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REVIEW

Longevity nutrients resveratrol, wines and grapes

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Abstract A mild-to-moderate wine drinking has been linked with reduced cardiovascular, cerebrovascular, and peripheral vascular risk as well as reduced risk due to cancer. The reduced risk of cardiovascular disease associated with wine drinking is popularly known as French Paradox. A large number of reports exist in the literature indicating that resveratrol present in wine is primarily responsible for the cardioprotection associated with wine. Recently, resveratrol was shown to extend life span in yeast through the activation of longevity gene SirT1, which is also responsible for the longevity mediated by calorie restriction. This review summarizes the reports available on the functional and molecular biological aspects of resveratrol, wine and grapes in potentiating the longevity genes.

Keywords Resveratrol · Red wine · Longevity · SirT1

Introduction

Resveratrol (3,5,4′-trihydroxystilbene), a member of a family of polyphenols called viniferins possesses diverse health benefits from chemoprevention to cardioprotection [1, 4, 15, 18, 25, 37, 38, 42, 54, 56]. Also known as 3,4′,5-stilbenetriol, resveratrol has a molecular formula of $C_{14}H_{12}O_3$, and its molecular weight is 228.25 Daltons (Fig. 1). Resveratrol exists in *cis* and *trans* isomeric forms. Although, both *cis*- and *trans*-resveratrol (with their glucosides) occur naturally and seem to exert similar biological effects, the actions of the *trans*-isoform are more widely investigated and better known. Resveratrol-3-*O*-beta-D-glucoside is called piceid.

Resveratrol is also a phytoalexin that possesses many biochemical and physiological properties including estrogenic, antiplatelet, and anti-inflammatory actions [14, 19, 32, 34, 43, 47, 49, 55, 57]. Several recent studies revealed that resveratrol-mediated protections against a wide variety of degenerative diseases. The most important point about resveratrol is that at a particular range of concentration, it inhibits apoptotic cell death, thereby providing protection from various diseases including myocardial ischemic reperfusion injury, atherosclerosis, ventricular arrhythmias, and cerebral ischemia [17, 60]. Both in acute and in chronic models, resveratrol-mediated cardioprotection is achieved through the preconditioning effect (the state-of-the-art technique of cardioprotection), rather than direct effect as found in conventional medicine [11]. The same resveratrol when used in higher doses facilitates apoptotic cell death, behaving in contrast as a chemo-preventive agent [17, 51]. Resveratrol likely fulfills the definition of a pharmacological preconditioning compound and gives hope for its therapeutic promise of alternative medicine [6, 11].

Resveratrol is biosynthesized from one molecule of *p*-coumaroyl CoA and three molecules of malonyl CoA by the stilbene synthase (STS) present in certain higher order plants, such as eucalyptus, spruce, lily, mulberries, and peanuts [28]. External stimuli such as fungal attack and UV-radiation activate the stilbene synthase genes in the grapes to produce resveratrol in order to provide adequate protection. This STS gene is also found in peanut root,

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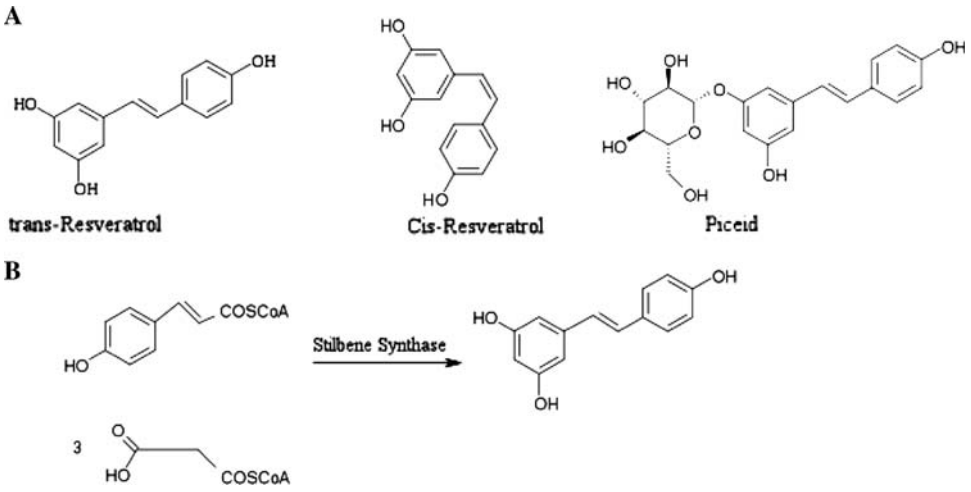

Fig. 1 **a** Structure of *cis*-, *trans*-resveratrol and piceid, **b** synthesis of resveratrol

strawberry, blueberry, mulberry, grapes, etc. and other plants like eucalyptus, spruce, and lily [39, 50]. *Vitis vinifera*, labrusca, and muscadine types of grapes contain high concentrations of resveratrol. The skins and seeds of these types of grapes contain 50–100 μg/g of resveratrol [17]. These varieties of grapes are particularly suitable for making red wine. Thus, grapes and red wines are considered as the major sources of resveratrol. In addition to grapes, a large variety of fruits including mulberry, bilberry, lingo berry, sparkle-berry, deer berry, partridgeberry, cranberry, blueberry, jackfruit, peanut, and a wide variety of flowers and leaves including gnetum, white hellebore, corn lily, butterfly orchid tree, eucalyptus, spruce, poaceae, Scots pine, rheum, and *Polygonum cuspidatum* (Japanese knotweed) also contain resveratrol [13]. In contrast to the constitutive isoform of stilbene synthase occurring in the *Rheum rhaponticum* (rhubarb), an inducible enzyme is expressed in the Vitaceae family [23, 50]. Resveratrol is a naturally occurring phytoalexin ("defender of the plant") that is produced in response to injury, such as mechanical trauma, ultraviolet light and infection by pathogenic microorganisms, especially fungi, providing means for defense [31, 45, 52, 53]. Since fungal infections are more common in cooler climates, grapes grown in cooler climates have a higher concentration of resveratrol [9, 29]. However, grapes cultured in the zone of equator also contain resveratrol in high concentration, because of higher ultraviolet irradiation [29]. During the wine making process, resveratrol as well as other polyphenols, including quercetin, catechins, gallocatechins, procyanidins, and prodelphidins (condensed tannins) are primarily extracted from grape skins. Red wines of different origin contain about 0–15 μg/ml *trans*-resveratrol, while the level of *cis*-resveratrol ranges between 0 and 5 μg/ml. Furthermore, red wines contain *trans*- or *cis*-piceid at 0–30 or 0–15 μg/ml, respectively [29]. Recently, resveratrol has been found to induce life through the activation of longevity gene, SirT1, and to mimic caloric restriction [2, 7, 27]. More recently, resveratrol as well as wines were found to induce SirT3 and SirT4 in addition to SirT1 as well as PBEF and regulate FoxO1 and 3, all these genes are being linked with longevity [41]. This review will focus on the ability of resveratrol and wine to promote life span through the induction of longevity genes.

Resveratrol, grapes, wine, and French Paradox

One of the richest natural sources of resveratrol is the dark grapes and the wines that are produced from these grapes. Resveratrol became popular when the consumption of red wine was linked with the term French Paradox [58]. A mild-to-moderate wine drinking habit attenuates cardiovascular, cerebrovascular, and peripheral vascular risk due to reduced platelet and monocyte adhesion, attenuates the risk of prostate as well as a variety of cancers including pancreatic, gastric, and thyroid cancer, and slows down some neurodegenerative diseases like Alzheimer diseases [8, 20, 33, 35, 46, 48, 59]. Among approximately 500 different antioxidants, recent studies revealed that resveratrol and proanthocyanidins are the two most important polyphenolic antioxidants present in wine that attenuate various health problems [12]. In fact, most believe that resveratrol is the secret compound present in red wine that is responsible for French Paradox.

Indeed the existing reports support the role of resveratrol for the diverse health benefits of wines, especially red wines. Both resveratrol and wine are able to function as cardioprotective compounds through their abilities to induce nitric oxide, adenosine, and protein kinase C, all of which being implicated for cardiac preconditioning [11]. Moderate wine consumption was shown to inhibit platelet activity [16]. Striking similarities between the mechanisms of action between wines and resveratrol strongly suggest

the role of resveratrol for cardioprotection achieved by wine consumption. More recent studies have demonstrated induction of longevity genes such as SirT1 by both red wine and resveratrol [7, 27]. It is also believed that the grape extracts can similarly induce anti-aging genes. In fact, muscadine grapes loaded with resveratrol (average 40 times more resveratrol than regular grapes) mainly grown in Southern part of America like North Carolina, can induce the same longevity gene SirT1.

Longevity Genes

The most important longevity gene detected to date is SirT1, yeast homolog of SIR2 (Silent Information Regulator 2) [21]. This gene was detected more than 40 years ago in conjunction with low-caloric diet and/or fasting [26]. In yeast resveratrol was found to mimic calorie restriction by stimulating SIR2 and increase the DNA stability as well as the life span about 70% [24]. Restriction of calorie intake of yeast caused the activation of SIR2 deacetylase. Caloric restriction could extend life as much as 40% over the average life span in animals and induces SirT1 gene [10]. SirT1 can deacetylate the DNA repair factor Ku70 thereby inhibiting apoptotic cell death [22, 50]. SirT1 and Ku70 can work together to inhibit Bax activation, which is responsible for apoptosis [22, 51]. SirT1 also negatively regulate the p53-dependent apoptosis by deacetylating and down regulating p53 [22, 36]. FOXO family proteins were also shown to be deacetylated and down regulated by SirT1, this deacetylation and down regulation lead to decreased apoptotic response and increased stress resistance under stressed condition [22, 40]. Recently, another longevity gene PHA-4 was discovered in conjunction with low-calorie diets [44].

More recently, red wine and its component resveratrol as well as white wine and its components tyrosol and hydroxytyrosol were found to act on SirT, FoxO, and PBEF, all linked with survival genes [41]. In this study, the Sprague–Dawley rats weighing 250–300 g were gavaged for 14 days with experimental compounds, and then the animals were sacrificed for isolated working heart preparation. The rats were randomly assigned to one of the following groups: (i) control (water only); (ii) alcohol control (1 ml 12%); (iii) white wine (6.5 ml/kg); (iv) red wine (6.5 ml/kg); (v) resveratrol (2.5 mg/kg); (vi) tyrosol (2.5 mg/kg); and (vii) hydroxytyrosol (2.5 mg/kg). The most surprising findings in this study was that not only did white wine induce the longevity proteins including SirT1, SirT3, SirT4, and the phosphorylation of FoxO1, FoxO3A in the heart, but also the amounts of the induced proteins were higher than those induced by red wine or resveratrol; the ability to induce anti-aging proteins followed an order: white wine > resveratrol > tyrosol > red wine/hydroxytyrosol. All of these compounds enhanced the survival of the heart through the phosphorylation of the survival protein Akt in the order of resveratrol > red wine > hydroxytyrosol > white wine > tyrosol. These results suggest that while all of the tested compounds induced anti-aging/longevity proteins and provided cardioprotection, their molecular targets/signaling pathways appear to be different.

At least seven SirTs (SirT1–7) are known to exist in mammalian system. These SirTs are located in different subcellular compartments including mitochondria (SirTs3–5), nucleus (SirT1, 2, 6, and 7), and cytoplasm (SirT1 and 2). SirT1 is a NAD^+-dependent histone deacylase, which plays a role in chromatin remodeling associated with longevity [21, 22]. SirT1 is also involved in the regulation of several transcription factors including FoxO1 that becomes inactivated by phosphorylation via Akt [41, 54]. The results of the above study also demonstrated activation of SirT3 and SirT4, which are localized in mitochondria where they regulate aging through energy metabolism. These results suggest that FoxO could be the substrates for SirT activated by resveratrol and/or wines. PBEF, a nicotinamide phosphoribosyltransferase, supplies NAD^+ to SirT1, which is a NAD^+-dependent HDAC. It appears that resveratrol not only activates SirT1 but also activates PBEF, which can supply NAD^+ to the SirT1. PBEF-mediated activation of SirT1 enables it to promote cell survival and longevity through SirT1 FoxO pathway [41] (Fig. 2a).

The most intriguing results of this study include the ability of both red and white wines and their components resveratrol, tyrosol, and hydroxy tyrosol to activate the longevity genes and promote cell survival. Thus, resveratrol may not be the only longevity nutrient, but wines and grapes, especially muscadine grapes, are likely to be involved in the promotion of longevity genes and proteins.

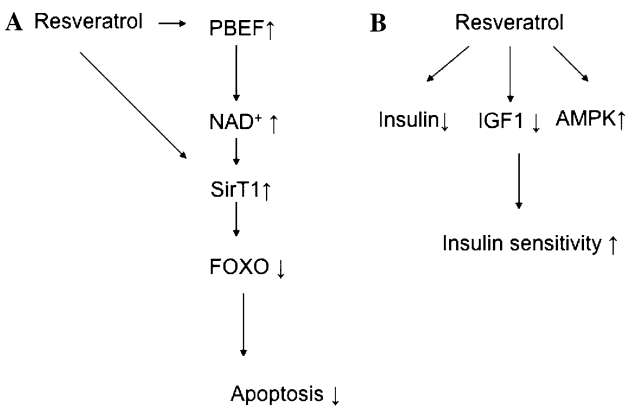

Fig. 2 **a** Induction of cell survival and longevity by resveratrol via SirT1–FoxO pathway. **b** AMPK IGF1-mediated increment of insulin sensitivity by resveratrol

How resveratrol mimics calorie restriction?

Mounting evidence suggests that resveratrol mimics the effects of calorie restriction in promoting the longevity. However, the mechanisms of action remain unknown. The only common link could be that both resveratrol and calorie restriction improve insulin sensitivity, which in turn reduces insulin and glucose levels in the body [3, 5, 30]. Indeed, blocking of insulin receptors located in the adipose tissue could extend the life spans of mice by about 18% [5]. It is quite possible that both calorie restriction and resveratrol function in the same way, i.e., by improving insulin sensitivity in the body. Resveratrol mimics the effects of calorie restriction in reducing blood glucose, insulin levels, and insulin like growth factor-1 (IGF-1) and by increasing HDL [3, 5]. The other common mechanism includes the activation of longevity gene SirT1 by both calorie restriction and longevity.

A recent study showed that resveratrol could mimic the effects of calorie restriction through alterations in chromatin structure and transcription [2]. These authors could not find the reduction of IGF-1 in resveratrol-treated mice, while IGF-1 was reduced by calorie restriction, as expected. However, both calorie restriction and resveratrol could reduce blood glucose levels. This study also revealed that SirT was not affected by either resveratrol or calorie restriction, and calorie restriction but not resveratrol induced PGC-1α transcriptional activity. Four gene ontology terms were impacted by both calorie restriction and resveratrol that included chromatin assembly or disassembly regulation of transcription from RNA polymerase II promoter, and ubiquitin cycle. The detailed analysis within these classes revealed that these genes had important role in chromatin remodeling and included de novo methylase Dnmt3a, the chromodomain helicase DNA binding protein I (chd1), SirT5, SWI/SNF complex member (SmarccI, Smarca4, Smarca5, and Smarca2). The Smarca gene encodes Brahma that regulates a transcriptional switch for the chromatin remodeling. In addition, both resveratrol and calorie restriction altered the expression of several histone encoding genes.

Other studies demonstrated the beneficial effect of resveratrol in mice kept on high fat calorie diet [3]. In this study, the authors found that resveratrol treatment increased the survival rate of the mice on high fat diet, and shifted the metabolic activity close to the mice on normal diet. The study also demonstrated that the resveratrol decreased the level of insulin and IGF-1, and increased the insulin sensitivity possibly by activating AMPK. The report documented an increment in the number of the mitochondria. Further, they showed significantly lower acetylating status of the PGC alpha after resveratrol treatment; however, the expression of the SirT1 remained same, suggesting that resveratrol increased the enzymatic activity of SirT1 (Fig. 2b).

Other study also reported that resveratrol improved the mitochondrial function and increased the aerobic capacity of mice on high fat diet, by activating SirT1 and PGC alpha [30]. In this study, it was also reported that resveratrol slowed down the gaining rate of mice on high fat diet, and increased insulin sensitivity.

Summary and conclusion

In conclusion, longevity nutrient resveratrol mimics calorie restriction through the induction of the expression of several longevity genes. These longevity genes include SirTs and FoxOs that act coordinately for the regulation of cell survival and longevity. Resveratrol does not appear to be the only longevity nutrient, because both white and red wines as well as grapes can also induce these longevity genes.

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