



# Resveratrol and pterostilbene: A comparative overview of their chemistry, biosynthesis, plant sources and pharmacological properties

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## ABSTRACT

Both resveratrol and pterostilbene are monomeric stilbenes having a 6–2–6 carbon skeleton with two phenyl rings linked by a double-bonded ethylene bridge. Resveratrol has three hydroxyl (–OH) groups, while pterostilbene has two methoxy (–OCH<sub>3</sub>) groups and one –OH group. They commonly occur in the *trans* form rather than the *cis* form. Red grapes and red wines are the main dietary sources of the resveratrol. Pterostilbene occurs in blueberries and grapes. Resveratrol and pterostilbene exhibit many similarities in pharmacological properties, including antioxidant, neuroprotective anti-cancer, cardioprotective, analgesic, anti-atherosclerosis, anti-aging, anti-diabetic, anti-inflammatory, and anti-obesity activities. The stronger pharmacological properties in pterostilbene than resveratrol have been attributed to its two –OCH<sub>3</sub> groups. As a result, pterostilbene is more lipophilic which enhances its membrane permeability, bioavailability, and biological potency. Some future studies on resveratrol and pterostilbene are suggested. The sources of information cited in this comparative overview were from Science Direct, Google Scholar, and PubMed.

## INTRODUCTION

Stilbenes are phenolic compounds having two aromatic rings with –OH groups and are linked by a double-bonded ethylene bridge (Akinwumi *et al.*, 2018; El Khawand *et al.*, 2018). Found in higher plants, stilbenes exist as monomeric, dimeric, trimeric, oligomeric, and polymeric forms, or as glycosides. Stilbenes possess biological activities, such as anti-diabetic, anti-obesity, cardioprotective, neuroprotective, anti-inflammatory, anti-atherosclerosis, and anti-cancer properties (Akinwumi *et al.*, 2018). Resveratrol and pterostilbene represent two of the

monomeric stilbenes with well-studied biological activities and molecular effects (Tsai *et al.*, 2017).

It was reported that the consumption of red wine in France has cardioprotective effects and reduces the risk of cardiovascular diseases (Renaud and de Lorgeril, 1992). The low occurrence of coronary heart diseases among the French people, despite their high-fat diet, is popularly known as the French paradox (Sun *et al.*, 2002). These health benefits of red wine have been attributed to resveratrol (Siemann and Creasy, 1992). Since then, much research was conducted on the cardioprotective and other medicinal properties of resveratrol, a major compound of red grapes and red wine (Catalgol *et al.*, 2012). Pharmacological activities of resveratrol include cardioprotective (Hsieh and Wu, 2018), antioxidant (Cavallini *et al.*, 2016), anti-inflammatory (de Sá Coutinho *et al.*, 2018), anti-atherosclerosis (Bonfont-Rousselot, 2016), anti-aging (Bhullar and Hubbard, 2015; Li *et al.*, 2018), anti-diabetic (Szkudelski and Szkudelska, 2011),

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anti-osteoporosis (Tou *et al.*, 2015), and anti-obesity (de Ligt *et al.*, 2015; Pan *et al.*, 2018) properties.

Among the many pharmacological activities of resveratrol (Baur and Sinclair, 2006; Berman *et al.*, 2017), its anti-cancer properties are most well-known. Since its first report by Jang *et al.* (1997), there are many reviews on the subject (Rauf *et al.*, 2018; Varoni *et al.*, 2016). Displaying various molecular mechanisms, resveratrol has shown to be a promising and multi-target agent for cancer prevention and treatment.

In recent years, the neuroprotective effects of resveratrol have also gained much research interest. The overall health benefits of resveratrol toward age-related diseases have become a topic of intense investigations (Timmers *et al.*, 2012). Reviews on the neuroprotective properties of resveratrol are mostly age-related neurodegenerative disorders related to Alzheimer's disease and Parkinson's disease (Tellone *et al.*, 2015), brain degeneration (Poulose *et al.*, 2015), and neurological disorders, such as stroke and CNS injury (Lopez *et al.*, 2015). Currently, there is one comprehensive review by Bastianetto *et al.* (2015) that summarized recent findings on the molecular mechanisms of action and discussed possible roles of resveratrol in the prevention of various neurological disorders.

Pterostilbene was reported by Remsberg *et al.* (2008) to have anti-cancer, anti-inflammatory, antioxidant, and analgesic effects on rats. These findings generated much research excitement in pterostilbene and subsequently, properties, such as anti-cancer (McCormack and Mc Fadden, 2012; Nutakul *et al.*, 2011), anti-inflammatory (Dvorakova and Landa, 2017), neuroprotective (Poulose *et al.*, 2015; Wang *et al.*, 2016), anti-obesity (Aguirre *et al.*, 2016; Pan *et al.*, 2018), anti-diabetic (Tastekin *et al.*, 2018), antioxidant (McCormack and McFadden, 2013; Rimando *et al.*, 2002), anxiolytic (Al Rahim *et al.*, 2013), and anti-aging (Li *et al.*, 2018) activities have been documented. Recently, the promising therapeutic potential of pterostilbene and its mechanistic insight based on recent preclinical evidence was reviewed by Kosuru *et al.* (2016).

This comparative overview on the pharmacological properties of resveratrol and pterostilbene is appropriate and timely as the surge in the number of research studies in recent years has generated a wealth of new knowledge. Such useful information will set the platform for scientists to conduct further research on resveratrol, pterostilbene, and other derivatives. References cited in this overview were procured from databases downloaded from Science Direct, Google Scholar, and PubMed.

## CHEMISTRY

Resveratrol or *trans*-3,4',5-trihydroxystilbene is a monomer stilbene with a molecular formula of C<sub>14</sub>H<sub>12</sub>O<sub>3</sub> and a molecular weight of 228.25 g/mol. The molecule has two aromatic rings, linked by an ethylene bridge with an ethene double bond (Fig. 1). Ring A has two hydroxyl (–OH) groups at C3 and C5, and ring B has one –OH group at C4' (Tsai *et al.*, 2017). Resveratrol has a 6–2–6 carbon skeleton with *m*-hydroquinone and 4'-hydroxystyryl moieties involving rings A and B, respectively (Niesen *et al.*, 2013).

In food products, resveratrol commonly occurs in the *trans* form rather than in the *cis* form (Anisimova *et al.*, 2011). When resveratrol is exposed to ultraviolet and visible light,

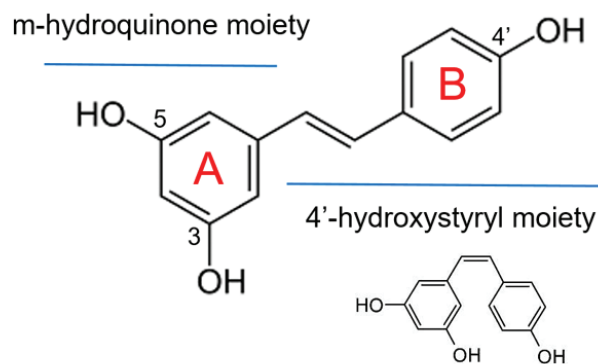
*trans* to *cis* isomerization occurs (Silva *et al.*, 2013). The rarer *cis*-resveratrol is less stable and is not commercially available (Cottart *et al.*, 2010). Red wine is rich in *trans*-resveratrol, and its moderate consumption has health benefits of lower rates of prostate cancer (Schoonen *et al.*, 2005). Against PC-3 prostate cancer cells, *trans*-resveratrol was reported to be a more effective anti-cancer agent than *cis*-resveratrol and dihydro-resveratrol (Anisimova *et al.*, 2011). Earlier, *trans*-resveratrol has been reported to be 10 times more potent in inducing apoptosis of HL60 leukemia cells as compared to *cis*-resveratrol (Roberti *et al.*, 2003).

Pterostilbene or *trans*-3,5-dimethoxy-4'-hydroxystilbene has a molecular formula of C<sub>16</sub>H<sub>16</sub>O<sub>3</sub>, molecular weight of 256.30 g/mol (Kosuru *et al.*, 2016; McCormack and Mc Fadden, 2012; Tsai *et al.*, 2017). Its other names are dimethoxy resveratrol, 3,5'-dimethoxy-4-stilbenol and 4-[2-(3,5-dimethoxyphenyl) ethenyl] phenol. Being a dimethylated analog of resveratrol, pterostilbene is structurally similar to resveratrol by having one hydroxyl group at C4' of ring B but differs by having two –OCH<sub>3</sub> groups at C3 and C5 of ring A (Fig. 2). Like resveratrol, the *trans* form of pterostilbene is more abundant than the *cis* form (Kosuru *et al.*, 2016).

## BIOSYNTHESIS AND PLANT SOURCES

In plants, the biosynthesis of resveratrol and pterostilbene shares similar substrates and biosynthetic pathway as flavonoids (Jeandet *et al.*, 2010; Poulose *et al.*, 2015). Unlike flavonoids which are produced by most plants, only a few plant species synthesize these stilbenes. The biosynthetic pathway of resveratrol begins with phenylalanine of the shikimate pathway, which undergoes various enzymatic reactions to produce *p*-coumaroyl-CoA. In the presence of malonyl-CoA and stilbene synthase, *trans*-resveratrol is produced *via* an aldol reaction. *Trans*-resveratrol is then converted to pterostilbene by *O*-methyl transferase.

Resveratrol was first isolated from the roots of *Veratrum grandiflorum* and later from the roots of *Polygonum cuspidatum* (Nonomura *et al.*, 1963). From *P. cuspidatum*, an important traditional medicine in China, the content of resveratrol has been reported to be 1.8 mg/g (Zhao *et al.*, 2005). The compound has been isolated from more 70 plant species, including grapes and red wine (Rege *et al.*, 2014). Red grapes and red wine, as shown in Figure 3, are the main dietary sources of resveratrol. Red grapes



**Figure 1.** The molecular structures of *trans*-resveratrol with *cis*-resveratrol as inset.

contain mainly of piceid (1.5–7.3 µg/g), while red wine is rich in resveratrol (1.0–18 µg/ml) (Burns *et al.*, 2002). From the skin of grapes, the content of resveratrol ranged from 2.48 to 6.47 µg/g (Rimando *et al.*, 2004). The concentration of *trans*-resveratrol in red wine is six times higher than in white wine, which contains high levels of *cis*-resveratrol (Rege *et al.*, 2014). A possible explanation is that red wine is produced without removing the skin of grapes, whereas white wine is fermented after the removal of the skin.

Pterostilbene was first isolated from *Pterocarpus santalinus* (sandalwood) in 1940 (Seshadri, 1972), and later identified in *Vitis vinifera* (grape vine) (Adrian *et al.*, 2000; Langcake *et al.*, 1979), *Pterocarpus marsupium* (Indian kino) (Manickam *et al.*, 1997; Maurya *et al.*, 1984), *Vaccinium* berries (Rimando *et al.*, 2004), and *Arachis hypogaea* (peanut) (Sobolev *et al.*, 2011).

### PHARMACOLOGICAL PROPERTIES

Resveratrol and pterostilbene exhibit many similarities in pharmacological properties (Akinwumi *et al.*, 2018; Tsai *et al.*, 2017; Wang and Sang, 2018). They include antioxidant, neuroprotective anti-cancer, cardioprotective, analgesic, anti-atherosclerosis, anti-aging, anti-diabetic, anti-inflammatory, and anti-obesity activities.

Studies have shown that both resveratrol and pterostilbene are able to cross the blood–brain barrier and influence brain activity (Lange and Lee, 2017). The blood–brain barrier is a diffusion barrier essential for the normal functioning of the central nervous system. Located at the capillaries between the blood and cerebral tissue, the blood–brain barrier has endothelial cells with tight junctions that impede the influx of most blood-borne compounds from entering the brain (Ballabh *et al.*, 2004; Kanwar *et al.*, 2012). Small lipophilic molecules, such as oxygen (O<sub>2</sub>) and carbon dioxide (CO<sub>2</sub>), can diffuse through plasma membranes while nutrients, such as glucose and amino acids, and larger molecules, including insulin, leptin, and iron transferrin, enter the brain via transporters and receptor-mediated endocytosis, respectively. The blood–brain barrier has been reported to prevent 98% of small molecules and 100% of large molecules from reaching the brain (Kanwar *et al.*, 2012).

A study by Wang *et al.* (2002) demonstrated that the resveratrol can cross the blood–brain barrier and protects

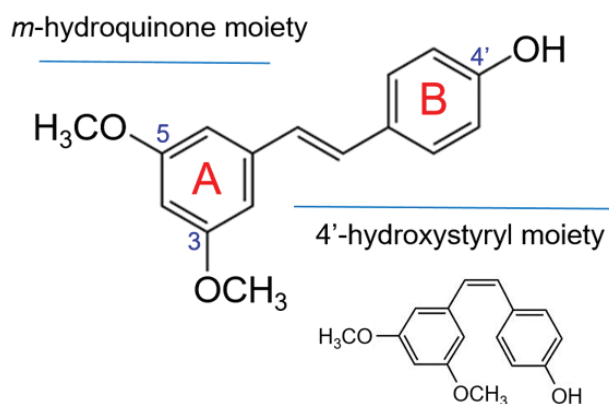
against cerebral ischemic injury in gerbils. The study noted that after injection into these animals, resveratrol rapidly enters the bloodstream as glucuronide conjugate, crosses the blood–brain barrier, and is subsequently enters the brain tissue. Resveratrol was retained in the brain for up to 4 hours.

Although there are structural and bioactivity similarities between resveratrol and pterostilbene, pharmacological properties of pterostilbene are often stronger than those of resveratrol (Table 1).

The stronger pharmacological properties in pterostilbene than resveratrol have been attributed to the dimethoxy groups at C3 and C5 of ring A (Fig. 2). With these structural characteristics, pterostilbene is more lipophilic, enhancing its membrane permeability, bioavailability, and bioactivity (Kapetanovic *et al.*, 2011; McCormack and Mc Fadden, 2012; Wang and Sang, 2018). Overall, pterostilbene performs better in membrane permeability and metabolic stability than resveratrol. This increases the bioavailability, and enhances the pharmacokinetic profile and pharmacological activities of pterostilbene.

Studies have shown that both resveratrol and pterostilbene are safe for human consumption. In a clinical trial conducted on 40 healthy volunteers, resveratrol was found to be safe after daily doses of 0.5, 1.0, 2.5, and 5.0 g for 29 days, with the exception of 2.5 and 5.0 g doses which caused some gastrointestinal discomfort (Brown *et al.*, 2010). In two studies, 28 daily doses of 50, 150, or 500 mg/kg body weight, and 90 daily dose of 700 mg/kg body weight of Resvida™ (high-purity resveratrol) did not have any adverse effects on rats (Williams *et al.*, 2009). For pterostilbene, a clinical trial (randomized, double-blind, and placebo-controlled) conducted in 80 healthy volunteers for 6–8 weeks, demonstrated that the pterostilbene is generally safe for consumption at doses of up to 250 mg/day (Riche *et al.*, 2013). Biochemical analysis showed that the pterostilbene had no adverse reactions on liver, kidney, and glucose markers.

Kapetanovic *et al.* (2011) reported that there was greater oral absorption and cellular uptake of pterostilbene in rats than resveratrol. One of the studies indicated that the pterostilbene (orally administered) displayed 95% bioavailability, as compared to resveratrol with only 20% bioavailability. In addition, the half-life of resveratrol in the blood was found to be 14 minutes (Asensi *et al.*, 2002), whereas pterostilbene with two –OCH<sub>3</sub> groups had



**Figure 2.** The molecular structures of *trans*-pterostilbene with *cis*-pterostilbene as inset.



**Figure 3.** Red grapes (left) and red wine (right).

**Table 1.** Comparative pharmacological properties of pterostilbene (PS) and resveratrol (RV).

Activity	Pharmacological property	Reference
Anti-cancer	Against HT-29 human colon cancer cells, PS (IC <sub>50</sub> = 22.4 μmol/l) was a more potent inhibitor of proliferation when compared with resveratrol (IC <sub>50</sub> = 43.8 μmol/l).	(Paul <i>et al.</i> , 2009)
Anti-cancer	PS displayed stronger growth inhibitory activities than RV against HT-29, HCT-116 and Caco-2 human colon cancer cells. With IC <sub>50</sub> values of 15, 12, and 75 μM, PS was 4.3, 2.1, and >1.3 times stronger than RV, respectively.	(Nutakul <i>et al.</i> , 2011)
Anti-cancer	Against HeLa human cervical cancer cells, the cytotoxicity of PS (IC <sub>50</sub> = 42.3 μM) was almost two times that of RV (IC <sub>50</sub> = 83.5 μM).	(Chatterjee <i>et al.</i> , 2018)
Antioxidant	PS protected human erythrocytes against lipid peroxidation with IC <sub>50</sub> value of 44.5 μM. RV was significantly less effective.	(Mikstacka <i>et al.</i> , 2010)
Antioxidant	Against mammalian cells with oxidative DNA damage induced by hydrogen peroxide (H <sub>2</sub> O <sub>2</sub> ), results on the protective effects of RV and PS showed the strongest inhibition in PS (85.5%) followed by RV (21.1%).	(Rossi <i>et al.</i> , 2013)
Neuroprotective	Among 21 resveratrol derivatives tested for their inhibitory effects on lipopolysaccharide-induced nitric oxide (NO) production in microglia, the strongest activity was observed in PS (IC <sub>50</sub> value of 1.9 μM). Its IC <sub>50</sub> value was 8.2 times stronger than RV (IC <sub>50</sub> value of 15.5 μM).	(Meng <i>et al.</i> , 2012)
Neuroprotective	In mice, PS is a more potent neuro-modulator of cognition function and cellular stress than RV, suggesting that PS can be used as a drug to improve cognitive function in aging and to slow down the progress of Alzheimer's disease.	(Chang <i>et al.</i> , 2012)
Anti-diabetic	PS is relatively more effective than RV in improving the metabolic parameters of streptozotocin-induced diabetic rats.	(Tastekin <i>et al.</i> , 2018)
Hypolipidemic	PS is more potent as an agonist of peroxisome proliferator-activated receptor alpha, and as a stronger hypolipidemic and glucose-lowering agent than RV.	(Rimando <i>et al.</i> , 2005)
Anti-inflammatory	Anti-inflammatory activities of PS were stronger than RV when assessed using human subjects with rheumatoid arthritis.	(Choo <i>et al.</i> , 2014)
Anti-platelet aggregation	Both RV and PS strongly inhibited platelet aggregation, and stimulated NO production in platelets.	(Messina <i>et al.</i> , 2015)
Anti-androgenic	Among the analogs of RV tested, PS exhibited the strongest anti-androgenic activity. Its hydrogen bonding interactions pattern and binding energy resembled that of anti-androgenic flutamide.	(Chakraborty <i>et al.</i> , 2014)
Antifungal	PS was 5–10 times more effective than RV in inhibiting the germination of <i>Botrytis cinerea</i> conidia and <i>Plasmopara viticola</i> sporangia.	(Jeandet <i>et al.</i> , 2002)
Bioavailability	The half-life of PS in rat serum was 1.73 hours, while those of RV and RV glucuronide 1.31 and 1.52 hours in rat plasma, respectively. The half-life of RV was only 0.24 hours in rabbit plasma. The significantly longer half-life of PS can be translated into greater bioavailability.	(Asensi <i>et al.</i> , 2002; Remsberg <i>et al.</i> , 2008)
Bioavailability	Higher oral bioavailability was observed in PS (80%) vs. RV (20%) of rats. Following oral administration, plasma levels of PS and PS sulfate were markedly higher than those of RV and RV sulfate.	(Kapetanovic <i>et al.</i> , 2011)
Pharmacokinetics	Following equimolar dose administration to rats, PS displayed superior pharmacokinetic profile than RV. The oral bioavailability of PS (67%) was 2.2 times that of RV (30%).	(Kapetanovic <i>et al.</i> , 2011)
Pharmacokinetics	RV and PS were mainly excreted as metabolites in the faeces (non-renal) and not in the urine (renal), suggesting the importance of enterohepatic cycling in their metabolism.	(Marier <i>et al.</i> , 2002; Remsberg <i>et al.</i> , 2008)

a half-life of 105 minutes or seven times longer than resveratrol (Remsberg *et al.*, 2008).

## CONCLUSION

Future research on the pharmacological properties of resveratrol and pterostilbene would focus on elucidating a better understanding the mechanisms of action involved. The overall health benefits of resveratrol and pterostilbene will continue to be topics of intense investigation. In addition, further studies on various aspects of metabolism, absorption, bioavailability, pharmacokinetics, biotransformation, structure-activity relationships, dose-response, synergism, and side-effects of resveratrol and pterostilbene are warranted. Overall, research findings on the mechanisms and health benefits of resveratrol and pterostilbene in humans need to be confirmed *via* more detailed and convincing clinical trials. It is acknowledged that clinical trials of resveratrol and pterostilbene are at the cross-road of establishing human evidence from *in vitro* and *in vivo* information. Resveratrol and pterostilbene molecules could be used as the scaffold for producing synthetic compounds with enhanced pharmaceutical attributes and other added-values. The prospects of developing resveratrol and pterostilbene into nutritional and/or pharmacological biomolecules for use as multi-target therapeutic drugs are indeed promising.

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## CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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