ERRATUM

Erratum to: Resveratrol and red wine, healthy heart and longevity

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Abstract Resveratrol, a polyphenol phytoalexin, present in red wine and grapes possesses diverse biochemical and physiological properties, including estrogenic, antiplatelet, and anti-inflammatory properties as well as a wide range of health benefits ranging from chemoprevention to cardioprotection. Recently, several studies described resveratrol as an anti-aging compound. This review focuses on the anti-aging aspects of resveratrol, the possible mechanisms of action, and emerging controversy on its life-prolonging ability. It appears that resveratrol can induce the expression of several longevity genes including *Sirt1*, *Sirt3*, *Sirt4*, *FoxO1*, *Foxo3a* and *PBEF* and prevent aging-related decline in cardiovascular function including cholesterol level and inflammatory response, but it is unable to affect actual survival or life span of mice.

Keywords Resveratrol · Red wine · White wine · Cardioprotection · Longevity genes · Anti-aging · SIRT · FoxO · PBEF

Abbreviations

SIRT	Sirtuins.
FoxO	Forkhead transcription factor.
PBEF	Pre B cell colony enhancing factor.
LDL	Low-density lipoprotein.
BMR	Basal metabolic rate.
CR	Calorie restriction.

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IGF1	Insulin-dependent growth factor 1
ROS	Reactive oxygen species
NOS	Nitric oxide synthase
VEGF	Vascular endothelial growth factor
GLUT	Glucose transporter type 4
PUFA	Polyunsaturated fatty acids
HO-1	Heme oxygenase-1
PKC	Protein kinase C
PI3 kinase	Phosphatidylinositol-3-kinase
LPS	Lipopolysaccharide
PGE2	Prostaglandin E2
TNFα	Tumor necrosis factor α

Introduction

Resveratrol, a phytoalexin polyphenol that is found naturally in the grape skins and red wines, possesses diverse health benefits ranging from chemoprevention to cardioprotection. Although red wines are generally recognized as the source of resveratrol, actual resveratrol content of resveratrol is very low and varies from wine to wine [1]. Commercially, resveratrol is manufactured from Polygonum cuspidatum, a giant knotweed belonging to the Polygonaceae family, and cultivated mainly in China and Japan (popularly known as Ko-J-Kon in Japan). In addition to red wine and grape, a large variety of fruits including mulberry, bilberry, cranberry and blueberry as well as peanut contain resveratrol.

Although resveratrol has been used from time immemorial, the name became popular after the discovery of French paradox, which described cardioprotective properties of red wine [2]. Subsequent studies determined that resveratrol present in red wine possesses numerous health

benefits including cardioprotection [3]. A majority of its cardioprotective properties are associated with its ability to exert vasorelaxation, anti-inflammatory response and ROS scavenging. It is believed that cardioprotective ability of resveratrol is linked with its ability to induce preconditioning [4]. Among other health benefits, resveratrol possesses antitumor activity [5] and neuroprotective abilities [6].

Recently, a number of studies described resveratrol as an anti-aging compound. The first study came from the Harvard Medical School and Biomol Research Laboratories, which reported in a revolutionary discovery that resveratrol could activate anti-aging gene *SIRT1* [7]. Based on the animal study, the authors noted that depending on the concentration of resveratrol present in red wine, one needs to consume several bottles of red wine per day to get such a dose [8]. Subsequent studies found that resveratrol in a very small dose could activate not only *Sirt1* but also *Sirt* 3 and *Sirt* 4 as well as FoxOs and PBEF, all being linked with longevity proteins [9]. Interestingly enough, this study found that in addition to red wine and resveratrol, white wine and its components tyrosol and hydroxytyrosol could also activate the same longevity genes suggesting that activation of *Sirt1* could be a non-specific phenomenon. A recent study reported that resveratrol prevented age-related and obesity-related cardiovascular functional decline in mice, but did not affect the overall survival or maximum life span for mice on a standard diet, compared to mice on the same diet with resveratrol [10].

The word longevity means life expectancy in demography, but in general term this word means long life. In contrast, aging is a process that contributes to health deterioration decline in productivity, disability and ultimately to death with time. Since chronic diseases like coronary heart disease, cancer, etc. are the major causes of death, and nutrition plays a key role in the fight against these degenerative diseases, it can also be assumed that nutrition plays a key role in expanding life span too. Proper diets containing a proper variety of grains, fruits, vegetables and foods low in saturated fat, *trans* fat and cholesterol protect human beings from several degenerative diseases. Of course, nobody can ever be immortal, but they can definitely invigorate their short life span and lead a healthy life, free from diseases and disorders. Proper nutrition is essential for health; people who are well nourished are more likely to be healthy, productive and live long. Efforts were put on this direction from time immemorial, and many ancient sacred texts point the necessity for a balanced diet constituting of fruits and vegetables with proper amount of beverages in maintaining the individual health and acquiring a longer life span. Nowadays, with the rapid development of material science, the introspective human mind started to try to find the reason behind such age-old

instructions. With the rise of diabetes, obesity-related organ failures and deaths; people should be much more conscious regarding their health by not only doing daily physical exercise but also by disciplining dietary habit. This is particularly true for the elderly people because the incidence of heart failure increases with age. The risk factors for heart attack rapidly increase for the people 65 and older. In a multicenter longitudinal cohort study in elderly Americans, it was found that the prevalence of chronic congestive heart failure ranged from 12 to 25% for women 65–85 years old, and from 19 to 32% for men in the same age range [11]. The risk factor for heart failure among the elderly consists of multiple causes including hypertension, diabetes and obesity. Healthy life style and intelligent choice of food are likely to reduce the risk factors.

The body has a tendency to store extra amount of nutrients as fat in the belly region that a healthy diet can prevent. Conscious calorie intake and calculated burning can do a really remarkable job in this direction. Calorie restriction (CR) should not be confused with malnutrition nor with deliberate starvation as the former can lead to anemia, muscle loss, dizziness, lethargy, nausea and the latter slows down the metabolism rate a lot, resulting in a decrease in weight loss. Caloric restriction (CR) helps improving the age-related health degeneration as evidenced in some rodents and fungi [12].

CR has been shown to lower cholesterol, fasting glucose and blood pressure in human subjects. In CR, energy intake is minimized, but sufficient quantities of vitamins, minerals and other important nutrients containing no calories must be swallowed, through pills if necessary. Decrease in Basal Metabolic Rate (BMR) is the foremost observation from calorie-restricted diet group [12]. Also, a long-term CR brings in lesser amount of LDL cholesterol and a simultaneous increase in HDL cholesterol, controlled blood pressure both systolic and diastolic, fasting glucose, fasting insulin, significantly low triglyceride level, better body mass index and body fat percentage [12, 13]. Perhaps, the system of fasting or maintaining a controlled diet chart in some holy month or day came out after deep observations of the effects of CR. A good diet mimicking CR can manipulate the effect of CR on the serum levels of insulin-dependent growth factor 1 (IGF 1) as seen in rodents [14]. Good diet activates the survival proteins and suppresses the expression of pro-apoptotic proteins when the system is in vulnerable condition. It triggers the anti-oxidant mechanism to scavenge the free radicals in both the initial and the later phases and thus protects the system, heals the discord and induces longevity.

Several studies have shown that resveratrol, a phytoalexin, obtained from grape skin can mimic the effect of caloric restriction and extend life span. In this review, we

Table 1 Resveratrol content of selected fruits and vegetables

No	Foods	Resveratrol/cup serving in mg
1.	Blueberry	∼32 ng/gm
2.	Bilberries	∼16 ng/g
3.	Cranberry raw juice	∼0.2 mg/L
4.	Mulberry	∼0.0021–0.0053 mg/g
5.	Peanuts (raw)	∼0.01–0.26 (per serving of 146 gm)
6.	Peanuts (boiled)	∼0.32–1.28 (per serving of 180 gm)
7.	Peanut butter	∼0.04–0.13 (per serving of 258 gm)
8.	Red grapes	∼0.24–1.25 (per serving of 160 gm)
9.	Red grape juice (Spanish)	∼0.17–1.30 (per serving in a 5 oz glass)

Table 2 Resveratrol content of wines

No	Wines	Total resveratrol (mg/ L)	Total resveratrol/5 oz glass
1.	White wine(Spanish)	∼0.05–1.80	∼0.01–0.27
2.	Rose wine (Spanish)	∼0.43–3.52	∼0.06–0.53
3.	Red wine (Spanish)	∼1.92–12.59	∼0.29–1.89
4.	Red wine (Global)	∼1.98–7.13	∼0.30–1.07
5.	Pinot noir	∼0.0–2.0	∼0.06–0.30
6.	Italian red wine	∼8.63–24.84 μmol/L	∼1.30–3.75 μmol
7.	Chilean Merlots wine	∼2.25	∼0.35

will discuss resveratrol and its ability to expand life span from molecular viewpoint.

Chemistry of resveratrol

Resveratrol belongs to stilbene family of compounds that consist of two aromatic rings joined by a methylene bridge. IUPAC (International Union of Pure and Applied Chemistry) nomenclature for resveratrol is 3,4′,5-trihydroxystilbene, although it is also known as 3,4′,5-stilbenetriol with a chemical formula $C_{14}H_{12}O_3$ and molecular weight of 228.25 D_a. Resveratrol exists as both cis- and trans- isoforms, but the action of the later isoform has been widely investigated. The trans isomer possesses greater biological activity due to the presence of the 4′-hydroxystyryl group.

Resveratrol is a naturally occurring phytoalexin, which is produced in response to an injury, such as mechanical trauma, UV light and infection by pathogenic microorganisms such as fungi. It is formed via a condensation reaction between three molecules of malonyl CoA and one molecule of 4-coumaroyl CoA catalyzed by resveratrol synthase that also produces four molecules of CO_2.

Resveratrol and health benefits

Grape is well known in medicinal science from time immemorial. In *Ayurveda*, one of the ancient medicinal books of Hindus, and in the Bible, grape juice was described as cardiotonic and as a gift of god. Resveratrol is present in grape skin. Its chemical name is trans-3,5, 4′-trihydroxy stilbene. Resveratrol exists in two isomeric form *cis* and *trans* resveratrol. Because of its higher reactivity and anticancer, anti-inflammatory, blood sugar–lowering properties, *trans* resveratrol drew the attention of scientist worldwide. However, resveratrol is not only found in grape skin, it is also present in cranberry, mulberry, lingberry, bilberry, jackfruit, peanut gnetum, and the butterfly orchid tree (Table 1). Red wine also contains resveratrol, also its content vary from wine to wine (Table 2). External stimuli such as fungal attack and UV radiation activate the synthesis of resveratrol.

Cardiovascular benefits of resveratrol

It is now well known that resveratrol protects human health by diverse mechanisms. Mild-to-moderate wine drinking has been linked with reduced cardiovascular, cerebrovascular and peripheral vascular risks as well as reduced risk due to cancer (Fig. 1). On the other hand, French people, in spite of taking high-fat diet regularly, are less susceptible to risk factors of cardiovascular diseases, because of the presence of moderate amount of wine in their diet [2, 15]. This phenomenon is known as the French paradox. Certain wines, grape juices, especially grape skins can provide cardioprotective effects due to the presence of resveratrol. Resveratrol is a natural anti-oxidant; it can scavenge some intracellular reactive oxygen species (ROS). It has been shown that resveratrol induces NO synthesis in case of ischemic reperfused heart, brain and kidney and lower the oxidative stress [16, 17]. Results from the available
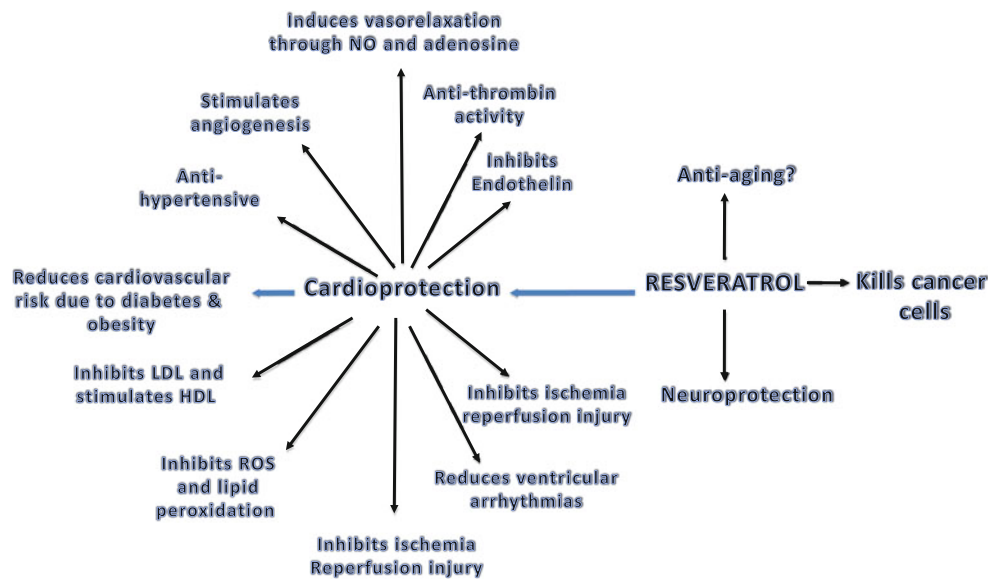
Fig. 1 Diverse health benefits of resveratrol including cardioprotection

literature show that resveratrol protects perfused rat hearts through increased iNOS expression [16, 18]. It is also shown that resveratrol provides cardioprotection via upregulation of catalase activity in the myocardium. Resveratrol has been found to pharmacologically precondition hearts by a nitric oxide (NO)-dependent mechanism [16, 18]. Das et al. [19] showed that resveratrol-induced preconditioning was derived through the upregulation of iNOS–VEGF–KDR–eNOS signaling cascade. A number of studies have successfully demonstrated that in the rat myocardial infarction (MI) model, resveratrol significantly upregulates the protein expression profiles of vascular endothelial growth factor (VEGF) and its tyrosine kinase receptor Flk-1 which in turn ameliorates myocardial damage [20]. Several studies from our laboratory have shown that resveratrol protects mammalian hearts from ischemia/reperfusion-induced injury evidenced by improvement on postischemic ventricular function, reduction in myocardial infarction and cardiomyocyte apoptosis, activation of survival signal, reduction of death signal [19, 21–25]. It has been also shown that resveratrol increased GLUT-4 expression and reduced endothelin expression in ischemic-reperfused hearts of Zucker obese rats in the presence or absence of glucose intake [26], indicating that resveratrol could provide protection against obesity-related cardiac injury.

Resveratrol regulates the redox homeostasis in mammalian system by maintaining the amounts of several anti-oxidant enzymes, including glutathione peroxidase, glutathione-S-transferase and glutathione reductase [27]. It is also known that resveratrol prevents LDL oxidation [28]. There is evidence that resveratrol is a potent inhibitor of the oxidation of polyunsaturated fatty acids (PUFA) found in LDL [29]. In fact, resveratrol was shown to be more potent than flavonoids in preventing copper-catalyzed oxidation, thus preventing oxidative modification of LDL [28]. Hebbar et al. [30] showed that high doses (0.3, 1.0 and 3.0 g/kg day) of resveratrol upregulate phase II and anti-oxidant genes in female and male rats. Due to high rate of oxygen consumption and low levels of anti-oxidant defense enzymes, the brain and the heart are particularly vulnerable to hypoxic conditions and oxidative stress injuries. Heme oxygenase -1 (HO-1) has been shown to be neuroprotective [31]; it degrades the pro-oxidant heme into biliverdin/bilirubin, iron and carbon monoxide. Bilirubin can scavenge free radicals. Carbon monoxide is a cell cycle modulator and vasodilator. It has been reported that CO provides anti-inflammatory and anti-apoptotic effects via NFκB regulation [32]. Resveratrol induces HO-1 in primary neuronal cultures [33] and aortic smooth muscle cells [34] at low concentrations (1–10 mM). At higher concentrations (>20 mM), NFκB activation was suppressed, and HO-1 was inhibited. Moderate resveratrol or red wine rich in resveratrol intake (presumably low concentration) could, therefore, have a considerable neuroprotective and vasculoprotective effect against oxidative stress.

Resveratrol inhibits platelet aggregation, another major contribution in the process of atherosclerosis [35, 36]. Platelets through the activation of the process of thrombus formation and their aggregation could set into motion the process of vascular occlusion. A dose-dependent decrease in platelet aggregation was shown with resveratrol treatment [37]. Resveratrol (0.15 and 0.25 micromole/l) was shown to inhibit collagen-induced platelet activation accompanied by [Ca^{+2}] immobilization, thromboxane A2 formation, phosphoinositide breakdown and protein kinase C (PKC) activation [38].

In summary, resveratrol has been found to exert cardioprotective effects by pre-conditioning the heart in addition to its ability to reduce oxidative stress developed during the reperfusion of the ischemic heart. As shown in Fig. 1, resveratrol is effective against hypertension, heart failure, cardiomyopathy, atherosclerosis, diabetes and obesity as well as against many other cardiac dysfunctions. More recently, resveratrol has been found to induce autophagy in the ischemic myocardium. Resveratrol at lower doses (0.1 and 1 μM in H9c2 cardiac myoblast cells and 2.5 mg/kg/day in rat) induced autophagy shown by enhanced formation of autophagosomes and its component LC3II after hypoxia/re-oxygenation or ischemia/reperfusion [39]. Since aging is now recognized to be directly related to autophagy, which decreases with age, it seems reasonable to speculate that resveratrol is somehow related to the cardiac dysfunction associated with the aging process.

Other health benefits of resveratrol

Resveratrol has been shown to possess potential anticancer activity in various cancer cells at the initiation, promotion and progression stages. For example, high-dose resveratrol (50 mM) has been shown to induce cell death in mouse xenograft models of human neuroblastoma cells (SH-SY5Y, NGP and SK-N-AS) [40]. Moreover, 48-h exposure of 100 mM resveratrol induced cell death in human colorectal cancer cells (DLD1 and HT29 cells) [41]. Inhibitory effects of resveratrol against breast cancer progression has been reported in both estrogen-positive (MCF-7) and estrogen-negative (MDA-MB-231) breast cancer cells as a result of 1 μM resveratrol treatment in vitro and in nude mice inoculated with any of these cell lines. Ten mg per kg body weight (BW) resveratrol treatment for 2 days reduced the cancer progression [42]. Resveratrol is also well known to possess anticancer properties in animal model. It was shown that 625 mg/kg body wt resveratrol treatment reduced the progression of prostate cancer in transgenic adenocarcinoma prostate (TRAMP) mice [43]. Bhardwaj et al. [44] showed that 50 uM resveratrol could reduce the proliferation of human multiple myeloma. Most of its anticancer properties attributes to its ability to induce apoptosis in cancer cells [41, 44–47]. For example, resveratrol induces loss of mitochondrial membrane potential, leading to release of cytochrome C and Smac/Diablo, and subsequent activation of caspase-9 and caspase-3 [40, 48]. In addition to these mechanisms, resveratrol can also induce cell cycle arrest at G0/G1 phase and reduce the expression of cell growth factors in human prostate cancer cell lines [40, 48]. Resveratrol was also shown to activate pro-apoptotic Bax, p53 and p21waf in T-cell acute

lymphoblastic leukemia cells [49], reduced the levels of anti-apoptotic Bcl-xL, Bcl-2, cyclin D1 and TNF receptor-associated factor [44, 48, 50]. In case of human breast cancer cells, resveratrol inhibited the anti-apoptotic phosphatidylinositol 3′-kinase (PI3 K)/Akt pathway [51] and activated the Forkhead transcription factor (FOXO3a) [42], which mediate cellular apoptosis through the activation of proapoptotic genes [42]. In addition, in earlier studies, resveratrol had been proposed to downregulate the expression of tumorigenic nuclear factor NFκB and its regulated proapoptotic gene products as well as growth factors in multiple myeloma cells [46].

In addition to its anticancer activity, resveratrol has displayed beneficial activity against inflammatory responses via the inhibition of COX1 and COX2 expression [52]. Resveratrol was reported to reduce the production of prostaglandin E2 (PGE2) and the formation of ROS in lipopolysaccharide (LPS)-activated microglial cells [53, 54]. Moreover, resveratrol was reported to suppress the activity of T- and B-cells, and macrophages [55]. Singh et al. [56] showed that resveratrol induced both caspase-dependent and caspase-independent apoptosis in activated T-cells in experimental allergic encephalomyelitis-induced mice. One study from our own laboratory showed that resveratrol possesses analgesic property by the inhibition of COX1 and COX 2 [57].

Resveratrol also possesses neuroprotective properties. It has been reported that resveratrol could protect against Huntington's disease [58], Alzheimer's disease [59] and Parkinson's disease [60].

Resveratrol and longevity

Resveratrol is one of the main longevity nutrients which can mimic the effects of calorie restriction which includes expanded life span, improved tissue pathology, increased endurance, mitochondrial biogenesis, energy expenditure and insulin sensitivity, and decreased fat accumulation, blood insulin and IGF-1 [61, 72]. A significant number of reports exist in the literature indicating that resveratrol can activate the longevity assurance genes, Sirtuins (SirTs) [62–66]. Resveratrol was initially reported to increase the activity of SIRT1 in vitro [67]. Despite the uncertainty of how resveratrol functions in vitro, in vivo it extend the life span in Drosophila [68] and C. elegans [69] Resveratrol also increases the life span of vertebrates such as Notho-branchius furzeri, a shortlived seasonal fish, and delays its age-dependent degenerations [70]. It is now well known that in mammalian system resveratrol plays a crucial role in fighting against several degenerative diseases, which results in extension of life span. Resveratrol fights against

many diseases of aging, such as cancer, heart diseases, inflammation, brain damage, hearing loss, anorexia and injuries to various tissues [8].

Bauer et al. [61] showed for the first time that resveratrol could extend life span in mammals. In this study, it was found that high-calorie diets (60% of calories from fat) induced obesity, triggering inflammatory response and comorbidities, such as diabetes and atherosclerosis, which decreased life span in case of middle-aged (1-year-old) mice, but resveratrol treatment (22.4 mg/kg/day) along with the high-fat diets extended the life span by inducing Sirt1 similar to calorie-restricted animals with greater SIRT1 coexpression [71]. Evidence is available to show the positive effects of resveratrol and SIRT1 activation on several age-related disorders including type-2 diabetes, cardiovascular disease, neuro-degeneration and inflammation [10, 61, 72, 73]. In yeast, resveratrol was found to activate SIR2 and expand life span about 70% [67]. Studies have also shown that resveratrol can deacetylate PGC-1α which is consistent with the activation of SIRT1 [61, 72]. Resveratrol increases longevity through SIRT1, which is activated with NAD^+ supplied by an anti-aging enzyme PBEF (nampt/visfatin). SIRT1 interacts with an anti-aging transcription factor, FOXO1, which is negatively regulated by Akt. We have shown in one of our recent studies that resveratrol induced the activation of SIRT1, SIRT3 and SIRT4, and the phosphorylation of FOXO1 and FOXO3a as well as PBEF proteins [9]. In this study, we fed a group of rats with resveratrol, red wine and white wine, and we found that levels of SIRT1, SIRT3, SIRT4 and PBEF protein as well as the phosphorylation of FOXO1 and FOXO3a were induced [9]. Thus, resveratrol and red wine can provide protection against age-related cardiac diseases. Furthermore, resveratrol triggers the mammalian cells toward survival by stimulating p53 deacetylation [67], inhibiting adipocyte differentiation, promoting fat mobilization [74] and sensitizing cells to tumor necrosis factor alpha (TNFα)-induced apoptosis by stimulating NFκB deacetylation [75]. It is a general opinion that the life span expanding properties of resveratrol is due to its ability to activate SIRT1, but it is also possible that the effects of resveratrol in mammals are only partially mediated by SIRT1. Resveratrol is a well-known regulator of many other enzymes and molecular pathways that might contribute to life span extension and disease suppression [8] which are not related to SIRT1. For example, resveratrol inhibits the insulin pathway independently of SIRT1 [76].

Resveratrol as an anti-aging compound: fact or fiction?

A growing body of evidence suggests that resveratrol mimics caloric restriction and expands life span. As

mentioned earlier, the first scientific evidence originated from the revolutionary observation that resveratrol similar to calorie restriction could activate *Sirt1* gene [7, 86, 107]. Subsequent studies determined that resveratrol, wines and certain polyphenols could also induce Sirtuins, along with certain other longevity genes including FoxOs and PBEF [9]. More recent studies, however, have questioned the ability of resveratrol to increase life span [10].

The ongoing search for identifying an anti-aging compound has not been successful. To date, calorie restriction is the only effective mean to increase the life span [108], although the mechanisms whereby calorie restriction increases life span remain speculative. Several reports are available in the literature suggesting that exercise and certain chemicals like rapamycin as well as wine could also increase life span [113], although they have not been studied as widely as calorie restriction. A recent study using microarray revealed that out of 6,347 modified genes by calorie restriction, about 58 genes displayed at least twofold alterations in gene expression [109]. There is striking similarities between resveratrol and calorie restriction on the alteration of metabolic pathways. Both resveratrol and calorie restriction improve insulin sensitivity and thus reduce the insulin and glucose levels in the body [61, 72, 77], which in turn reduce the life-threatening cardiovascular risk factors. Resveratrol and calorie restriction can trigger the expression of GLUT4 [26]. The most important anti-aging gene that is up-regulated by calorie restriction and resveratrol is Sirt1.

In summary, resveratrol has been found to activate several longevity genes, but whether activation of these genes is the cause or consequence is not known. The original report of Sinclair's group with yeast [114] has not been confirmed by subsequent studies [6]. The only study that showed increased life span of mammalians with resveratrol is the study reported by a group of Italian scientists who found resveratrol could increase the life span of fish Nothobranchius furzeri by 56% [115]. A further study by Sinclair and others showed that resveratrol could not increase longevity of resveratrol-fed mice [116]. In more recent studies, the scientists from two pharmaceutical companies, Pfizer and Amgens, could not verify the results of Sinclair and questioned the effectiveness of resveratrol as an anti-aging compound [116, 117]. A brief description of the longevity genes that have been found to be upregulated by resveratrol is furnished below.

Sirtuins

The revolutionary finding that resveratrol mimics the effects of calorie restriction in the upregulation of anti-aging gene/protein SIRT1 recognized resveratrol as an anti-aging compound [8]. The authors determined that one

bottle of red wine should consume at least 1,000 to reproduce anti-aging effect of resveratrol. Recent studies, however, indicate that SIRT1 could not only activated by resveratrol or red wine, it was activated with white wine and its components tyrosol and hydroxytyrosol also [9, 96]. The same study demonstrated that both red and white wines could also activate other sirtuins, SIRT3 and SIRT 4.

SIRT1, which is a NAD$^+$-dependent protein deacetylase, may not be directly activated by resveratrol since an artificial SIRT1 substrate, fluor de lys SRT1 could also activate SIRT1 and resveratrol could not activate SIRT1 in vitro in the presence of a acetylated PGC1α. The mechanism of action of SIRT1 is not completely understood. It is believed that SIRT1 deacetylase may directly bind to constituents in the chromatin complex leading to structural reorganization [110].

Several physiological activators of SIRT1 have been identified. For example, increased activation of PNC1, a nicotinamidase converting nicotinamide into nicotinic acid, can activate SIRT 1 in yeast [111]. Enhancement of PBEF/Nampt/visfatin stimulates cellular NAD thereby increasing the transcriptional activity of catalytic domain of SIRT1 [112]. Whether resveratrol induces SIRT through PNC1 and/or visfatin is not known. SIRT1 can regulate many transcription factors and proteins, and the number of molecular targets for SIRT1 is continuously increasing. It is, however, interesting to note that modulation of the molecular targets by SIRT1 is differentially regulated.

FOXO

Forkhead box O (FOXO) is a transcription factor that belongs to the large Forkhead family of proteins and contains a conserved DNA-binding domain termed the 'forkhead box (FOX)' [78]. Four FOXO family members are present in mammals: FOXO1 (or FKHR), FOXO3 (or FKHRL1), FOXO4 (or AFX) and FOXO6 [79]. Not only in mammals, the FOXO transcription factors are present in *C. elegans* and *Drosophila elanogaste* [79]. FOXO transcription factors are associated with several biological processes like apoptosis, DNA repair, cell cycle arrest, anti-oxidative stress [80, 81]. Studies have shown that FOXO transcription factors increase life span [79, 82–84]. FOXO can shuttle between nucleus and cytoplasm through protein phosphorylation on multiple threonine and serine residues and some accessory proteins such as importins and exportins. It also interacts with 14-3-3 proteins and nuclear transport machinery. Nuclear FOXO interacts with DNA and regulates the transcription of specific target genes through multiple modes of action. After deactivation via phosphorylation or acetylation, it translocates to the cytosol [85]. There are several signaling pathways that can regulate FOXO transcription factors. Among these, PI3 K-Akt signaling pathway that responds to insulin/IGF-I and several other growth factors [85].

FOXO is a key downstream effector of the PI3 K-Akt pathway [86, 87]. Studies showed that inactivating mutation of insulin receptor (daf-2) or PI3 K (age-1) resulted in extension of life span [88–91]. This extension of life span is reversed when FOXO ortholog daf-16 is mutated [86, 87]. Several studies have shown that Akt can phosphorylate FOXO1, FOXO3 and FOXO4 at The24, Ser256 and Ser319 and inactivate them [85, 92, 93]. When Akt is inactivated and unable to phosphorylate FOXO factors, they remain activated and localized in nucleus. Activated FOXO induced the transcription of several pro-apoptotic genes. When Akt is activated by several growth factors, the FOXO proteins are directly phosphorylated and translocate to the cytoplasm via binding to 14-3-3 proteins [85, 94], which are a family of cellular chaperones interacting with the protein ligands in a phosphorylation-dependent manner [95]. Thus, by translocating phosphorylated FOXO transcription factors into the cytoplasm, the Akt signaling pathway prevents the transcription of pro-apoptotic genes. Several studies have shown that resveratrol can activate Akt via phosphorylation [23, 96] which in turn inactivate FOXOs and translocate into cytoplasm. Not only that, but our own study demonstrated that resveratrol and red wine containing a significant amount of resveratrol can inactivate FOXOs by phosphorylation [9].

Oxidative stress leads to damage and death of cells, so that increase in oxidative stress resistance is related to longevity [97]. Several recent studies have shown that JNK, a member of MAPK superfamily, is a upstream modulator of FOXO factors [98–100]. JNK signaling pathway is known to activate by external stress stimuli. Wang et al. showed for first time that JNK regulates FOXO in *Drosophila* and plays important role in life span regulation [100]. Another study showed that JNK requires dFOXO, a FOXO ortholog to expand life span [100]. In the same study, it was demonstrated that JNK promotes the nuclear translocation of dFOXO overexpression of some small heat shock proteins. These heat shock proteins prevent the protein aggregate accumulation due to oxidative stress [100]. Furthermore, JNK activity promotes nuclear translocation of FOXO4 and upregulates the expression of MnSOD [98]. It is clear that Akt and JNK both finally regulate FOXO activity, but they are working in apposite fashion to promote life span. Akt translocates FOXO into the cytosol and reduces the transcription of pro-apoptotic genes. But JNK translocates FOXO into the nucleus and upregulates some anti-oxidant proteins. However, it is known that resveratrol inhibits the activity of JNK, so it can be assumed that resveratrol modulates FOXO transcription factors via AKT signaling path way.

PBEF [Visfatin]

Pre-B cell colony enhancing factor (PBEF), also known as visfatin, is a cytokine that is stress-inducible regulator of NAD^+ [101]. PBEF is associated with increased Sirtuin activity, suggesting that it could be linked with anti-aging component [9]. I PBEF is also highly expressed in visceral fat of diabetes and obese patients [102]. PBEF is secreted by activated lymphocytes, monocytes and neutrophils and exerts insulin-mimetic effects [103]. A functional equivalent of PBEF, PNC1 is also a longevity gene, whose biochemical activity feeds into the Sirtuin pathway, and is upregulated by mRNA mistranslation [104].

Pre B cell colony enhancing factor has been given a new name visfatin after the discovery that it is preferentially expressed in visceral fat [101]. PBEF/visfatin functions as a nicotinamide phosphoribosyltransferase within the cell, catalyzing the rate-limiting step in the biosynthesis of NAD + [105]. PBEF functions as anti-apoptotic protein and regulates energy metabolism during stress responses [106, 107]. Recently, yeast Sir2 and its mouse ortholog SIRT1 have been found to be NAD-dependent deacetylases based on the finding that SIRT2 can extend life span of yeast, suggesting that NAD could be the missing link between longevity and ATP. A recent study demonstrated increased expression of PBEF with resveratrol and wine [9]. However, our knowledge of the regulation of longevity with PBEF is very limited.

Summary and conclusion

It should be clear from our discussion that resveratrol, a phytoalexin polyphenolic anti-oxidant, can potentiate diverse functions in the body ranging from gene regulation to cell arrest. Resveratrol acts like a miracle compound, which can protect the cells from many degenerative diseases including cardiovascular complications and cancer. Recent studies implicated resveratrol as an anti-aging compound from the observation that it could mimic the effects of calorie restriction by activating SIRT. Subsequent studies demonstrated activation of several other

Fig. 2 Induction of the expression of Longevity genes by resveratrol

longevity genes by resveratrol including SIRT3, SIRT4, FOXO1, FOXO3a and PBEF (Fig. 2). Recent studies conducted and supported in part by the National Institute of Aging (NIA), however, challenged the ability of resveratrol to increase longevity [10]. The authors determined that resveratrol mimicked some, but not all the effects of calorie restriction in mice. More importantly, resveratrol abolished age-related and obesity-related decline in cardiovascular function including cholesterol level and inflammatory response, but could not affect survival or life span of mice suggesting that resveratrol could not modulate the basic aging process.

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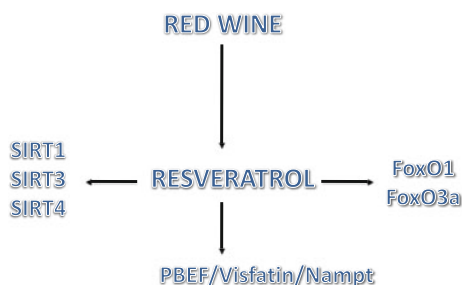
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