Journal of Applied Pharmaceutical Science Vol. 13(09), pp 001-008, September, 2023
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2023.99205
ISSN 2231-3354

3'-Hydroxypterostilbene and pinostilbene: Their chemistry, sources, anticancer and other pharmacological properties, pharmacokinetics, and patents

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ARTICLE INFO

Received on: 14/03/2023
Accepted on: 11/08/2023
Available Online: 04/09/2023

Key words:
3'-hydroxypterostilbene, pinostilbene, methoxylated stilbenes.

ABSTRACT

In this article, the chemistry, sources, anticancer and other pharmacological properties, pharmacokinetics, and patents of 3'-hydroxypterostilbene (HPS) and pinostilbene (PS) are reviewed for the first time. Their chemical structures consist of a catechol moiety with two aromatic rings A and B. HPS has two hydroxyl groups and two methoxy groups, while PS has two hydroxyl groups and one methoxy group. Both methoxylated stilbenes are commercially available. The anticancer properties of HPS have been reported in leukemia, colon, and skin cancer cells, while those of PS have been reported in colon, tongue, and nasopharyngeal cancer cells. Other pharmacological properties of HPS include anti-inflammatory, antioxidant, hepatoprotective, anticolitis, antiadipogenesis, sirtuin 1 modulatory, and α-glucosidase inhibitory activities. Those of PS include anti-inflammatory, cytochrome P450 inhibitory, neuroprotective, antioxidant, antityrosinase, α-glucosidase inhibitory, antiplasmodial, lactase dehydrogenase activity release, antimelanogenesis, antiadipogenesis, suppression of hepatic stellate cell activation, and tight junction protection activities. Some fields for further research are suggested. Sources of information in this review were Google, Google Scholar, ScienceDirect, PubMed, J-Stage, and PubChem.

INTRODUCTION

Stilbenes are phenolic compounds having a C6–C2–C6 skeleton and two aromatic rings with hydroxyl groups and are linked by a double-bonded ethylene bridge (Akinwumi *et al*., 2018; El Khawand *et al*., 2018). A total of 459 natural stilbenes from 45 plant families and 196 plant species have been identified (Teka *et al*., 2022). These compounds possess biological activities such as antioxidant, antimicrobial, antidiabetic, antiobesity, cardioprotective, neuroprotective, antineurodegenerative, anti-inflammatory, antiatherosclerosis, antiaging, and anticancer properties (Akinwumi *et al*., 2018; Teka *et al*., 2022). Stilbenes are often hydroxylated and/or methoxylated.

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Resveratrol is a hydroxylated stilbene and pterostilbene is a methoxylated stilbene with well-studied biological activities and molecular effects (Chan *et al*., 2019; Tsai *et al*., 2017). Resveratrol is the most well-known stilbene that is abundant in nature and plays a significant role due to its antioxidant and anti-inflammatory properties (De Filippis *et al*., 2017). Pterostilbene is structurally related to resveratrol. It is a dimethoxylated derivative of resveratrol with similar biological activities but with more potent antioxidant and anticancer properties (McCormack and McFadden, 2012, 2013). It has better bioavailability due to the two methoxy groups at C3 and C5 that increase lipophilicity (Kapetanovic *et al*., 2011).

In this article, the chemistry, sources, anticancer and other pharmacological properties, pharmacokinetics, and patents of 3'-hydroxypterostilbene (HPS) and pinostilbene (PS) are reviewed. Despite their essential pharmacological properties, there have been no reviews on these two methoxylated stilbenes. The review of stilbenes that included HPS focused only on their anticancer properties (Tsai *et al*., 2017). Therefore, this review of

HPS and PS is useful for scientists interested in pursuing research on methoxylated stilbenes.

CHEMISTRY

3'-Hydroxypterostilbene

HPS or 3,5-dimethoxy-3',4'-dihydroxystilbene is a pterostilbene analog (Liu, 2014). HPS was first isolated from the whole plant of *Sphaerophysa salsula* (Fabaceae) (Ma *et al*., 2002). HPS has a molecular formula of $C_{16}H_{16}O_4$ and a molecular weight of 272 g/mol. The chemical structure of HPS has a catechol moiety at ring B consisting of two hydroxyl (–OH) groups at C3' and C4' (Fig. 1). The two methoxy (–OCH_3) groups at C3 and C5 of ring A make this compound more lipophilic with better cellular permeability and bioavailability (Tsai *et al*., 2017). The chemical structure of HPS is similar to that of pterostilbene except for an –OH group at C3' at ring B, which is absent in pterostilbene. The two –OH groups at ring B suggest stronger bioactivity than pterostilbene, and the two –OCH_3 groups at ring A suggest that it is more lipophilic and has better cellular permeability than resveratrol (Liu, 2014).

Pinostilbene

PS (3-methoxyresveratrol or 3,4'-dihydroxy-5-methoxystilbene) has a molecular formula of $C_{15}H_{14}O_3$ and a molecular weight of 242 g/mol. PS was first isolated from the bark of *Pinus sibirica* (Tyukavkina *et al*., 1972). A naturally occurring analog of resveratrol (3,5,4'-trihydroxystilbene), the chemical structure of PS consists of two –OH groups at C3 and C4′ and a –OCH_3 group at C5 (Fig. 1). Its structure is similar to that of pterostilbene except for an –OH group at C3 instead of a –OCH_3 group at ring A as in pterostilbene.

SOURCES

HPS (≥99%) and PS (≥95%) are commercially available from Sigma-Aldrich. HPS has been isolated from the whole herb of *S. salsula* (Ma *et al*., 2002). PS has been reported in the bark of *P. sibirica* (Tyukavkina *et al*., 1972), the stem wood of *Dracaena loureiri* (Likhitwitayawuid *et al*., 2002), the bark of *Soymida febrifuga* (Awale *et al*., 2009), the resin of *Dracaena cochinchinensis* (Liu *et al*., 2013), and stem bark of *Commiphora africana* (Segun *et al*., 2019).

Besides isolation from natural sources, HPS and PS can be synthesized. HPS was synthesized from 3,4-dihydroxybenzaldehyde in five steps with an overall yield of 33% (Venkateswarlu *et al*., 2003). The spectral data of the synthesized HPS agreed with that of the natural product and displayed potent antioxidative activity. The process for the manufacture of HPS has been patented by Majeed *et al*. (2016). HPS is synthesized via ortho-formylation of pterostilbene to obtain 3'-formyl pterostilbene followed by Dakin oxidation of 3′-formyl pterostilbene to yield HPS. PS can be biosynthesized using the recombinant *Escherichia coli* that harbors an artificial biosynthetic pathway (Kang *et al*., 2014).

ANTICANCER PROPERTIES

3'-Hydroxypterostilbene

The apoptotic activity of HPS was evaluated in different leukemia cell lines. In HL60, K562, and HUT78 drug-sensitive leukemia cells and in HL60-R and K562-ADR multidrug-resistant (MDR) leukemia cells, the HPS concentration capable of inhibiting 50% cell growth (IC_{50}) was 0.8, 0.8, 0.6, 0.9, and 1.2 µM, respectively (Tolomeo *et al*., 2005). For the same leukemia cell lines, the HPS concentration capable of inducing 50% cell apoptosis (AC_{50}) was 1.0, 3.0, 0.7, 5.0, and 3.5 µM, respectively. HPS was much stronger than pterostilbene, especially against MDR leukemia cells. For example, against HL60-R cells, the IC_{50} and AC_{50} values of HPS were 44 and 17 times stronger than those of pterostilbene. In addition, HPS exhibited low toxicity in normal stem cells. Against colony-forming units-granulocyte macrophage normal bone marrow cells, HPS was not cytotoxic with an IC_{50} value of 50 µM (Tolomeo *et al*., 2005).

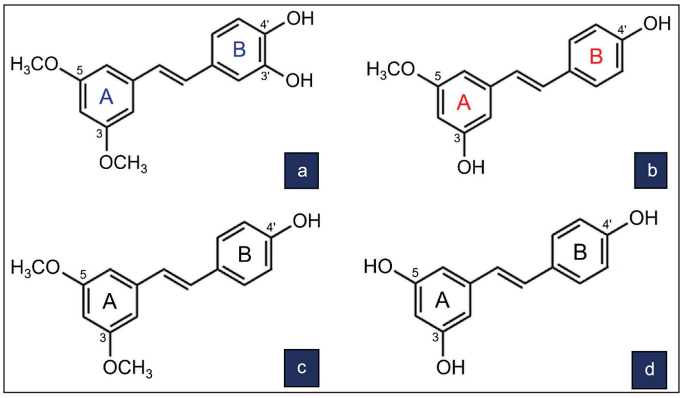

Figure 1. Chemical structure of HPS (a) and PS (b) in comparison with pterostilbene (c) and resveratrol (d)

HPS inhibited the growth of COLO 205, HCT-116, and HT-29 colon cancer cells with IC_{50} values of 9, 40, and 71 µM, respectively (Cheng *et al*., 2014; Pan *et al*., 2015). Cytotoxicity of HPS was more potent than pterostilbene with IC_{50} values of 33, 47, and 81 µM, respectively. HPS was cytotoxic toward HCT 116 colon, MDA-MB-231 breast, PC-3 prostate, and HepG2 liver cancer cells with IC_{50} values of 7.6, 18, 23, and 8.4 µg/ml, respectively (Takemoto *et al*., 2015). The anticancer effects and mechanisms of HPS have been reported in colon cancer cells and leukemia cells, including colon and skin tumors (Table 1). Against colon cancer cells (COLO 205, HCT-116, and HT-29), cytotoxic activities involved apoptosis and autophagy, accompanied by activation of caspase-3, downregulation of cyclooxygenase- (COX-) 2, matrix metallopeptidase- (MMP-) 9, vascular endothelial growth factor (VEGF), and cyclin D1, and inhibition of phosphatidylinositol 3-kinase (PI3K)/Akt, mammalian target of rapamycin (mTOR), and mitogen-activated protein kinase (MAPK) pathways (Cheng *et al*., 2014; Pan *et al*., 2015). Inhibition of leukemia cells (K562, HL60-R, and K562-ADR) involved triggering of the intrinsic apoptotic pathway via disruption of mitochondrial membrane potential and suppression of caspase inhibitors (Z-VAD-fmk and Z-LEHD-fmk) (Takemoto *et al*., 2015). Amelioration of colon tumors in mice involved inhibition of IL-6/signal transducer and activator of transcription 3 (STAT3) signaling and inhibition of the expression of inflammatory enzymes and β-catenin signaling (Lai *et al*., 2017). Suppression of skin tumors in mice included protection against inflammation in mouse skin papilloma and suppression of p38 and signal transducer and STAT3 signaling pathways (Lee *et al*., 2021).

Table 1. Anticancer properties of HPS and PS.

Cancer cell (type)	Compound, effect, and mechanism involved (reference)
HPS	
HL60, K562, HL60-R, & K562-ADR (leukemia)	HPS triggered apoptosis in leukemia cells through the intrinsic apoptotic pathway by causing a marked disruption of the mitochondrial membrane potential and suppression of caspase inhibitors (Z-VAD-fmk and Z-LEHD-fmk) (Tolomeo *et al*., 2005).
HL-60 (leukemia)	When leukemia cells were treated with different concentrations of HPS, the lowest cell viability was observed at the lowest dose of 5 µM, indicating that HPS was a potential, efficient anticancer agent (Liu *et al*., 2014).
COLO 205, HCT-116, & HT-29 (colon)	Cytotoxic activities of HPS against colon cancer cells involved apoptosis and the inhibition of PI3K/Akt, mTOR, and MAPK pathways (Cheng *et al*., 2014; Pan *et al*., 2015).
COLO 205 (xenograft)	Tumor inhibitory effects of HPS (10 mg/kg) on COLO 205 xenografted nude male mice involved apoptosis, autophagy, activation of caspase-3, and downregulation of COX-2, MMP-9, VEGF, and cyclin D1 (Cheng *et al*., 2014; Pan *et al*., 2015).
Tumor (colon)	HPS suppressed colitis-associated tumorigenesis in AOM/DSS-treated mice by inhibition of IL-6/STAT3 signaling and inhibition of the expression of inflammatory enzymes and β-catenin signaling (Lai *et al*., 2017).
Tumor (skin)	Topically applied HPS inhibited DMBA/TPA-induced mouse skin carcinogenesis by protecting against inflammation in mouse skin papilloma and suppressing p38 and STAT3 signaling pathways (Lee *et al*., 2021).
PS	
HCT116 & HT29 (colon)	PS at 20 and 40 µM significantly inhibited the growth of colon cancer cells via apoptosis and cell cycle arrest (Sun *et al*., 2016).
SCC-9 & HSC-3 (tongue)	PS suppressed oral cancer cell metastasis by downregulation of MMP-2 via the MAPK signaling pathway (Hsieh *et al*., 2018.
NPC-BM & NPC-039 (nasopharyngeal)	PS inhibited the migration and invasion of nasopharyngeal carcinoma cells by downregulating MMP-2 expression and suppressing EMT through the MAPK signaling pathway (Tseng *et al*., 2019).

AOM = azoxymethane, COX = cyclooxygenase, DMBA = 7,12-dimethylbenz[a]anthracene, DSS = dextran sodium sulfate, EMT = epithelial-mesenchymal transition, MAPK = mitogen-activated protein kinase, MMP = matrix metallopeptidase, mTOR = mammalian target of rapamycin, PI3K = phosphatidylinositol 3-kinase, STAT3 = signal transducer and activator of transcription 3, TPA = 12-*O*-tetradecanoylphorbol-13-acetate, and VEGF = vascular endothelial growth factor.

Related to HPS anticancer properties is its ability to inhibit histone deacetylase (HD). At 50 µg/ml, HPS significantly inhibited HD activity compared to trichostatin A, the positive control (Takemoto *et al*., 2015). HD inhibitors are a relatively new class of anticancer agents that play important roles in inducing apoptosis and cell cycle arrest in cancer cells (Kim and Bae, 2011). Several ongoing clinical trials are testing HD inhibitors for use as anticancer drugs (alone or in combination with other ant-cancer drugs). The molecular mechanisms underlying HD inhibitors in cancer patients, such as HPS, are not fully understood.

Pinostilbene

PS inhibited 26-L5 colon, HeLa cervical, and B16-BL6 melanoma cancer cells with IC_{50} values of 3.0, 9.4, and 16 µg/ml (Awale *et al*., 2009). Against MCF-7 breast, A549 lung, PC3 prostate, and HepG2 liver cancer cells, the IC_{50} values of PS were 29, 42, 38, and 33 µg/ml (Segun *et al*., 2019). Against PNT2 normal prostate cells, cytotoxicity of PS was very weak at 225 µg/ml. PS significantly reduced the viability of MCF-7 breast cancer cells by 50% at 14 µM and reduced tumor cell migration by 12% (van den Brand *et al*., 2019). When HT29 and HCT116 colon cancer cells were treated with different concentrations of PS and pterostilbene for 24 and 48 hours, both stilbenes showed similar potency in inhibiting cell growth inducing apoptosis and cell cycle arrest (Sun *et al*., 2016). Against normal colon cells, neither PS nor pterostilbene showed any growth inhibition up to 40 µM.

The anticancer effects and mechanisms of PS have been reported in colon, tongue, and nasopharyngeal cancer cells (Table 1). PS significantly inhibited the growth of HCT116 and HT29 colon cancer cells via apoptosis and cell cycle arrest (Sun *et al*., 2016). PS suppressed the metastasis of SCC-9 and HSC-3 oral cancer cells by downregulation of MMP-2 via the MAPK signaling pathway (Hsieh *et al*., 2018). PS inhibited the migration and invasion of NPC-BM and NPC-039 nasopharyngeal carcinoma cells by downregulating MMP-2 expression and suppressing epithelial-mesenchymal transition (EMT) through the MAPK signaling pathway (Tseng *et al*., 2019).

An earlier study reported that PS possessed anticancer properties toward childhood acute lymphoblastic leukemia (Katik *et al*., 2006). In primary lymphoblasts, PS induced apoptosis with an LC_{50} value of 10 µM. Among the anthracyclines used to treat childhood leukemia, daunorubicin- and doxorubicin-induced apoptosis with response rates of 27% and 23%, respectively. However, a much higher response rate was observed in PS (73%). In daunorubicin-resistant lymphoblasts, PS induced apoptosis with a response rate of 60%.

OTHER PHARMACOLOGICAL PROPERTIES

3'-Hydroxypterostilbene

Other pharmacological properties of HPS include anti-inflammatory, antioxidant, hepatoprotective, anticolitis, antiadipogenesis, sirtuin 1 (SIRT1) modulatory, and α-glucosidase inhibitory activities (Table 2).

Pinostilbene

Other pharmacological properties of PS include anti-inflammatory, cytochrome P 450 (CYP) inhibitory, neuroprotective, antioxidant, antityrosinase, α-glucosidase inhibitory, antiplasmodial, lactase dehydrogenase (LDH) activity release, antimelanogenesis, antiadipogenesis, suppression of hepatic stellate cell (HSC) activation, and tight junction (TJ) protection activities (Table 2).

Table 2. Other pharmacological properties of HPS and PS.

Activity	Compound, effect, and mechanism involved (reference)
HPS	
Anti-inflammatory	When tested with RAW 264.7 cells using the Griess assay, HPS displayed significant anti-inflammatory activity at 10 µM (Liu *et al*., 2014).
	Using the PGE_2 assay, the inhibitory effect of HPS was significant at 10 µg/ml compared to dexamethasone, the positive control (Takemoto *et al*., 2015).
	At 10 µg/ml, HPS showed inhibitory activities toward COX-1 (significant) and COX-2 (approaching significant) (Takemoto *et al*., 2015).
Antioxidant	The antioxidant activity of synthesized HPS was 33, 66, 77, and 88 times more potent than that of resveratrol, vitamin E, vitamin C, and BHT, respectively (Venkateswarlu *et al*., 2003).
	At 10 and 54 µg/ml, the total antioxidant capacity of HPS was five times stronger than that of Trolox, the standard, and at higher concentrations of 100 and 250 µg/ml, the antioxidant capacity of HPS was comparable to that of Trolox (Takemoto *et al*., 2015).
Hepatoprotective	HPS ameliorated FFA-induced steatosis in HepG2 cells by enhancing lipolysis through the upregulation of SIRT1/AMPK and insulin signaling pathways (Tsai *et al*., 2022).
Anticolitis	HPS prevented HFD-promoted colitis in mice by downregulating COX-2, PV-1, and STAT3 expressions (Lee *et al*., 2020).
Antiadipogenesis	At 50 and 100 µg/ml, HPS significantly reduced adipogenesis in 3T3-L1 cells, comparable to that of genistein, the positive control (Takemoto *et al*., 2015).
SIRT1 modulatory	HPS was a SIRT1 activator at 10 and 50 µg/ml (mid-range), and a SIRT1 inhibitor at 1.0 and 100 µg/ml (lower and upper range) (Takemoto *et al*., 2015).
α-Glucosidase inhibitory	HPS inhibited yeast α-glucosidase with an IC_{50} value of 0.23 mg/ml or 7.7 times weaker than PS with IC_{50} value of 0.03 mg/ml (Zhang *et al*., 2017).
	Inhibition of mammalian α-glucosidase by HPS with an IC_{50} value of 0.11 mg/ml (sucrase) and 0.30 mg/ml (maltase) was stronger than PS with IC_{50} values of 0.50 and 0.52 mg/ml, respectively (Zhang *et al*., 2017).
PS	
Anti-inflammatory	The anti-inflammatory effects of PS were displayed by the inhibition of COX-1 and COX-2 with IC_{50} values of 4.9 and 2.2 µM, respectively (Likhitwitayawuid *et al*., 2002).
	PS inhibited COX-1 and COX-2 with IC_{50} values of 1.9 and 0.4 µM, respectively (Kutil *et al*., 2015).
	PS exerted anti-inflammatory effects by inhibiting IL-6 and NF-κB activity in A549 cells with IC_{50} values of 27 and 53 µM, respectively (Yeo *et al*., 2015).
	The inhibition of COX-1 and COX-2 by PS (IC_{50} values of 1.4 and 0.3 µM, respectively) was much stronger than that of ibuprofen (IC_{50} values of 6.9 and 2.1 µM, respectively), the positive control (Leláková *et al*., 2019).
CYP inhibitory	PS displayed strong and weak inhibition toward CYP1A2 and CYP2E1 catalytic activity with K_i values of 0.94 and 42.6 µM, respectively (Mikstacka *et al*., 2006).
	PS strongly inhibited CYP1A1 and CYP1B1 catalytic activity with K_i values of 0.13 and 0.90 µM, respectively (Mikstacka *et al*., 2007).
Neuroprotective	PS protected against parkinsonian mimetic 6-OHDA-induced neurotoxicity in SH-SY5Y cells by reducing LDH release and caspase-3 activity and by attenuating the phosphorylation of JNK and c-Jun (Chao *et al*., 2010).
	PS protected against dopamine-induced SH-SY5Y cell death by promoting cell survival, inhibiting age-related motor function, and activating ERK1/2 pathways (Allen *et al*., 2018).
Antioxidant	The ORAC value of PS (5.0 TE/µM) was slightly lower than those of PS glucosides (3.1 and 1.9 TE/µM) (Uesugi *et al*., 2017).
Antityrosinase	The IC_{50} value of tyrosinase inhibition of PS (594 µM) was 7 and 9 times weaker than those of PS glucosides (66 and 85 µM) (Uesugi *et al*., 2017).
α-Glucosidase inhibitory	Yeast α-glucosidase inhibition by PS with an IC_{50} value of 0.03 mg/ml was 7.7 times stronger than that of HPS (Zhang *et al*., 2017).
	Inhibition of mammalian α-glucosidase by PS with an IC_{50} value of 0.50 mg/ml (sucrase) and 0.52 mg/ml (maltase) was weaker than that of HPS with IC_{50} values of 0.11 and 0.30 mg/ml, respectively (Zhang *et al*., 2017).
Antiplasmodial	Antiplasmodial or antimalarial activity of PS was stronger than pterostilbene but weaker than resveratrol with IC_{50} values of 66, 70, and 60 µM, respectively (Bajsa *et al*., 2007).
LDH activity release	LDH activity release by PS (50 µM) from Caco-2 cells was 2.9% and 41% after 3 and 48 hours, respectively (Storniolo and Moreno, 2018).
Antimelanogenesis	PS inhibited melanogenesis in B16F10 melanoma cells by activating ERK and Akt, and by inhibiting p38 phosphorylation in MAPK/Akt signaling pathways (Chung and Hyun, 2020).
Antiadipogenesis	PS inhibited adipogenesis in 3T3-L1 adipocytes by activation of the AMPK signaling pathway and inhibition of MAPK and Akt pathways (Chung and Hyun, 2021).

Continued

Activity	Compound, effect, and mechanism involved (reference)
Suppression of HSC activation	PS suppressed the activation of HSC via the activation of WIF1 and inhibition of miR-17-5p-mediated Wnt/β-catenin pathway (Zhou *et al*., 2020).
TJ protection	PS exerted suppressive effects on obesity, hepatic steatosis, and chronic inflammation in western diet-fed mice by protecting against JT disruption (Koh *et al*., 2022).

AMPK = AMP-activated protein kinase, BHT = butylated hydroxytoluene, COX = cyclooxygenase, CYP = cytochrome P 450, ERK = extracellular signal-regulated kinase, FFA = free fatty acid, HD = histone deacetylase, HFD = high-fat diet, HSC = hepatic stellate cell, IL-6 = interleukin-6, JNK = c-Jun N-terminal kinase, LDH = lactate dehydrogenase, MAPK = mitogen-activated protein kinase, NF-κB = nuclear factor-κB, 6-OHDA = 6-hydroxydopamine, ORAC = oxygen radical absorbance capacity, PGE_2 = prostaglandin E2, PV-1 = plasmalemma vesicle-associated protein-1, SIRT1 = sirtuin 1, STAT3 = signal transducer and activator of transcription 3, TE = Trolox equivalent, TJ = tight junction, and WIF1 = Wnt inhibitory factor 1.

Terminologies

The following terminologies used in Tables 1 and 2 are explained for more clarity to readers:

- Apoptosis is the process of programmed cell death that is characterized by distinct changes in morphological characteristics and biochemical mechanisms (Elmore, 2007).
- Xenograft is a widely used model to study anticancer effects where human cancer cells are transplanted under the skin of shaven mice (Richmond and Su, 2008).
- Metastasis is the spread of cancer cells to tissues and organs beyond where the tumor originated and led to the formation of new tumors. It is the major cause of death of a patient with cancer (Martin *et al*., 2013).
- SIRTs are a class of deacetylase enzymes that are linked to metabolic control, apoptosis and cell survival, DNA repair, inflammation, neuroprotection, development, and healthy aging (Villalba and Alcaín, 2012). Modulation of the activities of SIRTs has beneficial effects on human diseases.
- HSC activation causes the formation of proliferative fibrogenic myofibroblasts, which eventually leads to hepatic fibrosis and liver cancer (Tsuchida and Friedman, 2017).
- Intestinal epithelial TJs function as physical intestinal barriers (Lee *et al*., 2018; Suzuki, 2013). TJs control permeability and regulate the movement of ions, solutes, and water across the intestinal epithelium. The dysfunction of TJs is associated with the initiation and development of intestinal, metabolic, and inflammatory diseases.
- STAT3 belongs to the STAT family of latent cytoplasmic transcription factors that is very transient and tightly regulated (Kamran *et al*., 2013). When persistently activated, STAT3 plays a central role in tumorigenesis. In tumor cells, blocking STAT3 signaling inhibits tumor growth, angiogenesis, and metastasis without affecting normal cells.

PHARMACOKINETICS

3'-Hydroxypterostilbene

A high-performance liquid chromatographic method was successfully developed and applied to detect and quantify HPS in rat urine and serum samples (Takemoto and Davies, 2009). After intravenous administration of HPS, the predominant compound excreted in the rat urine was HPS glucuronide. Some data on the pharmacokinetic parameters of HPS were as follows: mean half-life in serum and urine was ~0.45/hour and ~1.02/hour, respectively; mean elimination rate constant was ~0.69/hour; mean fraction excreted in the urine unchanged was 17.2%; mean renal clearance was 2.23 l/hour/kg.

In a study on the urinary metabolites of pterostilbene, female mice were administered with pterostilbene in dimethyl sulfoxide by oral gavage (200 mg/kg). Their urine samples were collected after 24 hours, and the metabolites in urine were analyzed using liquid chromatography-mass spectrometry (LC-MS). Results showed that HPS was one of the nine metabolites identified as mono=hydroxylated pterostilbene (Shao *et al*., 2010).

After ingestion of HPS and pterostilbene (50 mg/kg) separately, the serum of rats was examined (Chen *et al*., 2017). Rats that ingested HPS revealed the presence of two unidentified metabolites without the parent compound, while rats that ingested pterostilbene had only one metabolite (glucuronide or sulfate conjugate) and the parent compound. These results showed that the biotransformation of HPS might not be glucuronide or sulfate conjugation, unlike pterostilbene (Chen *et al*., 2017).

In a recent study on the metabolites of pterostilbene incubated with rat, dog, and human hepatocytes for 2 hours, HPS was one of the six primary metabolites identified (Jiang *et al*., 2021). HPS was formed by hydroxylation at C3' of ring B of the phenol moiety in all three types of incubated hepatocytes.

Pinostilbene

The pharmacokinetics of PS was studied by intravenous injection (5 or 10 mg/kg) into Sprague-Dawley rats (Chen *et al*., 2016). LC–MS/MS method was developed to determine and quantify PS in the rat plasma. Results showed that PS displayed rapid clearance of 129 or 107 ml/minute/kg and extremely short mean transit time of 6.2 or 8.5 minutes. The bioavailability of PS was limited but highly erratic. It was inferred that stilbenes with meta-hydroxyl group(s) may be associated with metabolic instability and subsequently more rapid clearance and lower oral bioavailability.

CD-1 mice were fed a diet containing pterostilbene for 3 weeks, and their colon content was examined (Sun *et al*., 2016). PS was found to be a major metabolite of pterostilbene in the colon. The quantity of PS in the colon content and mucosa was relatively high, comparable to the amount of pterostilbene. PS was likely formed by the demethylation of pterostilbene by gut microbiota demethylases. Therefore, PS is a colonic metabolite of pterostilbene. An earlier study also found that PS (identified as monodemethylated pterostilbene) was one of the nine metabolites in the urine of mice after an oral gavage of pterostilbene (Shao *et al*., 2010).

PS was another primary metabolite formed by pterostilbene incubated with rat, dog, and human hepatocytes (Jiang *et al*., 2021). PS was formed by the demethylation of pterostilbene incubated in all three types of hepatocytes. An

earlier study reported that PS was among the 21 compounds identified in the rat urine after oral administration of the resin from *D. cochinchinensis* (Liu *et al*., 2013).

PATENTS

3'-Hydroxypterostilbene

A patent on HPS was filed by Majeed and Nagabhushanam from New Jersey, US, and by Ganjihal from Bangalore, India, as inventors, and by Sami Labs Ltd. in Bangalore, India, as the assignee (Majeed *et al*., 2016). The United States patent US 9,458,075 B1, dated October 2016, was entitled "process for the manufacture of HPS." The invention disclosed a novel and high-yielding novel scheme for synthesizing HPS. Using pterostilbene as the starting material, the invention uses favorable reactants and reagents, is cost-effective and industrially scalable, involves minimal reaction steps, is economically viable, and produces a high yield (60%–70%) of HPS. Concurrently, another patent was filed by Majeed as the inventor and by Nagabhushanam as the assignee (Majeed and Nagabhushanam, 2016). The World Intellectual Property Organization patent WO 2016/032925, dated March 2016, was entitled "3-hydroxypterostilbene and therapeutic applications thereof." The invention discloses the therapeutic potential of HPS in colon cancer and prostate cancer, specifically, the apoptotic and autophagy properties of HPS in controlling colon and prostate tumors.

Pinostilbene

A patent on PS was filed by Hong, Kang, Heo, and Lee from Daejeon, Korea, and by Ahn from Seoul, Korea, as inventors, and by the Korea Research Institute of Bioscience and Biotechnology in Daejeon, Korea, as the assignee (Hong *et al*., 2018). The patent WO 2018/008979 A1, dated November 2018, was entitled "recombinant vector for producing PS or pterostilbene." A method was developed to produce PS or pterostilbene using a recombinant vector. The single vector system is economical and capable of mass production via a single microbial metabolic pathway. PS or pterostilbene produced possesses anticancer, anti-inflammatory, antihyperlipidemic, and antioxidant effects and thus can be beneficially used in the pharmaceutical industry.

CONCLUSION

Methoxylated stilbenes such as pterostilbene are well studied but not the lesser known HPS and PS reviewed in this article. Both HPS and PS have promising prospects for further research. The cellular and molecular mechanisms underlying the effects of HPS and PS on various types of cancer cells would yield exciting results. Further research on their structural modifications is needed to synthesize novel derivatives with enhanced anticancer properties. The effects of methoxylation and hydroxylation on HPS and PS, together with studies on their pharmacokinetics and structure-activity relationships, would be interesting. Clinical research on HPS and PS is warranted to evaluate their chemopreventive efficacy and safety when used alone or in combination with other chemotherapy agents.

FINANCIAL SUPPORT

The Lead and Sole Author declares that the funds for the publication of this review article in JAPS (Article Processing Charges) are from World's Top 2% Scientist Research Grant, CERVIE, UCSI University (Grant Code: T2S-2023/004). The author is grateful for the financial support.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

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How to cite this article:
Chan EWC. 3′-Hydroxypterostilbene and pinostilbene: Their chemistry, sources, anticancer and other pharmacological properties, pharmacokinetics, and patents. J Appl Pharm Sci, 2023; 13(9):001–008.