and excreted, it is expected that the results of many *in vitro* studies will not have a good correlation with *in vivo* studies. Here, the discussion is limited to the *in vivo* biological effects of RSV, excluding work in which extracts or mixtures of compounds were investigated.

The review is largely based on a PubMed search using the search terms as 'resveratrol and animal model', 'resveratrol and in vivo', or 'resveratrol and animal study'. A literature search using SciFinder® (research topic: resveratrol, document type: review, publication year: –2008, accessed November 22, 2014) resulted in 244 review articles that include "resveratrol" in the titles. As an attempt to avoid redundancy, this article focuses on *in vivo* studies that were published during the time period of 2009 to 2014.

2. Carcinogenesis/cancer

Studies on the cancer chemopreventive effect of RSV increased dramatically following the paper published in 1997 describing the ability of RSV to inhibit skin carcinogenesis in an animal model [8]. Since comprehensive reviews on the cancer chemopreventive and anti-cancer potential of RSV have been published, we currently summarize data appearing over the past 5 years. Molecular alterations observed with different carcinogenesis/cancer models (including lung, breast, prostate and colon) are illustrated in Fig. 2.

2.1. Skin

The first report on the cancer chemopreventive potential of RSV was against skin carcinogenesis [8]. In rodent models, skin cancer can be induced by the treatment with 7,12-dimethylbenz[*a*]anthracene (DMBA) plus 12-*O*-tetradecanoylphorbol-13-acetate (TPA), benzo[*a*]pyrene (BP), and UV irradiation [10,11]. To evaluate the skin cancer chemopreventive or anti-cancer capacity of RSV, *in vivo* studies have been conducted using DMBA/TPA [8,12–16], DMBA alone [17–21], TPA alone [22–24], DMBA/croton oil [25], UVB exposure [26–29], BP [18], and xenograft [30] models. Topical application of RSV is the most commonly used route of treatment in skin cancer models. In DMBA/TPA models, RSV treatment reduced the incidence [8,12–15], multiplicity [8,12,14,15], and tumor volume [14–16], and delayed the onset of tumorigenesis [14]. At biomarker levels, RSV induced apoptosis: RSV decreased the expression levels of Bcl-2 while it increased p53 and Bax. Also, RSV enhanced the release of cytochrome c, induced apoptotic protease-activating factor-1(APAF-1), and cleaved caspase-9,-3, and poly (ADP-ribose) polymerase (PARP) [14]. On the other hand, it decreased cell survival-related proteins including phosphatidylinositol-3-kinase (PI3K) and Akt [17], and inflammatory markers including *interleukin* (*IL*)*-6*, *cyclooxygenase-2* (*COX-2*), and c-Jun [16].

With UVB models, RSV decreased bi-fold skin thickness [26,27], hyperplasia [27], infiltration of leukocytes [27], and incidence [28], and delayed the onset of tumorigenesis [28]. In addition, biomarkers were affected by RSV treatment. Activities of ornithine decarboxylase (ODC) [26] and COX [26] and expression levels of ODC [26], proliferating cell nuclear antigen (PCNA) [27], cyclin-dependent kinase (CDK)2, CDK6, and cyclinD2 [27], mitogen-activated protein kinase kinase (MEK) [27], extracellular signal-regulated kinase (ERK) [27], survivin, and phosphorylated (p-)survivin were downregulated. On the other hand, the expression of p21 [27], p53 [27], and Smac/DIABLO [28] was upregulated. Furthermore, RSV exerted the antioxidant effect with the reduction of H_2O_2 and lipid peroxidation in the skin [26].

Notably, oral administration of RSV, but not topical treatment, also resulted in positive effects, including decreases in the tumor multiplicity [29] and volume [29], and delay in the onset of tumorigenesis [29]. The anti-tumor effect of RSV was associated with decreased expression levels of TGF-β1 [29] and Rictor [31], and increased expression levels of E-cadherin [29].

With the human cutaneous skin squamous carcinoma A431 cell line xenograft model, tumor volume was decreased by RSV treatment, along with increased expression levels of p53 and ERK [30], and decreased levels of survivin [30,32]. Although ERK is considered as a proliferation and survival protein in general, ERK was also reported to form a complex with p53, leading to an increase in p53 phosphorylation and expression [30]. Also, RSV enhanced the activation of caspase-3 [32].