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Mini-review

# Resveratrol and chemoprevention

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ABSTRACT

Resveratrol is a phytoalexin, highly abundant in skins of red grapes and moderately abundant in peanuts and blueberries. Originally a constituent of oriental medicines, it has lately been rediscovered for a plethora of beneficial properties such as anti-cancer, anti-aging, antiviral, cardiovascular and neuroprotective effects, thereby making it one of the most sought after phytochemicals for supplementing human diet. Studies done in various laboratories have shown its modulatory effects on multitudes of cell signaling and gene expression pathways. Although most of its effects have been observed in cultured cells, quite a few have also been validated in whole animals as well. It is thus necessary to have a comprehensive look at all those effects of resveratrol in an organismal context. The following review summarizes the effects of resveratrol in the context of chemoprevention.



## 1. Introduction

Over the past 50 years, increased medicinal and surgical interventions have substantially reduced the incidences of death by heart attack and stroke. On the contrary, in spite of significant progress in our understanding of the biology of cancer, the number of death caused by this dreaded disease remained unabated until the end of the twentieth century, followed by a reverse trend only for the past several years [1]. Public health policy initiatives have thus been focused on the "chemoprevention" of cancer, wherein naturally occurring or synthetic chemical agents are used for the inhibition, delay or even reversal of carcinogenesis [2]. The term "chemoprevention" was first coined by Dr. Michael B. Sporn, with reference to the observed potentials of vitamin A and its synthetic analogs in preventing certain forms of cancer [3]. Since, a large number of naturally occurring and synthetic compounds have been shown to have such properties, albeit with diverse modes of action [4]. In recent years, the term "chemoprevention" has also been used in a wider contexts like describing the beneficial effects of altered life style and dietary intakes, wherein the active principles are often undefined and their modulatory effects on tumorigenesis remains unknown [5]. The National Cancer Institute, USA; has thus been maintaining a resource base for phytochemicals with potential chemopreventive properties (http://resresources.nci.nih.gov/database.cfm?id=1165). Taken together, chemopreventive phytochemicals are constituents of fruits and vegetables with potential pharmacological or nutritional functions [6–8]. Also, they can be as diverse as phenolic acids, tannins, stilbenes, coumarins and flavonoids [9]. Interestingly, in spite of their diverse chemical natures, many of these phytochemicals have antioxidant properties; thereby subscribing towards the "Antioxidant Hypothesis" of chemoprevention [10].

## 2. Resveratrol, French paradox and cardioprotection

Resveratrol is a phytoalexin, first isolated from roots of *Veratrum grandiflorum* O. Loes (white hellebore) and then

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*Abbreviations:* ERK, extracellular signal-regulated kinases; CYP 450, cytochrome P450; SIRT-1, sirtuin 1/silent mating type information regulation 2 homolog; IGF-II, insulin like growth factor II; ErbB2, erythroblastic leukemia viral oncogene homolog 2; FOXA1, forkhead box A1; FOXO3a, forkhead box protein O3; COX-2,cyclooxygenase 2; cIAP-2,cellular inhibitor of apoptosis 2; XIAP, X-linked inhibitor of apoptosis protein; Bcl-2, B-cell leukemia/lymphoma 2; TRAF2, TNF receptor-associated factor; PPAR, peroxisome proliferator-activated receptors.

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from *Polygonum cuspidatum,* but remained in obscurity for almost 50 years [11,12]. It got into prominence in early nineties in the context of "French paradox"; the phenomena wherein certain population of France (and Greece), in spite of regular consumption of high fat diet, gets much less heart diseases [13]. The apparent cardioprotection was attributed to the regular consumption of moderate doses of red wine rich in resveratrol [14]. Initially resveratrol was characterized by its anti-platelet aggregation properties [15] and thereafter other beneficial effects such as vasorelaxation, antioxidant functions, etc., became apparent [16,17].

In experimental animals, resveratrol is rapidly metabolized by the liver and its plasma half-life remains quite low with a concomitant decline in its concentrations in tissues like brain, lung, liver and kidney [18]. However, in human, about 70% of orally administered resveratrol (25 mg) is absorbed with a peak plasma level of ~2 μM (including its metabolites) and a half-life of ~10 h [19]. In plasma, it binds with lipoproteins and albumin which facilitates its carrier-mediated cellular uptake [20]. Upon metabolism, the phenolic groups are sulfated and conjugated with glucuronic acid. Hydrogenation of the aliphatic double bonds is also prevalent [21].

## 3. Occurrence and natural derivatives of resveratrol

Resveratrol is a trans-3, 5, 4′-trihydroxystilbene highly abundant in grapes, moderately abundant in blueberries, peanuts and sparsely abundant in may other plants. In grapes, its highest concentration is in the skin (50–100 μg per gram), thereby making red wines (but not white wines) the richest dietary source. Roots of *P. cuspidatum*; an ingredient of "Ko-jo-kon", the oriental concoction for treating vessels and heart diseases; is also rich in resveratrol [22].

Resveratrol has a number of naturally occurring analogs. Pterostilbene, the methoxylated analog of resveratrol, has antioxidant properties and can prevent carcinogen-induced preneoplastic lesion formation. However, unlike resveratrol, which is a potent inhibitor of cycloxygenase-1 and 2; pterostilbene it is only a moderate inhibitor of the former and a weak inhibitor of the other [23]. Piceatannol (trans-3, 4, 3′, 5′-tetrahydroxystilbene) is another naturally occurring analog of resveratrol with antileukaemic and tyrosine kinase inhibitory activities. CYP1B1, a cytochrome P450 enzyme overexpressed in a wide variety of human tumors, converts resveratrol to piceatannol by incorporating an aromatic hydroxyl group [24,25]. Oxyresveratrol (2, 3′, 4, 5′-tetrahydroxystilbene), found in white mulberry, is also a potent inhibitor of tyrosinase [26].

## 4. Resveratrol and chemoprevention

Interest in resveratrol took a further upsurge when it was reported in 1997 that it also has anti-neoplastic activities [27]. Since, burst of activities followed, resulting in its characterization as an anti-inflammatory, anti-platelet aggregation, anti-carcinogenic, anti-tumorigenic, anti-aging, cell cycle inhibitory, cardioprotective and a phytoestrogen [28–32]. In agreement with such diverse pleiotropic effects, it was also shown to activate ERK [33] and inhibit a plethora of enzymes and other regulatory proteins such as ribonucleotide reductase [34], nitric oxide synthase [35], $F_0F_1$–ATPase/ATP synthase [36], protein kinase D [37]; transcription factors NF-κ B [38] and aryl hydrocarbon receptor [39]. It also inhibits the transcription of CYP 4501Y1 [40] and cyclooxygenase-2 [41], thereby raising question about its precise mode of action in the *in vivo* context [42]. Number of laboratories have thus tested the cellular targets resveratrol and have come up with molecules as diverse as type II phosphatidylinositol 4-kinase [43], SIRT-1 [44], cytochrome P450 3A4 [45], quinone reductase 2 [46], redox factor-1 [47], Integrin alphaVbeta3 [48], sulfonylurea receptor [49], estrogen receptor [50] and F1-ATPase [51], making it one of the most versatile phytochemicals [52]. It is thus possible that such apparently diverse mode(s) of action of resveratrol is due to its unique ability to influence multiple cellular modules rather than having a single target as in the case of synthetic drugs. Thus, while evaluating the therapeutic potential of resveratrol, it might be premature to emphasize its effects on one cellular pathway against another. Accordingly, the following sections describe recent advances in our understanding of the chemopreventive effects of resveratrol in various cellular contexts.

### 4.1. Resveratrol as a phytoestrogen

17beta-Estradiol (E2) plays a critical role in the development and functions of the reproductive organs. In addition, it also contributes towards the functions of certain non-reproductive tissues. It binds to the estrogen receptors-α and -β (ER-α and -β) which then targets the estrogen response elements (EREs) located in the regulatory regions of the estrogen responsive genes, modulating their expression. Induction and progression of breast cancers has often been associated with estrogen and based upon the receptor profiles, breast cancers are categorized as ER positive and negative [53]. ER-positive tumors respond to anti-estrogen therapies and estrogen analogs (synthetic and natural) have been extensively tested for their therapeutic and chemoprevention potentials [54]. Resveratrol binds to the estrogen receptors (ER), induces estrogen responsive genes and thus could be considered a phytoestrogen [55]. It inhibits the carcinogen-induced preneoplastic lesions and mammary tumors, suggesting its chemoprevention potential [56]. Resveratrol also antagonizes certain functions of estrogen such as lowering of serum cholesterol and inducing proliferation of human breast cancer cells MCF-7 (estrogen receptor positive [56–58]). Treatment of MCF-7 and T47D cells with resveratrol at a relatively low dose ($10^{-6}$ M) causes stimulation of IGF-II expression that is blocked by 17beta-estradiol; while at a higher dose ($10^{-4}$ M) it inhibits IGF-II secretion and cell growth [59]. Also in MCF-7 cells, low concentrations of resveratrol (1–10 μM) reduces the basal expression of ErbB2 in estrogen-free medium, while in presence of estrogen, it increases the ErbB2 level in a dose-dependent manner [60]. Taken together, in absence of 17beta-estradiol, resveratrol can be both estrogen-agonist and antagonist; while in presence of 17beta-estradiol, it is an anti-estrogen