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Potential of Resveratrol in Inhibiting Cancer and Slowing Aging

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Abstract

Resveratrol (3, 4', 5 trihydroxystilbene) is a natural phytoalexin produced in response to injury by various plants including grapevines, berries and peanuts. Extensive evidence has indicated the beneficial effects of resveratrol on neurological, hepatic, cardiovascular, and inflammatory diseases. One of the most striking biological activities of resveratrol is its cancer chemopreventive potential. It has been shown recently that resveratrol blocks multiple processes during carcinogenesis including tumor initiation, promotion and progression. In addition, resveratrol has been shown to delay aging and age-associated diseases. Potential mechanisms involving resveratrol-induced age delay may be due to its effect on anti-oxidation and increased expression of SIRT1 (silence information regulator 1) by mimicking CR-induced longevity processes. However the precise mechanisms for resveratrol on its anti-cancer and anti-aging effects are still under investigation.

In this review, we will also introduce a new resveratrol-derived product, pterostilbene, known as one of the analogues of resveratrol. Pterostilbene has been considered as a bioactive dietary compound for its anti-cancer and anti-aging properties. Better understanding of the important role of resveratrol and its derived bioactive dietary compounds in regulation of cancer and aging processes may lead to clinical advances in the prevention and therapy of human diseases by applying this novel dietary regimen.

Keywords: Resveratrol; Cancer chemoprevention; Aging; Pterostilbene; Calorie restriction

Abbreviations: SIRT1: Silence Information Regulator 1; hTERT: Human Telomerase Reverse Transcriptase; HPLC: High-Performance Liquid Chromatography; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; HSF: Heat Shock Factor; HSP-70/90: Heat Shock Protein-70/90

Introduction

Interest in phytopharmaceuticals is accelerating since a growing group of studies has indicated that nutritional factors play an important role in many human diseases. Large and heterogeneous groups of botanicals, nutraceuticals and herbal drugs have been identified and evaluated during recent years, especially for their activities against cancer [1-13]. These agents include curcumin from turmeric, green tea polyphenols, boswellic acid from genus *Boswellia*, genistein from soybean, vitamin E, rosmarinic acid from rosemary and lavender, 6-shoagol from ginger rhizome and resveratrol from berries, which will be primarily introduced in this review. Foods enriched in nutraceuticals, especially fruits and vegetables, are known to be important to human health. One such food is berries, which are rich sources of a wide variety of antioxidant phytochemicals including flavonoids, stilbenes, tannins and phenolic acids.

Stilbenes are natural phenolic compounds found in a wide range of plant food sources, especially in berries. Resveratrol, pterostilbene and piceatannol are stilbene-derived dietary compounds found in deerberry, cowberry, blueberry and lingonberry. Resveratrol (3, 4', 5 trihydroxystilbene) is a polyphenolic compound with two isoforms such as trans-resveratrol and cis-resveratrol, and the trans-isomer is the stable form. Trans- to cis-isomerization is generated by UV light and high pH, whereas the cis- to trans-isoform conversion is induced by visible light, high temperature and low pH. Resveratrol was first detected in the roots of white hellebore (*Veratrum grandiflorum*) in 1940 [14]. Resveratrol is also enriched in the skin of red grapes, mulberries, peanuts, pines and root extracts of the weed polygonum cuspidatum [15]. The biological role of resveratrol is to protect plants against fungal infections [16], especially against infection with *Botrytis cinerea*. It is found that if grapes are infected with this fungus, the concentration of resveratrol in the adjacent grapes increases. Moreover, environmental stress as such as UV light and heavy metals play a significant role in increasing the level of resveratrol in plants [17-19].

A number of studies have focused on investigating the beneficial effects of resveratrol on cardiovascular systems [20,21]. There have been contradictory observations indicating a low incidence of cardiovascular diseases may occur with intake of a high-fat diet accompanied with a moderate consumption (150-300 mL) of red wine per day, a phenomenon known as the French paradox [22,23]. French paradox is a phenomenon observed in French people, suffering a relatively low rate of coronary heart diseases despite a diet rich in saturated fats. This fact led to widespread use of resveratrol in dietary supplements [24].

Great interest in resveratrol over the past decade is mainly due to its anti-carcinogenic, anti-aging, anti-inflammatory and cardio-protective

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properties [25-27]. Potential mechanisms of resveratrol's anti-cancer and anti-aging properties include its effect on regulation of various transcription factors such as AP-1, NF-κβ, HSF-1, p53, as well as many anti- and pro-apoptotic genes. It also modulates the activity of p53, a key tumor suppressor gene, and thus triggers apoptosis processes in cancer cells. Resveratrol can affect histone acetylation patterns by activating SIRT1 expression, suggesting resveratrol may influence gene expression though epigenetic controls.

Thus this review article presents a comprehensive detail of resveratrol's chemopreventive effect on cancer and age-related diseases. It also raises some concerns of the limitations of resveratrol with respect to its low bio-availability, and effective concentration in target cells. We therefore introduced a new resveratrol-derived compound named pterostilbene and the potential synergistic combination effect of pterostilbene and resveratrol against aging and age-associated diseases such as cancer. In summary, understanding how resveratrol works may provide important clinical implication for disease prevention and therapy, and further aid the development of new drugs to deliver some of the health benefits of this dietary regimen.

Biological characteristics of resveratrol

Synthesis, occurrence and content of resveratrol in wine and fruit juices: Resveratrol is a phytoalexin which is synthesized in plants and its synthesis can be induced by microbial infections, ultraviolet radiation (UV) and exposure to ozone [28]. Resveratrol is synthesized in the leaf epidermis and the skin (pericarp) of grape berries, but not in the flesh [29] (Table 1). It can also be synthesized in lignified plant tissues, such as stalks and kernels of the berries [30]. In the grape species, this polyphenol reaches concentrations of 50-400 μg/g fresh weight in the leaves [31]. Subsequently, the amount of resveratrol varies considerably in different types of grape juices and wines depending on the grape variety, environmental factors in the vineyard, juice extraction and wine processing techniques. In grapes and wine, resveratrol presents both as free resveratrol and piceid, which is a stilbenoid glucoside (3 β-glucoside of resveratrol), a major resveratrol derivative in grape juices [32,33].

The concentrations of resveratrol in red wine and fruit juices have been detected by using high-performance liquid chromatography (HPLC) and highly sensitive fluorimetric detection method (Table 2) [33-40]. The different concentrations of resveratrol in the red and white wines may be due to the different fermentation procedures followed with the wines. In particular, red wine requires a long contacting time between the berry skins, whereas white wine is immediately separated from berry residues after mashing [41]. Recent studies have shown that total resveratrol and piceid levels in wines could vary from 0 to 25000 μg/L [42].

Other than wines, fruit juices can also be a good source of resveratrol. The level of free resveratrol is rather low in grape juice in which cis- and trans-piceid are the major derivatives of resveratrol [41]. One study performed by Wang et al. investigating the concentration of resveratrol in different fruit juices found that resveratrol could be detected in grapes and cranberry juices [43]. Further studies found that concentrations of resveratrol were found to be similar in cranberry and grape juice at 1.07 and 1.56 nmol/g, indicating that cranberry may serve as an alternative dietary source for resveratrol and the form of resveratrol in it was present primarily as trans-resveratrol. Initially,

Natural sources of resveratrol	Scientific Name	Location	Reference
Grapes	Vitis vinifera	Skin	[29]
White hellobore	Veratrum grandiflorum	Roots	[14]
Muscadine	Raubinea sp	Skin	[160]
Ko-jo-kon	Polygonum cuspidatum	Roots	[15]
Cranberry	Vaccinum sp	Skin	[155-157]
Mulberry	Morus rubra	Skin	[158]
Peanut	Arachis hypogea	Fruits	[154]
Blueberry	Vaccinium myritillus	Skin	[155-157]

Table 1: Potential sources of resveratrol.

Sources	Concentration of resveratrol*	References
Red wine	1.5- 5.0 mg/L	[33-38]
Rose wine (Spanish)	0.07-1.06 mg/L	[34]
White wine (Spanish)	0.011-0.547 mg/L	[34]
Red wine (Slovenian)	0.9-8.7 mg/L	[33]
White wine (Slovenian)	0.6 mg/L	[33]
Grapes juices	0.003-0.15 mg/L	[40]
Grapes juices	0.69-14.5 mg/L	[41]

*As determined by HPLC and highly sensitive fluorimetric detection.

Table 2: Concentrations of resveratrol in red wine and fruit juices.

resveratrol used for all the studies was derived from plant sources and it was hard to get an optimal yield, which may affect the quantity as well as quality of research on resveratrol thus true research for resveratrol started after its organic synthesis.

Characterization and analysis of resveratrol: Resveratrol (3, 4', 5 trihydroxystilbene) in nature exists in two isomeric forms, cis- and trans-isomer. The trans-isomer is the most dominating form of resveratrol, which is present in grapes extracts [44,45]. Resveratrol was identified from its UV-spectral characteristics and infrared absorption peaks in the range of 2800 to 3500 cm^{-1} (OH band) and at 965 cm^{-1} (Trans form of the double bond) by Jeandet et al. [31]. Trans-resveratrol (MW = 228) is now commercially available and the cis-form of resveratrol can be obtained by UV irradiation [45,46]. It was found that trans-resveratrol is stable for several months under the condition when protected completely from light. The values for molar absorptivity are: trans resveratrol [$UV_{\lambda max}$(EtOH) nm (ε) 308 (30000)], cis-resveratrol [$UV_{\lambda max}$(EtOH) nm (ε) 288 (12600)] [47].

Several methods have been developed to analyze the biological properties of resveratrol, which are mainly based on HPLC and gas chromatography (GC) coupled with mass spectrometric (MS) detection. Generally, HPLC methods use a C_{18} reverse phase column to detect the trans- and cis-resveratrol absorbance at 307 and 280 nm, respectively [45]. To determine the contents of resveratrol and pterostilbene (an analogue of resveratrol) in grapes, berries and wine, the highly sensitive fluorimetric method is used, which is more specific than the UV detection method [48].

Biometabolism and bioavailability of resveratrol: To date, the information relating to the biometabolism and bioavailability of resveratrol is questionable. *In vivo* studies in mice, rats, and dogs suggested consistently that resveratrol is satisfactorily absorbed and distributed in the bloodstream which can be concentrated in the blood and a number of organs [49]. It is rapidly metabolized by modifications

of glucuronidation and sulfation both in the liver and intestinal epithelial cells [49-54]. Studies performed by Meng et al. [55] found that more than 90% of total resveratrol, given as pure aglycone or as constituent of grape juice, circulated in the plasma in the conjugated forms. Similarly, Marier et al. [56] analyzed the pharmacokinetics as well as bioavailability of resveratrol in its aglycone and glucuronide forms and observed that there was a sudden decline of aglycone in plasma after intravenous administration with a rapid elimination half-life ($T_{1/2}$, 0.13 hrs), and a sudden increase was followed in plasma after 4-8 hrs of drug administration. With respect to resveratrol's bioavailability, the aglycone form was found to be 38% when administered orally because of extensive first-pass glucuronidation in the liver and intestine, and the enterohepatic recirculation contributed to the overall systemic exposures of aglycone and glucuronide forms of resveratrol in rats. Preclinical studies in rats showed that plasma peak levels were obtained after 5–10 min of oral administration of resveratrol, rendering a rapid plasma elimination half-life of 12-15 min [57]. This suggested that glucuronidation predominates the metabolic form of resveratrol [58,59], with a small contribution by sulfation, using *in vivo* studies in the rat. However, the metabolic pathway of resveratrol in humans is not yet clear.

To further determine the cellular transportation and metabolism of resveratrol in humans, Kaldas et al. [24] studied resveratrol in the human intestinal epithelial cell line, Caco-2. The concentration of resveratrol used for this study was 5–40 μM and the authors reported that resveratrol may show an increased intestinal absorption *in vitro* but with a relatively low bioavailability which could be due to extensive metabolism. Further metabolic studies demonstrated contrasting results, suggesting that sulfate conjugation was the major pathway for resveratrol in the Caco-2 cells and probably also in humans.

The efficiency of a therapeutic substance is related to its capacity to bind protein transporters. The transportation and distribution of resveratrol throughout the human body still remains a mystery. In order to be effectively transported across the cellular membrane, resveratrol must be bound to proteins and/or conjugated to certain molecules to remain at a high concentration in the serum as a consequence of its low water solubility [60,61]. Hence, in order to determine the relationship of resveratrol intake and its effect *in vivo*, it is necessary to determine its interaction with plasma and the cellular uptake. In plasma, resveratrol was shown to interact with lipoproteins. To further strengthen these findings, an *in vitro* study was performed by Leila et al. indicating that an increased concentration of stilbene and resveratrol was more associated with lipoproteins rather than with lipid-free proteins depending on the concentration of lipid content in plasma. Further, it was found that albumin protein appeared to be one of the serum proteins to transport resveratrol in blood which delivers it to the cell surface and finally allows its intracellular biological effects. With respect to resveratrol's intracellular targets, Jannin et al. [62] also proposed a hypothetical schematic representation suggesting that resveratrol transported in blood was relatively low via passive diffusion. It was more dominated by carrier-mediated diffusion through albumin and resveratrol-albumin complex which was retained by albumin membrane receptors and thus resveratrol would then be delivered to cell membrane. But it only occurs with the transportation of the unconjugated form of resveratrol. In terms of resveratrol's distribution, it is reclaimed mainly in liver and kidney, but also in other tissues such as colon, lung, heart and brain [54,63]. However, it is still uncertain how resveratrol reaches the target organs *in vivo* after oral ingestion, especially in humans.

Pathological effects of resveratrol

Anticancer effects of resveratrol: Besides the protective effects on diabetes, acute pancreatitis and cardiovascular diseases [20,21,25-27], resveratrol can affect the processes underlying all stages of carcinogenesis, involving tumor initiation, promotion and progression. It has also been shown to suppress angiogenesis and metastasis in various tumors. In the past few years, plant-derived pharmaceuticals have come to the forefront of anticancer therapy research, and many are currently under critical evaluation for their clinical utility and efficacy [64-66]. Resveratrol has been shown to exhibit significant chemopreventive and chemotherapeutic activities both *in vitro* and *in vivo* [67,68]. Potential anti-carcinogenic targets of resveratrol may involve inhibition of activator protein 1 (AP-1) and nuclear factor-kappa B (NF-κβ) pathways, modulation of intracellular reactive intermediates, down-regulation of survivin, activation of p53 and suppression of cyclooxygenase 2 (COX-2) overexpression [66,69-71], and affecting the cellular cycle resulting in cellular growth inhibition and apoptosis in tumor cells (Table 3) [72-74].

Apoptosis is a programed cell death, which maintains a regulation between cell death and cell proliferation and results in tissue homeostasis. However, an imbalance between cell death and proliferation may result in tumor initiation [75]. According to studies by van Ginkel et al. [76], elevated levels of resveratrol led to tumor suppression, associated with massive tumor cell death. There are many possible ways in which resveratrol may affect apoptosis processes including direct and indirect effects on apoptosis and the cell cycle. The direct effects of resveratrol in regulation of apoptosis and the cell cycle involve the regulation of apoptosis-related genes such as Bcl-2 and BAX and the indirect effects may involve modulation of transcription factors such as HSF-1, NF-κβ, p53. The underlying mechanism of resveratrol in inhibiting tumor

Molecular target of resveratrol	Expression changes by resveratrol treatment	Cellular responses by resveratrol treatment	References
NF-κβ	Down-regulation	Result in apoptosis and cell cycle arrest	[81,159]
p53	Up-regulation	Induce apoptosis	[80]
HSF-1	Down-regulation	Inhibit expression of survivin	[99]
AP-1	Down-regulation	Cell cycle G1 arrest	[159]
hTERT	Down-regulation	Inhibit telomerase activity	[97]
Bax	Up-regulation	Induce apoptosis	[78,79]
Bcl-2	Down-regulation	Induce apoptosis	[77,79,81]
SIRT1/Sir2	Up-regulation	Result in de-acetylation of key genes	[104,114,122]
Survivin	Down-regulation	Result in apoptosis	[98]

Table 3: Different molecular targets of resveratrol.

cells may involve direct activation of mitochondrial intrinsic apoptotic pathway [77]. Studies have shown that resveratrol induced caspase-independent apoptosis through down-regulation of Bcl-2 and NF-κβ *in vitro* and *in vivo* [78]. In addition, resveratrol-induced apoptosis can also be mediated by down regulation of Bcl-2 and up-regulation of Bax, which is directly associated with apoptosis [78,79]. In human breast cancer cells such as MCF-7 and MDA-MB-231, treatment of resveratrol resulted nuclear accumulation of the COX-2 and phosphorylation of p53 resulting in apoptosis in breast cancer cells [80].

The other important anti-cancer mechanism of resveratrol is its indirect effect on regulation of transcription factors that mediate inflammatory reactions, which especially includes nuclear factor NF-κβ and AP-1. Resveratrol interferes with the activation of these critical transcription factors contributing to cancer inhibition [21]. TNF (tumor necrosis factor) has been shown to mediate tumor initiation, promotion and metastasis through activation of transcriptional factors such as NF-κβ. NF-κβ controls certain immune and inflammatory responses and has capacity to regulate multiple cellular pathways. For example, NF-κβ can inhibit apoptosis, increase cell proliferation and inflammatory responses and regulate immune response and stress responses as well as many other cellular processes. Recent evidence suggested that activation of NF-κβ contributed to development of several types of human cancers [65,80,81]. It has been observed that resveratrol blocks TNF -induced NF-κβ activation and suppresses TNF-induced phosphorylation and nuclear translocation of the p65 subunit of NF-κβ [82]. NF-κβ could also be activated by histone acetylation during tumorigenesis. Resveratrol can decreases NF-κβ expression via its de-acetylation mechanism mediated by SIRT1, a mammalian homologue of yeast silent information regulatory Sir2, which has an enzymatic activity of nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases. Other than its effect on histone acetylation, resveratrol also suppressed constitutively active NF-κβ through inhibition of I-κBa kinase. I-κBa are also called as IKK, it usually phosphorylates two serine residues located in an IκB (family of inhibitory of κB) regulatory domain, thus break the inhibitory complex of NF-κβ and set NF-κβ free to enter the nucleus to turn on the expression of specific genes leading to down-regulation of various proliferative and anti-apoptotic genes such as cyclin D1, survivin, Bcl-2, Bcl-xL, Bfl-1/A1, and TNF receptor-associated factor 2, TRAF2 [83-85]. Recent studies performed by Benitez et al. [86] showed an anti-proliferative and anti-apoptotic effects mediated by resveratrol through its inhibitory effects on NF-κβ expression in human prostate cancer cells. In one of these studies performed in human breast cancer MCF-7 cells, resveratrol suppressed NF-κβ activation and inhibited cellular proliferation at the S-G2-M phase of the cell cycle [38]. Other than its effect on NF-κβ resveratrol can also suppress AP-1, a dimeric transcription factor that plays a critical role in carcinogenesis and tumor transformation, leading to G1 cell cycle arrest which was accompanied with remarkable inhibition of G1 cell cycle-regulatory proteins, including cyclins A and D1 and cyclin-dependent kinase (CDK)-6, with up-regulation of $p21^{WAF1}$ (a CDK inhibitor) [62,87-90].

Resveratrol is also found to exhibit as an estrogen analog that can bind to both α- and β-estrogen receptors [91]. Thus, in mammary cancer cells, the effect of resveratrol on inhibition of apoptotic signaling and cell cycle may be due to its estrogen modulatory effects [92-94]. Besides its estrogen-modulating activities [95], resveratrol interferes with an estrogen receptor-associated phosphoinositide 3-kinase (PI3K) pathway and acts as an agonist for the cAMP/kinase protein a system [96].

In addition to its effects on a number of transcription factors, regulation of cell cycle and apoptosis, resveratrol can also inhibit telomerase activity. Telomerase is a ribonucleoprotein polymerase enzyme and is elevated in ~90% of cancers. The growth inhibitory effect of resveratrol on malignant cells was associated with reduced levels of telomerase activity. Previous studies showed that resveratrol treatment down-regulated telomerase activity and the nuclear levels of human telomerase reverse transcriptase (hTERT), a catalytic subunit of enzyme telomerase [97,98].

Survivin is one of the members of apoptosis-inhibitory proteins. It is expressed at high levels in most human cancers and may facilitate evasion from apoptosis and aberrant mitotic progression. Survivin expression can be down-regulated by resveratrol through transcriptional and posttranscriptional mechanisms. Other possible mechanisms by which resveratrol shows its effect on inhibition of cancer cell growth can be due to down-regulation of heat shock factor 1 (HSF-1). Cancer cells are under a state of stress and there is an increased level of HSF-1 phosphorylation, resulting in increased level of heat shock proteins or so called stress proteins such as HSP-90 and HSP-70. In addition, these proteins stabilize the production of survivin. Resveratrol-induced cell cycle arrest and apoptosis was associated with down-regulation of survivin expression, which was a result of inhibition of nuclear translocation of phosphorylated-HSF-1 by resveratrol [99].

One of important antitumor effects of resveratrol is mediated through its modulation of p53. p53 is a key tumor suppressive protein, encoded by the TP53 gene. The main function of p53 is to regulate the cell cycle and repair DNA damage during mitosis. Resveratrol can induce apoptosis through activation of p53 expression [100]. In prostate cancer cells, resveratrol can induce apoptosis by phosphorylation of p53 [101]. The effects of resveratrol inhibiting various tumor cell lines, but not normal human cells, suggest an important chemotherapeutic potential of resveratrol for human cancers. Thus by reviewing a number of *in vitro* and *in vivo* studies, we can conclude that resveratrol has excellent anti-cancer properties that could potentially combine with either a chemotherapeutic drug or cytotoxic factors leading to highly efficient treatment of human cancer cells.

Anti-aging effects of resveratrol: Over time, it has become increasingly clear that resveratrol, a plant-derived polyphenolic compound, displays an impressive therapeutic potential against cancer, cardiovascular, inflammatory diseases, diabetes as well as neurodegenerative diseases. In additional to the above therapeutic effects of resveratrol, recent studies have shown that resveratrol induced stress resistance and longevity in a variety of organisms, such as yeast, invertebrates and mammals [102,103]. This property of resveratrol may be due to its effect on sirtuin (SIR, silent information regulator) family and thus can act as a sirtuin activating compound (STAC's). Sirtuin family has shown to have NAD^+-dependent histone deacetylases enzymatic activity [104,105].

There are a number of factors which contribute to aging processes. The primary contributor of aging is oxidative stress during normal metabolism [106]. Oxidative stress that results from normal metabolism is often intensified by a wide variety of factors including food metabolism [107], environmental toxins exposure [108] and infection [109]. The reactive oxygen species (ROS) and reactive

nitrogen species (RNS), which are generated during the metabolic processes, have the capacity to rapidly oxidize, and thus damage many important molecular structures in cells [110]. ROS has been shown to greatly contribute to age-related changes through destruction of all types of organic molecules including proteins, lipids, carbohydrates, and DNA [110,111]. It is the accumulative effects of these oxidation reactive compounds on the cellular components which partially contribute to cellular senescence [112].

It is well-established that reducing food intake (caloric restriction) extends lifespan in a wide range of species, from yeast to mammals. In yeast, the sirtuin (Sir2) gene mediates the life-extending effects of calorie restriction (CR) by nutrient withdrawal [113]. The same effect has been seen as a result of resveratrol treatment, -inducing over-production of the Sir2 that resulted into lifespan extension in yeast under normal condition [114]. The Sir2 gene belongs to a large family of evolutionarily conserved molecules termed SIRs, which has enzymatic activity of NAD^+-dependent histone and/or protein deacetylases [115,116]. Sir2 is known to regulate a wide range of cellular activities which involves gene silencing, DNA repair and DNA recombination [117-120], and to affect a number of molecular targets, which collectively influence lifespan in lower organisms, such as yeast and worms [73]. On the other hand, the mechanisms through which SIRs affect mammalian aging are not yet known, although recent investigations indicated that in mammalian cells SIRs appeared to act as regulators of programmed cell death and cell development [121]. In one of the studies performed by Howitz et al. [122], it was reported that resveratrol could extend lifespan in yeast, emphasizing the potential of resveratrol as an anti-aging agent on treatment of age-related human diseases through stimulation of SIRT1 activity. SIRT1 is a mammalian homologue of Sir2. It was also indicated that resveratrol was found to mimic CR-induced lifespan extension by activating Sir2 and thus the anti-aging function of resveratrol may be related to CR processes [104,122]. In order to determine the strength of resveratrol on SIRT1 stimulation, it was compared with other SIRT1 activators such as piceatannol, fisetin and quercetin and it was found that resveratrol decreased the Michaelis constant of SIRT1 to a greater extent and thus could possibly act as a more potent SIRT1 activator than the other tested compounds. SIRT1 can also cause deacetylation of lysine 382 of p53 and thus negatively affect the activity and half-life of p53 resulting in increased cell survival [123-125].

There is an increase in fat accumulation leading to an increased risk of obesity, atherosclerosis and inflammatory diseases during aging [126]. Adipogenesis was stimulated by activation of nuclear receptor peroxisome proliferator-activated receptor (PPAR) -γ. PPARs are a group of nuclear receptors proteins that function as transcription factors regulating gene expression [127-129]. Three isoforms of PPARs have been identified and all of these are encoded by separate genes: PPAR-α [NR1C1], PPAR-β (NUC-1 or PPAR-δ) [NR1C2] and PPAR-γ [NR1C3] [130]. These isoforms are homologous in structure and three-dimensional conformation, with only a few modifications. PPARs affect several pathophysiology processes such as obesity, diabetes, immune responses, aging, atherosclerosis and inflammatory response [130,131]. Picard et al. reported that SIRT1 modulated adipogenesis and fat mobilization in white adipocytes of mouse 3T3-L1 fibroblasts. To determine the effect of SIRT1 on fat cells, it was found that over-expression of SIRT1 attenuated adipogenesis by repression of PPAR-γ. In differentiated fat cells, up-regulation of SIRT1 triggered lipolysis and fat metabolism. Studies have indicated that resveratrol caused a strong fat reduction at concentrations of 50 and 100 μM in mouse 3T3 L1 cells due to activation of SIRT1 [130]. Therefore, resveratrol caused similar effects induced by CR in that increased SIRT1 resulted in a decrease in fat mass, reduced metabolism along with decreased expression of PPAR-γ. As a result, this effect on fat metabolism leads to aging delay and longevity [126].

Another highly studied molecular target of resveratrol is chaperones. Molecular chaperones are ubiquitous, highly conserved proteins that are responsible to maintain the cellular homeostasis. They play an important role in non-covalent folding, unfolding, assembly and disassembly of protein molecules. They also prevent the aggregation of nascent protein into non-functional structure, confer cytoprotection and assure survival after environmental stress. Chaperone induction is mediated at the transcriptional level. During aging there is an increase in proteins mis-folding resulting in a release of HSF-1 from the chaperon inhibitory complex and subsequent transcriptional activation of various heat-shock genes. It has been reported that HSF-1 overexpression induces a twofold life-span extension, whereas HSF-1 knockout markedly shortens the life-span [132-134]. It is also seen that during aging there is an increase in protein toxicity and cellular degeneration with a decrease in chaperone function [135-137]. The importance of molecular chaperons was determined since pharmacologic chaperone inducers were shown to be an efficient therapeutic approach in different acute and chronic diseases. Resveratrol activates heat-shock promoter and induces chaperone expression such as Hsp70 in different cell lines [138]. Putics et al. [139] also showed that resveratrol activated stress response in a way similar to that of mild to moderate heat shock protein up-regulation against a lethal heat shock.

Resveratrol is known to show hormetic properties [140]. Hormesis is a term used by toxicologists which describes a bi-phasic dose–response phenomenon characterized by low-dose stimulation and high-dose inhibition. Similarly to resveratrol, a number of other phytochemicals such as EGCG, sulforaphane, piceatannol and ferulic acid are known to show hormesis [141]. However, it is still hard to extrapolate this effect of resveratrol on the human lifespan, especially when the studies on yeast used much higher concentrations of resveratrol than is available from wine consumption [142] as well as its poor bioavailability after metabolism [53]. Therefore, the link between resveratrol consumption and longevity is still not proven in humans.

Pterostilbene, a new resveratrol: Despite of its effective results on cancer cells, there are several reports indicating that resveratrol showed less effect on inhibiting tumor growth in animal models. Therefore, the function of resveratrol in mammals still remains a mystery. Recent studies using a resveratrol analogue, pterostilbene, showed important biological properties including anti-inflammatory, anti-allergenic, anti-aging, anti-mutagenic, anti-carcinogenic and other activities [143-147]. Pterostilbene (3, 5-dimethoxy-4-hydroxystilbene), found in blueberries, grapes and in bark of Indian kino tree, has been used for centuries in Ayurvedic medicine. This compound has antioxidant

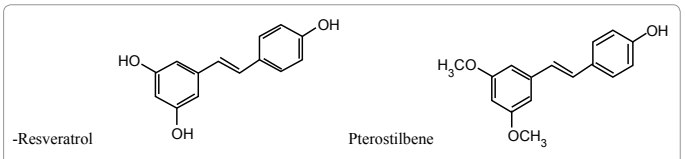

Figure 1: Structures of resveratrol and pterostilbene. Pterostilbene is a structural analogue of resveratrol with two methoxy groups. These two methoxy groups may provide pterostilbene a better bioavailability as compared to resveratrol.

capacity equivalent to resveratrol and is considered to be a powerful chemopreventive agent in inhibiting growth of cancer cells [148]. Pterostilbene has an increased oral absorption, a higher potential for cellular uptake and a reduced rate of elimination from the body as compared to resveratrol [149]. One of the studies determining the bioavailability and half-life of pterostilbene indicate that when administered orally, pterostilbene shows 95% bioavailability whereas resveratrol only has 20% bioavailability. In addition, it was found that resveratrol's half-life in the blood is approximately 14 minutes [59,150], whereas pterostilbene with the two methoxy groups (Figure 1) has a half-life of approximately 105 minutes, which is seven times longer than resveratrol [151].

When resveratrol and pterostilbene are used in combination, a synergistic effect can occur. An *in vitro* assay was set up to measure the ability of pterostilbene and resveratrol to protect human erythrocytes from damage caused by an oxidative stressor [152]. The results revealed that the combination of pterostilbene and resveratrol showed better effects than either of these compounds acting alone [152,153]. The combination of resveratrol and pterostilbene may exhibit complementary mechanisms affecting cancer and aging [153]. This harmonization could be obtained when resveratrol may primarily mediate upstream genes of interest and pterostilbene may mainly regulate downstream sites where resveratrol also acts; thus by doing so, these two compounds may affect a wide range of disease-preventing genes [153]. The way in which resveratrol and pterostilbene act on gene expression is an exciting area of biomedical research, since these two compounds exhibit a similar cellular effect. However, these compounds may act at different regulatory locations of gene control [104,122,153]. In summary, these two phytonutrients can likely complement one another which could be applied for future disease chemoprevention and therapeutic purposes.

Conclusion

A number of studies have focused on investigating resveratrol and its beneficial effects on neurological diseases, cardiovascular diseases, inflammatory diseases, diabetes and cancer. This review article highlights the clinical potential of resveratrol on its anticancer and anti-aging potential. Resveratrol exerts its effects on a number of molecular targets such as transcription factors, and key regulatory genes that control important cellular physiological processes thus impacting cancer and aging development. This study indicated that the effective concentration of resveratrol may vary in different cells and organs and clinical studies are urgently needed to verify the precise dosages of resveratrol for specific therapeutic purposes. We also discuss some limitations of resveratrol with respect to its low bioavailability and short half-life in blood and provide insight into the use of pterostilbene, an analogue of resveratrol. Pterostilbene might have a better potential for therapeutic purposes on cancer and age-associated diseases compared to resveratrol. Combined use of resveratrol and pterostilbene may provide an effective therapeutic approach in cancer and age-related diseases.

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