



Benefits of Resveratrol and Pterostilbene to Crops and Their Potential Nutraceutical Value to Mammals

Stephen O. Duke D

Review

National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University, MS 38677, USA; sduke@olemiss.edu

Abstract: Resveratrol and its dimethoxylated derivative, pterostilbene, are produced by several plant species, including a few edible crops such as peanut (*Arachis hypogaea* L.), grapes (*Vitis* spp.), and blueberries (*Vaccinium* spp.), as well some plants used in traditional medicine. Both compounds are inducible, antimicrobial compounds with activity against both plant pathogenic bacteria and fungi, an activity apparently not directly related to their strong antioxidant activity. An amazing number of nutraceutical properties have been claimed for both compounds, including antioxidant, antiaging, anti-cholesterol, anticancer, antidiabetic and other beneficial activities. Most evidence supports the view that pterostilbene is more active for most of these effects, due in part to its greater biological availability. However, the amount of these compounds in most diets is insufficient to provide these health benefits. Dietary supplements of formulated pure compounds can now provide sufficient dietary levels for these effects, as transgenic crops in the future might also do.

Keywords: dietary supplement; elicitor; natural fungicide; nutraceutical; pterostilbene



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1. Introduction

Stilbenes, such as resveratrol (3,5,4'-trihydroxystilbene) and its methoxylated derivative, pterostilbene (3',5'-dimethoxy-reseveratrol) (Figure 1), are products of the plant phenylpropanoid pathway that are synthesized by several plant species, including crops used in the human diet and as plants used in traditional medicine. Monomeric and oligomeric stilbene compounds as well as glycosylated forms are found in a wide range of taxonomically diverse plant species, some of which include human and animal food crops [1,2]. Resveratrol and pterostilbene are mostly found in the *trans* rather than the *cis* form, and this review refers to the *trans* forms unless otherwise specified. There are a number of reviews on these phytochemicals that discuss their chemistry and biosynthesis [3], topics that will not be dealt with in detail in this brief review. Instead, the focus of this review is on the two stilbenes in food that have been most implicated in human health effects, resveratrol and pterostilbene. There are tens of thousands of papers on these closely related compounds, more than on almost any other nutraceutical.



Figure 1. Resveratrol and pterostilbene.

A point that will be repeated several times is that most research on these compounds has been on resveratrol, with little recognition that pterostilbene is likely to be a more biologically active molecule, both for the plant as an antimicrobial and for humans as a nutraceutical. In most cases discussed below, where biological activity of the two have been compared, pterostilbene is more active. The difference in bioavailability is apparently largely due to the greater log*P* value of pterostilbene (4.1), compared to that of resveratrol (3.1) [4], which allows pterostilbene to cross membranes more readily than resveratrol and to more readily access other lipophilic cellular domains. Furthermore, there is some evidence that pterostilbene is not metabolized or excreted in humans as quickly as resveratrol [5–7], although the rate of metabolism is not clearly linked to bioavailability. The relative paucity of literature on pterostilbene is probably mostly due to its relatively low concentrations in food compared to resveratrol (see Section 3); however, the literature on potential health benefits of pterostilbene is growing rapidly.

This review will attempt to point out the gaps in our knowledge regarding the function of these two stilbenes in plants and their nutraceutical properties. A recent review briefly covered these topics, as well as others [8]. This review will update their coverage and discuss the topic from a somewhat different point of view.

2. Resveratrol and Pterostilbene Biosynthesis

The biosynthesis of these two stilbenes is briefly summarized to support later discussion. Both compounds are phenolic compounds produced from either phenylalanine or tyrosine, products of the shikimate pathway (Figure 2). These two amino acids are converted to coumarate and then to *p*-coumaryl-CoA, from which both stilbenes and a large number of other secondary products (e.g., flavonoids and lignins) are derived. Stilbene synthase converts this precursor to resveratrol, and an *O*-methyl transferase is required to methylate two of the resveratrol hydroxyl groups of resveratrol to form pterostilbene. Chong et al. [3] provide more detail on stilbene synthesis.



Figure 2. Biosynthetic pathway for resveratrol and pterostilbene and its relationship to other secondary products of the shikimate pathway.

3. Resveratrol and Pterostilbene in Food Crops

Both compounds have been found in a large number of taxonomically unrelated plant species [2,8], a few of which are found in human diet crops (Table 1).

Crop/Food	Resveratrol	Pterostilbene	References
Peanut (Arachis hypogaea)	Peanut butter 0.15–0.50, 0.3 Boiled peanuts 1.8–7.9 Roasted peanuts 0.02–0.08	- - -	[9,10] [9] [9]
Grape (Vitis) species berries	viniferaa L. 2.5–6.4 rotundifolia Michx. 1–10	6.47 0.1–1	[11] [12]
<i>Vaccinium</i> species (berries)	augustifolium Ait. 0.86 arboretum Marshall 0.3–0.52 ashei Reade 0.08–1.69 corymbosum L. 0.30–1.08 macrocarpon Ait. 0.90 stamineum L. 0.05–0.50 vitis-idaea L. 5.8 myrtillus L. 0.77 elliottii Chapm. 0.41–0.45	- 0.15 - 0.52 - - -	[11] [11] [11] [11] [11] [11] [11] [11]
Mulberry (Morus rubra L.) berries	51 32.5	-	[13] [14]
Artocarpus heterophyllus Lam. fruit	skin 3.56 pulp 0.87	-	[13] [13]
Itadori (<i>Polygonum cuspidatum</i> Sieb.et Zucc.) root	523	-	[13]
Jamun (<i>Syzygium cumini</i> (L.) Skeels.) seed	35	-	[13]
Pistachio (Pistacia vera L.)	0.09–1.67	-	[15]
Strawberry (<i>Fragaria</i> x <i>ananassa</i> Duchesne) berries	0.20	-	[16]
Date (<i>Phoenix dactylifera</i> L.) fruit	3.0	-	[16]
Tomato (<i>Solanum lycopersicum</i> L.) fruit	0–2.1	_	[16]

Table 1. Resveratrol and/or pterostilbene concentrations in some food crops and foods derived from these crops. All values are $\mu g/g$ dry wt. A dash (-) means that this value was not provided.

They are also found in plants used in traditional medicines, such as the genus *Dracaena* [17], although these sources will not be discussed. The amounts reported found are extremely variable within a species, which can be due to many factors, both genetic and environmental. For example, UV light can increase resveratrol levels in grapes manyfold [18,19]; however, the effect on pterostilbene content was minimal in one study [19]. Fungal infection elicits production of both compounds [20]. A recent review [21] catalogues the many environmental factors that can enhance stilbene synthesis.

In addition to the foods listed in Table 1, low concentrations of resveratrol have been reported in cherry fruit skin (*Prunus laurocerasus* L.) [14], potato [*Solanum tuberosum* L. [14], and raspberries (*Rubus idaeus* L.) [14]. Rhubarb species (*Rheum* spp.) have been reported to contain 35 stilbenes, including resveratrol in very low concentrations [22]. Peng et al. [23] reported resveratrol in low concentrations in a large number of different fruits and vegetables, although its glycosylated form (piceid) was more often found, and samples of the same species from different regions of China varied widely in concentration and even whether resveratrol was found at all. Considering the great interest in resveratrol and pterostilbene as nutraceuticals, the lack of papers on the content of both compounds in fresh and processed food products using standardized extraction and analytical methods is surprising.

The concentrations of resveratrol and pterostilbenes are generally higher in the fruit skins or epidermal tissues of plants [13], as one could expect for compounds involved in protection of the plant from harmful microbes that must penetrate the plant epidermis to infect.

Relatively few studies that have reported resveratrol in plants have looked for pterostilbene, but when it has been reported, it is often, but not always, found in lower amounts than resveratrol (Table 1) Resveratrol is the non-methylated form of pterostilbene and the non-glycosylated form of piceid (resveratrol 3- β -mono-D-glucoside), and all three can be present in plant tissues that produce resveratrol. Indeed, the glycosylated form of resveratrol is predominant in wine and Itadori root [10]. The relatively lower concentrations of pterostilbene reported could be due in part to an artifact of the extraction method. It is possible or even probable, depending on the extraction procedure, that the methylated and/or glycosylated forms of resveratrol could be enzymatically demethylated or deglycosylated during extraction, as has been found with other secondary phytochemicals such as podophyllotoxin [24].

Higher levels of resveratrol and pterostilbene can be generated in plants treated with certain chemical elicitors of plant immune responses. For example, treatment of grape (*V. vinifera*) plants with methyl jasmonate increased the content of resveratrol and piceid, but not pterostilbene [25]. Likewise, the well-studied plant immune response elicitor, chitin, elicits resveratrol production by peanut callus tissue [26]; however, I have not found that this elicitor has been used in the field to induce resveratrol and/or pterostilbene production in peanut plants. Treatment of plants with an appropriate environmental stimulus, such as UV irradiation [27], can be used to increase stilbene production in crops. The extreme variability of both resveratrol and pterostilbene caused by environmental and developmental factors in a single plant genotype suggests that one cannot assume that a good dietary source of these compounds from crops grown under some conditions will be a good source from the same crops grown under other conditions.

Another approach to higher concentrations of resveratrol and pterostilbene in food plants is to transgenically alter phenolic metabolism in crops to impart or increase their production. The literature on transgenically imparting or increasing resveratrol in yeast and plants has been reviewed [28,29]. Different promotors and copy numbers of genes for synthetic enzymes can be used to generate different levels of production, production in specific plant tissues, and production at specific stages of plant development. Such transgenic plants are generally more disease resistant to plant pathogens than untransformed plants of the same genotype. There have been few negative pleiotropic effects of such transgenes reported. When fed to mice (Mus musculus L.) that were on a metabolic syndrome-producing diet, rice (Oryza sativa L.) that was genetically engineered to produce resveratrol reduced the symptoms of this disease [30]. Less has been studied on imparting or increasing pterostilbene production in plants, but synthesis of pterostilbene was imparted to tobacco (Nicotiana tabacum L.) and Arabidopsis thaliana (L.) Heynh., two species that produce neither resveratrol nor pterostilbene, by transformation with a stilbene synthase transgene from peanut and an O-methyltransferase transgene from Sorghum bicolor (L.) Moench [31]. Imparting pterostilbene production into tobacco reduced flavonoid levels, which is expected, as synthesis of stilbenes and flavonoids compete for *p*-coumaryl-CoA (Figure 2). There were no other notable effects, nor on the growth and development of these transformed plants. Furthermore, pterostilbene production can be increased by metabolic engineering of crops that already produce the compound. For example, pterostilbene production in grape cells that were transformed with constitutively expressed V. vinifera O-methyltransferase was increased [32]. Considerable effort has been made to impart or improve production of both compounds in both plants and microbes by biotechnology [33,34]. A stilbene-synthesizing gut bacterium such as *Escherichia coli* (Migula, 1895) could be a means of providing animals with a constant supply of these stilbenes without their ingestion; however, similar transgenes to those that impart pterostilbene production in plants [31] result in the production of pinostilbene (resveratrol with only one hydroxyl

group methylated) in high amounts, but lesser amounts of pterostilbene in *E. coli* [35]. Such a transformant might not persist in the human gut.

4. Function of Resveratrol and Pterostilbene for the Plant

4.1. Antifungal and Antibacterial Properties

Both resveratrol and pterostilbene are toxic to plant pathogenic fungi and bacteria, providing protection to the producing plant as phytoalexins [36–41]. Pterostilbene is more fungitoxic than resveratrol, and some have considered resveratrol as a phytoalexin precursor to the more active pterostilbene [42]. Antibacterial studies are not as common with pterostilbene, but resveratrol is antibacterial against both Gram-positive and Gramnegative bacteria [43]. Pterostilbene is antibacterial against human pathogenic bacteria as well as toxic to human viruses, parasitic members of the order *Trypanosomatida* (*Leishmania amazonensis* Lainaon & Shaw and *Trypanosoma cruzi* Chagas), and to the parasitic nematode *Setaria cervi* Rudolphi [44–46]. Non-plant microbial pathogens are discussed in Section 5.2.

Plant pathogens stimulate (elicit) production of resveratrol and pterostilbene in grapes. For example, Sarig et al. [20] found *Rhizopus stolonifer* Vuillemin to elicit production of both compounds in grapes, with generally higher levels (4- to 8-fold) of resveratrol produced than pterostilbene. As berries matured, the capacity for elicitation of these stilbenes was reduced. They found a linear negative correlation between resveratrol elicited by UV radiation and infection of grape berries by *R. stolonifer*. Pterostilbene was more inhibitory in bioassays of germination and mycelial growth by *R. stolonifer* and *Botrytis cinera* Pers., but effective concentrations were higher in vitro bioassays for these than found in berries.

Spraying muscadine grape vines (*V. rotundifolia*) with commercial synthetic fungicides has been shown to result in much less resveratrol in skins of berries from the plants, presumably because of less fungi to induce production of this phytoalexin [47]. In addition to fungicide treatment, the amounts have been shown to vary considerably with cultivar; the concentrations were found to be higher in grape skins than in seeds, and levels in seeds were higher than in the pulp of the berry. Treatment with chemical elicitors to induce stilbene synthesis resulted in maximal levels of stilbenes in grapes without damage to the vines and fruit by pathogens [48]. If the elicitor is a natural compound such as chitin, this approach provides a synthetic pesticide-free product with enhanced levels of health-promoting phytochemicals.

Wang et al. [49] found that resveratrol, but not pterostilbene, synthesis is elicited by *Plasmopara viticola* Berk. & M.A. Curtis in the leaves of muscadine grapes (*V. rotundifolia*), but not in those of the Thompson seedless variety *V. vinifera*. This was attributed to induction of the resveratrol *O*-methyltransferase gene in the muscadine but not the Thompson seedless grape. Stilbene synthetase required for resveratrol synthesis is induced in both grapes by the pathogen.

The exact molecular target of pterostilbene in fungi is unknown, but transcript profiling of the fungal model yeast (Saccharomyces cerevisiae (Meyen ex E. C. Hansen, 1883)) has found that genes involved in methionine metabolism were significantly down-regulated in treated cells [50]. Additionally, transcription of a large number of genes involved in lipid metabolism were mostly upregulated, but some were downregulated. A primary target site of pterostilbene could not be determined from this study. Xu et al. [51] reported that pterostilbene up-regulates genes for laccase (fungal polyphenol oxidase) and increased laccase activity in B. cinera. At least some of the antibacterial activity of resveratrol may be due to antibiofilm activity and inhibition of expression of genes associated with quorum sensing [46,52]. Ren et al. [44] found reactive oxygen species (ROS) to increase and genes associated with cell wall synthesis to be downregulated by pterostilbene in E. coli and Staphylococcus aureus. They hypothesized that apoptosis is induced, but cell death by the mechanism that they described is not necessarily by apoptosis. My view is that all of these effects are probably secondary to a primary interaction of these stilbenes with one or perhaps two primary molecular targets. Bostanghardiri et al. [46] list a large number of biochemical effects of resveratrol on human pathogen bacteria and viruses, but provide no insight into primary effects from which these effects emanate. Proof of the primary effects of biocides is not trivial [53].

Clearly, the utilization of resveratrol and pterostilbene by the producing plant provides protection from fungal and bacterial plant pathogens. There are many patents on the use of resveratrol as an antifungal and/or antibacterial product [54].

4.2. Antioxidant Activity

Both resveratrol and pterostilbene are strong antioxidants [55]. Does the antioxidant activity of these compounds benefit the producing plant? Few papers have demonstrated their antioxidant activity in planta.

Plants produce a plethora of antioxidant compounds, as green plants produce molecular oxygen, and the reducing power of the photosystems can generate highly toxic ROS in abundance. The polyphenols of the shikimate pathway generate ROS quenchers other than the stilbenes, such as the flavonoids and even tocopherols derived from tyrosine. The antioxidant activity of quercetin, a common flavonoid, is as good as that of pterostilbene in an assay on human erythrocytes [55]. Severe plasma membrane damage to cucumber tissue from ROS produced by herbicide-caused accumulation of the photodynamic compound, protoporphyrin IX, was similarly inhibited by exogenously applied resveratrol, pterostilbene, and α -tocopherol [56]. The flavonoids and other strong, phytochemical antioxidants, such as the tocopherols, are more universally found in plants than stilbenes, but these compounds generally have no or very little antimicrobial activity. Thus, it is my view that the primary benefit of these compounds to the producing plants is as antimicrobial compound, especially because their production is largely induced by the presence of microbial pathogens.

5. Potential Nutraceutical and Pharmaceutical Value of Resveratrol and Pterostilbene

The amount of resveratrol and pterostilbene in the average human diet is quite low because of the limited number of food plants in which they are found, and the small concentrations found in foods and drinks derived from these plants (Table 1). Nevertheless, there has been considerable research over the past 25 years on the potential health benefits of these compounds, encouraged in part by the benefits of the Mediterranean diet, which includes red wine, with almost all of the emphasis placed on resveratrol. El Khawand et al. [57] concluded that, although it is difficult to generalize about the normal human consumption of stilbenes, wine is the primary source of stilbenes in the western diet, accounting for more than 98% of the intake. Rivière et al. [2] also conclude that the major dietary sources of stilbenes are the fruits of *Vitis* species and their derivatives (e.g., wine). The consumption of stilbenes from food can vary dramatically, even where wine is considered part of the diet. Dietary supplements of grape and blueberry-enriched preparations are available that could increase levels of resveratrol and/or pterostilbene to levels sufficient to provide health benefits.

Although the emphasis of the effects of stilbenes on human health has been with resveratrol, there is increasing evidence that pterostilbene may have more powerful effects [58], just as its activity as a phytoalexin is higher. As a result of numerous studies suggesting health benefits (discussed below), pure resveratrol and pterostilbene are sold as dietary supplements separately, together, or in combination with other dietary supplements (e.g., nicotinamide riboside) with many health benefit claims. Animal studies and clinical trials with high doses of resveratrol and pterostilbene have not identified any significant toxicity [58–60], although some harmful effects of high doses have been reported for resveratrol, and effects of long-term use and interactions with other pharmaceuticals have not been adequately studied [61].

As mentioned earlier, most of the literature supporting health benefits has been on resveratrol, but the growing literature to support better bioavailability, longer in vivo half-life, and stronger pharmacological activities of pterostilbene is making it clear that pterostilbene is a significantly more potent nutraceutical [62,63].

Koh et al. [64] and Liu et al. [65] provide recent detailed reviews of the potential health benefits of resveratrol and pterostilbene. The present short review will provide only a summary of pertinent literature on the different health claims for these compounds. I will begin with more general effects of the compounds that might be associated with more specific effects. Many of the reported effects, such as slowing of the aging process, are clearly due to several of the more specific effects. Most pharmaceuticals target a specific protein molecular target. The more general effects of these two compounds are probably due to interaction with one or more protein targets (discussed below), as well as to their antioxidant effects.

5.1. Antioxidant Effects

Many of the health claims of these compounds are insinuated to be due to their antioxidant properties, especially in the advertising for dietary supplements. Both resveratrol and pterostilbene are strong antioxidants [56,66], but many of the claimed health benefits are probably unrelated to this property of the compounds. Resveratrol is as good or a better antioxidant than most antioxidant food additives, such as butylated hydroxytoluene, butylated hydroxyacetone, and propyl gallate [66,67]. In several assays, pterostilbene is a similar or slightly more effective antioxidant than resveratrol [55,56]. There is no good evidence that antioxidants in foods provide health benefits, and in excess they could be harmful [68]. Clinical trials of the antioxidant vitamin E (a mixture of tocopherols and tocotrienols) have not clearly supported its health benefits [69]. Thus, the antioxidant effects of these two stilbenes may be irrelevant to their potential beneficial health effects, as there are several clearer primary beneficial effects discussed below.

5.2. Antimicrobial Properties

The toxic effects of resveratrol on the microbial pathogens of plants were discussed in Section 4.1. Likewise, these compounds are toxic to human pathogenic microbes, including fungi, bacteria, viruses, and even nematodes (reviewed in detail by Bostangharidi et al. [46]). Resveratrol and pterostilbene have been proposed for use in preventing contamination of food with human fungal and bacterial pathogens such as *Candida albicans, Staphylococcus epidermidis*, and *E. coli* [70]. There are claims that resveratrol and/or pterostilbene inhibit replication of influenza, middle east respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as other human viral pathogens [71–73]. The mode(s) of action against pathogenic microbes is/are unknown. These potentially beneficial antimicrobial effects are generally not considered to be associated with the health effects of ingestion of these compounds. However, pterostilbene fed to rats (*Rattus norvegicus* (Berkenhout, 1769) changed the gut microbiota in ways associated with reduced cardiovascular and neurogenerative diseases, as well as reduced diabetic syndrome [74].

5.3. Antiaging Effects

The general effects of resveratrol and pterostilbene on aging were recently reviewed in depth by Li et al. [75]. I would like to provide some history in this section. The seminal work of James Joseph found that feeding rats a blueberry-enriched diet reversed age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits [76,77]. The blueberry-enriched diet had a more beneficial effect on most metrics of aging than supplementation with extracts of any other fruit or vegetable tested. Later work by him and his collaborators, suggested that the memory enhancement in rats by blueberries was due to anthocyanins [78]. Effects of blueberries on improving neurofunctions in aging mice [79] were similar to those in rats. Grape juice diet supplementation had similar positive effects to those of blueberries [80]. The Joseph lab, perhaps inspired by the work of Rimando on pterostilbene in blueberries [11], found that pterostilbene was the most effective stilbene of six, including resveratrol, studied in reducing cognitive behavioral deficits associated with aging in rats [81]. Their results implicated pterostilbene in the beneficial effects of dietary blueberry and grape on loss of neuromotor and cognitive function in aging rats. Later work that included Rimando and Joseph reported that pterostilbene, but not resveratrol, fed directly to SAMP8 mice that are a model for accelerated aging and age-related Alzheimer's disease (AD), slowed the progression of both processes [82]. Some have claimed resveratrol provides protection from AD [83]. Markers of stress, inflammation, and AD pathology were improved by pterostilbene, and transcription factor peroxisome proliferator-activated receptor alpha (PPAR α) was upregulated by pterostilbene, but not by resveratrol. They concluded that diet-achievable doses of pterostilbene, and to a lesser extent resveratrol, can be a positive modulator of cognition and cellular stress, likely driven by increased PPAR α expression. The greater activity of pterostilbene was concluded to be due to its higher bioavailability in rodents than resveratrol. Kapetanovic et al. [84] found pterostilbene levels in blood plasma of rats orally fed with equimolar concentrations of resveratrol to be about 10-fold higher. Indeed, the physicochemical parameters of pterostilbene are closer to those of ideal pharmaceuticals [85], primarily due to its higher logP (lipophilicity), due to the two methylated hydroxyl groups. Despite the superior physicochemical attributes of pterostilbene over resveratrol, much of the literature until more recently focused on resveratrol, for example, compare [86] and [87].

5.4. Brain Function

Much of the aging process involves deterioration of brain function. Resveratrol and pterostilbene cross the blood-brain barrier and are reported to have several beneficial effects on brain function that may be more direct than indirect effects on such things as lowering cholesterol [88]. Many of the effects may be due to reduction of oxidative stress and inflammation causing damage to molecular components of the brain. Both compounds have been reported to reduce neuroinflammation and to modulate several signaling molecules involved in neuroinflammation in the brain or brain cells. Some of these effects are apparently due to upregulation of PPAR α [79]. Early work found resveratrol to slow neurogenerative diseases and to reduce effect of brain injury in mammals [89,90]. Joseph et al. [81] found pterostilbene to slow the loss of cognition resulting from aging in rats, and later research has verified this result [91]. Chang et al. [82] found pterostilbene, but not resveratrol to prevent loss of cognitive function in a mouse model for accelerated aging/AD, and Khan et al. [92] reported pterostilbene to provide some protection from certain types of brain damage. Pterostilbene has also been reported to reduce stressrelated abnormal behavior, neuroinflammation, and hypothalamic-pituitary-adrenal axis hyperactivity in mice [93], as well as ketamine-induced schizophrenia in mice [94]. Most of these effects have been at least partially attributed to the antioxidant properties of these stilbenes, but the positive effects on more specific processes, such as inflammation and cholesterol (see below) may be more involved.

5.5. Anticancer Effects

Resveratrol and pterostilbene, in particular, have been found to have anticancer properties in in vitro cell and animal models [95]. Pterostilbene appears to be more active than resveratrol. Both stilbenes prevent cancer and inhibit tumorigenesis and metastasis [94–96]. Positive effects have been reported for bladder, breast, colon, liver, lung, pancreas, prostate, stomach, and skin (melanoma) models, as well as leukemia cell lines [63,95–97]. Two reviews [95,96] summarize the literature on these cancer models, along with potential mechanisms of the effects. A major related effect appears to be the induction of apoptosis of cancer cells by pterostilbene [98]. Pterostilbene also regulates aberrant cellular mechanisms that are specific to cancer cells, as well as disrupting signal pathways that control tumorigenesis (listed in [65]) and metastasis [99].

5.6. Anti-Cardiovascular Disease-Associated Metabolic Effects

An ancient ayurvedic medicine, Drakshasava, used as a cardiotonic, contains both resveratrol and pterostilbene [100]. A major ingredient of this concoction is grape berries.

Cardiovascular disease is associated with high cholesterol, triglycerides, and blood glucose levels. Resveratrol and pterostilbene have been reported to reduce all of these [101–103]. For example, Rimando et al. [103] found both pterostilbene and a blueberry extract containing pterostilbene fed to hypocholesterolemic hamsters induced by an obesogenic diet to reduce low-density lipoprotein cholesterol levels. In the same study, pterostilbene was the only stilbene of several to activate the transcription factor PPAR α , an effect typical of pharmaceutical statins that lower cholesterol. A later study found the amount of pterostilbene in a blueberry preparation caused the same effect on PPAR α activation [104], indicating that the entire statin effect of the blueberry supplement was due to pterostilbene. Although some of the health benefits of blueberries have been attributed to anthocyanins, only resveratrol and pterostilbene activate PPAR α [105]. Molecular docking studies of pterostilbene and the ligand-binding domain of PPAR α found that it interacts with amino acids essential for activation [106]. This is the only clear link from a primary target of pterostilbene to a physiological effect. There is evidence that other PPAR α (PPAR γ and PPAR β/δ) that are involved in other metabolic effects are influenced by resveratrol and/or pterostilbene [107–109].

In rats fed a high fat and sucrose diet, a combination of resveratrol and pterostilbene were found to significantly reduce body weight [110]. Only pterostilbene prevented a dietcaused methylation pattern of a fatty acid synthase gene, but both decreased its expression. Similarly, resveratrol was shown to lower the weight of high fat diet-fed mice [109]. It downregulated PPAR γ expression in adipocytes, thereby inhibiting their differentiation. Activation of PPAR α can increase fat metabolism, and pterostilbene ingestion promotes metabolism [111]. Finally, pterostilbene complexed with a cyclodextrin, a controlled release formulation, improved cardiac function in a rat model for induced heart failure through modulation of calcium-handling proteins and a reduction of oxidative stress [112]. There appears to be multiple mechanisms by which pterostilbene can improve cardiovascular function. These improvements might provide some level of protection from viral diseases that attack the cardiorespiratory system, such as coronavirus disease 2019 (COVID-19) [113].

5.7. Anti-Type 2 Diabetes Effects

Several studies have shown that pterostilbene lowers blood sugar levels, another component of metabolic syndrome, in diabetic rodents [114–117]. In one of these studies, searching for a mechanism, pterostilbene reduced weight, fasting blood glucose, and insulin resistance, as well as lipid indicators of metabolic syndrome [117]. Protein expression of PPAR γ , a glucose transporter, and components of the phosphatidylinositol-3-kinase/protein kinase B (P13K/Akt) signaling pathway were increased. Insulin regulates glucose metabolism via the P13K/Akt signaling pathway. The type 2 diabetes thiazo-lidinedione drugs also activate PPAR γ . Pterostilbene reduces insulin resistance [118], an indicator of diabetes. The authors of this study examined the effect of pterostilbene on several genes, and they hypothesized that this effect of pterostilbene is through its antioxidant activity and its effects on reducing triglyceride levels. No evidence of a primary molecular target was found. More recently, pterostilbene was found to interact with several proteins, particularly the syntaxins involved with insulin secretion by the pancreatic β cells that produce insulin [119]. The authors of this study concluded that pterostilbene reduces insulin secretion, as do some diabetes medications.

5.8. Anti-Inflammation Effects

Many of the diseases discussed above are highly influenced by inflammation, and both resveratrol and pterostilbene are anti-inflammatory agents [63,120]. Inflammation increases the risk of cancer, thus anticancer effects of these compounds discussed above (Section 5.5) are linked to their anti-inflammatory effects. Pterostilbene treatment reduces levels of inflammatory cytokines (e.g., TNF- α , IL-6, IL-1 β , and IFN- γ) [121–125] and nitric oxide levels, another molecule involved in inflammation [123,125]. Pterostilbene is generally more active for reducing inflammation than resveratrol [124]. Several molecular effects associated with inflammation are affected by resveratrol and pterostilbene [63,120], but

there is no evidence of resveratrol and pterostilbene molecules affecting these targets by a direct molecular interaction. It is most likely that these molecules alleviate inflammation through their effects on PPAR γ , which when activated can reduce cytokine and NO production [126]. Indeed, Shi et al. [127] produced evidence that pterostilbene alleviates inflammatory ulcerative colitis in rats by activation of PPAR γ and suppression of nuclear factor-kB (NF-kB), although there is no evidence of direct interactions of pterostilbene and NF-kB. Yang and Jiang [128] hypothesize that resveratrol inhibits NF-kB via enhancing sphingolipid intermediate levels.

5.9. Activation of Sirtuins

The primary effects of these stilbenes on PPARs have been discussed above. This section was included because of claims that sirtuins are primary targets of resveratrol. Koh et al. [64] discuss potential molecular targets of resveratrol and pterostilbene, but most of the potential targets discussed, other than the PPARs discussed above and the sirtuins, do not have binding studies to support a primary effect. Sirtuins or Sir2 enzymes, such as SIRT1, are NAD⁺-dependent, protein deacetylase transcription factors that control transcription of genes associated with many cellular processes involved in processes influenced by resveratrol and pterostilbene (e.g., fatty acid metabolism) [129]. Resveratrol and pterostilbene promote SIRT1 activity [130,131], and resveratrol binding to SIRT1 was claimed to promote a conformational change that apparently activates it [130]; however, later work indicated that resveratrol has no direct influence on SIRT1 [132]. Later, pterostilbene was reported to bind the enzymatic pocket of SIRT1 and that inhibition of SIRT1 with splitomicin removed the positive effects of pterostilbene [133]. More recent work indicates that it does interact directly with SIRT1 [134], but a recent review concludes that resveratrol is not a direct inhibitor of SIRT1 [135]. An indirect effect of resveratrol on SIRT1 activity via inhibition of cAMP-degrading phosphodiesterases has been proposed [136]. Thus, there is evidence that there are at least two primary targets of resveratrol and pterostilbene, the PPARs and the sirtuins. Few pharmaceuticals target more than one molecule. Having multiple targets that can favorably influence human gene expression and metabolic activity may account for the large number of positive effects of the natural stilbenes.

5.10. Human Clinical Trials

Most of the potential beneficial effects for humans mentioned above have been extrapolated from a large number of in vitro model systems or rodent studies. Results of over a hundred clinical trials with resveratrol, mostly in Europe and the US, have been equivocal [135]. However, doses and other parameters of these trials have been extremely varied, making confirmation of any particular result difficult. Despite many of the pterostilbene papers on animal studies calling for human clinical trials, compared to resveratrol, there are relatively few human clinical trials to confirm any of the indicated benefits for pterostilbene. In fact, only 15 clinical trials are listed on ClinicalTrials.gov of the U.S. National Institute of Health, and only six of these studies have been completed. This is unfortunate, in that most studies indicate that pterostilbene is more likely to have beneficial effects on human health than resveratrol. Of the six studies completed, only one was on pterostilbene alone, the rest being on a combination of nicotinamide riboside with pterostilbene or inadequately chemically defined dietary supplements. The clinical trial on pterostilbene alone that found pterostilbene (125 mg twice daily) to reduce blood pressure after 8 weeks [137]. This effect was apparently not due to improvements in cholesterol levels, as LDL levels increased with this pterostilbene treatment, although this effect was not seen in participants taking anti-cholesterol medication. There was no effect on HDL. The effects of a combination of nicotinamide riboside with pterostilbene were examined in a clinical study [138]. Effects on lipid levels were equivocal, but blood levels of NAD⁺ were elevated by the two compounds. Unfortunately, there was no pterostilbene only treatment in the study. There are 63 clinical trials listed for blueberry preparations, and 40 of these are listed as completed. Several of these are confounded by other components taken with the blueberry preparations. Of

the remaining completed studies, none have published peer-reviewed results on potential health benefits that relate the results to resveratrol or pterostilbene. Several of the papers attribute positive effects to anthocyanins. The positive results (e.g., improved insulin sensitivity [139] and improved blood pressure and cardioprotective effects [140–142]) were found in several of the studies with blueberry supplements. A recent review concluded that clinical trials with supplementation of diet with blueberry products improves metabolic syndrome risk factors [143]. Unfortunately, pterostilbene concentrations in the preparations used in blueberry clinical trials have not been provided. The positive effects for blueberries are likely to be due to stilbenes, considering results from animal studies with resveratrol and pterostilbene, as mentioned earlier. There have been similar clinical trials with grape-based supplements, and the situation is similar to that for blueberries. If such studies are not carried out without standardization of resveratrol and pterostilbene levels, interpretation of what active components are responsible for the measured effects cannot be made. As mentioned in Section 3, the levels of these two stilbenes in fruits and vegetables can be extremely variable because they are not constitutive compounds.

6. Summary and Conclusions

Compared to other natural compounds, a relatively large number of potential health benefits of resveratrol and pterostilbene have been discovered in the last two decades. This amazing list of health-promoting effects includes the slowing of age-related diseases, prevention and treatment of cancers, reduction in inflammation and diabetic-related factors, improvement of cardiovascular and brain function, and antimicrobial activity; some of these effects are interrelated. The only clearly-proven mammalian molecular binding sites of these compounds are the PPARs, which act as transcription factors. The most established evolutionary advantage of these compounds to the producing plants is their antimicrobial activity. Their mode of action as antimicrobials is unknown, and this activity apparently has little to do with their many health benefits. Not all of the beneficial effects of pterostilbene are found with resveratrol, and those that are found in common are generally higher with pterostilbene. At least part of the reason for this is the significantly greater bioavailability of pterostilbene, some which is attributed to its higher lipophilicity. Although both resveratrol and pterostilbene have the potential to improve human health, most of the studies showing beneficial effects have been carried out with doses of these compounds that far exceed the levels that might be expected in a normal diet, or even a diet enriched in foods with unusually high levels of these compounds. Thus, without finding genetic, chemical, or environmental methods, such as genetic engineering, to produce higher levels of these compounds in crops, the diet will have to be augmented with readily available synthetic versions of these nutraceuticals in order to benefit from these compounds. For example, rice bioengineered to produce resveratrol reduces indicators of metabolic syndrome in mice [28]. Such genetically engineered crops with elevated resveratrol and pterostilbene content offer an effective method for providing substantial health benefits to the human diet. Indeed, such a beneficial use of biotechnology for biofortification would be similar to that of rice engineered to produce carotenoids (golden rice) that was recently approved for commercial production in the Philippines [144]. Before this can be carried out for high stilbene crops, more rigorous clinical trials must be performed to determine whether promising results from animal studies translate into human benefits and to establish the appropriate doses for these benefits.

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