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REVIEW ARTICLE

Polydatin: A review of pharmacology and pharmacokinetics

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Abstract

Context: Polydatin, also named piceid (3,4′,5-trihydroxystilbene-3-β-D-glucoside, PD), is a monocrystalline compound isolated from *Polygonum cuspidatum* Sieb. et Zucc. (Polygonaceae), but is also detected in grape, peanut, hop cones, red wines, hop pellets, cocoa-containing products, chocolate products and many daily diets. There are numerous investigations reported of PD in the past 22 years, but they are usually scattered across various publications, which may block further research and clinical use of PD.
Objective: The article summarizes and evaluates the published scientific information of PD pharmacological effects and pharmacokinetics since 1990.
Materials and methods: The information from 98 cases included in this review was compiled using major databases such as MEDLINE, Elsevier, Springer, PubMed, Scholar and CNKI.
Results: Numerous pharmacological investigations of PD mainly focus on cardiovascular effects, neuroprotection, anti-inflammatory and immunoregulatory effects, anti-oxidation, anti-tumor, liver and lung protection, etc.
Conclusion: A great number of pharmacological and pharmacokinetic investigations in the past 22 years have demonstrated that PD has favorable therapeutic properties, indicating its potential as an effective material. However, further research is needed to explore its molecular mechanisms of action and definitive target proteins.

Keywords

Cardiovascular effect, immune regulation, nerve protection, plant

History

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Introduction

Plants have been the most important source of traditional medicines throughout the world for thousands of years and provide continuously new remedies for humankind. Great efforts have been made to identify natural active ingredients from plants using various techniques. Polydatin (PD, also named pieceid, (*E*)-piceid, (*E*)-polydatin, *trans*-polydatin, 3,4′,5-trihydroxystilbene-3-β-D-glucoside) is a monocrystalline compound originally isolated from the root and rhizome of *Polygonum cuspidatum* Sieb. et Zucc. (Polygonaceae), a traditional Chinese medicine that has long been used in China as an analgesic, anti-pyretic, diuretic and expectorant. It is a glucoside of resveratrol (3,4′,5-trihydroxystilbene) in which the glucoside group bound to the position C-3 substitutes a hydroxyl group, belonging to stilbene phytoalexins (Figure 1). There are four main derivatives of PD in nature, including *trans*-polydatin, *trans*-resveratrol, *cis*-polydatin and *cis*-resveratrol. The bioactivity of *trans*-isomers is higher than that of *cis*-isomers (Mikulski & Molski, 2010).

PD can also be detected in grape, peanut, hop cones, red wines, hop pellets, cocoa-containing products, chocolate products and many daily diets. PD is the most abundant form of resveratrol in nature (Reqev-Shoshani et al., 2003). Previous studies have demonstrated that PD has many biomedical properties such as anti-platelet aggregation, anti-oxidative action of low-density lipoprotein (LDL), cardioprotective activity, anti-inflammatory and immune-regulating functions. In this review, we tried to present and assess the pharmacological and pharmacokinetic studies of PD.

Pharmacological effects

Effects on cardiac muscle cells

PD can protect myocardial cells (MCs) against injury elicited by oxygen and glucose deprivation (OGD) and chlorpromazine (Luo et al., 1990), increase Ca^{2+} in MCs with enhancement of MC contraction extent (Zhao et al., 2003). Zhao et al. (2010) observed the effect of PD on adriamycin-injured myocardial ultra-structure of rats and discovered that PD significantly reduces the toxicity of adriamycin on cardiomyocytes (CMs), showing an evident protective action. In myocardial infarction, using the canine model established by coronary left anterior descending branch ligation, injection of

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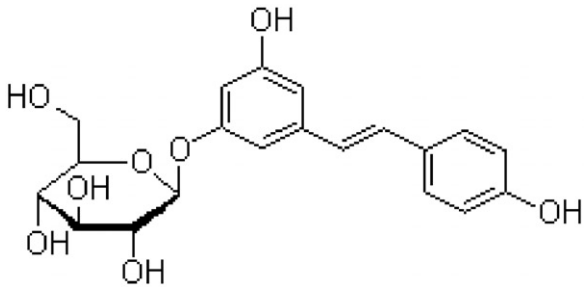

Figure 1. Chemical structure of polydatin.

PD markedly reduces the severity of ischemia, diminishes the ischemic and infarcted area, lowers the activities of serum lactate dehydrogenase (LDH) and creatine kinase, and thus alleviates the ischemic injury of CMs (Zhang et al., 2006). PD can significantly decrease the number of TdT-mediated dUTP nick end labeling-positive cells (apoptotic cells) and apoptosis rate in ischemia/reperfusion (I/R)-induced myocardial injury of rats through regulation of Bcl-2 and Bax protein expression (Zhang et al., 2009).

An extra-corporeal experiment was conducted by Zhao et al. (2004) to explore the impact of lipopolysaccharide (LPS) on β-adrenergic receptor (β-AR) and prevention/treatment effects of PD. The results indicate that LPS directly induces β-AR decrease and down-regulates its affinity in CMs, while PD reverses these alterations. It may be one of the important mechanisms of PD improving myocardial contraction (Zhao et al., 2004). Another experiment reveals that LPS induces obvious lowering of myocardial contraction and mitochondrial injury, while PD reverses these unfavorable changes to protect CMs by regulating protein kinase C activity and protecting the ultrastructure of myocardial fibers (Xue et al., 2008).

Intravenous administration of PD (20 μg/kg) causes a significant decrease in the release of creatine phosphokinase and LDH from the damaged myocardium by activation of protein kinase C-ATP-sensitive K^+ channel-dependent signaling (Miao et al., 2011, 2012). The electrophysiological mechanism is that PD shortens the duration of 50% repolarization (APD_{50}) and 90% repolarization (APD_{90}), but has no effects on resting potential, overshoot (OS), amplitude of action potential (APA) and the maximal rate of depolarization in phase 0 (Vmax) in normal papillary muscles. In partially depolarized papillary muscles, PD (50 μmol/L) not only shortens APD_{50} and APD_{90} but also decreases OS, APA and Vmax (Zhang et al., 2011a). The further study shows that PD down-regulates L-type Ca^{2+} channel activity and up-regulates ryanodine receptor activity, resulting in the moderate decrease of Ca^{2+} transient. Furthermore, PD increases myofilament Ca^{2+} sensitivity and at the same time modulates β-AR regulation of excitation–contraction (EC) coupling by remarkably alleviating β-AR stimulation-induced enhancement of Ca^{2+} signaling without impairing β-AR inotropic effect (Deng et al., 2012).

PD reduces cardiac weight indexes and the content of cyclic adenosine monophosphate and angiotensin II (Ang II) in isoproterenol-induced mice. It also decreases the size of CM and the levels of aldosterone (ALD), tumor necrosis factor-α (TNF-α), Ang II and endothelin-1 (ET-1), reduces ventricular collagen volume and depresses blood pressure in pressure-overload rats. These results demonstrate that PD has favorable effects on attenuating ventricular remodeling by inhibiting the activation of neurohormone, especially in rennin-angiotensin-ALD system (Gao et al., 2010). PD can also protect rats against myocardial I/R injury by up-regulating the levels of superoxide dismutase (SOD), nitric oxide synthase (NOS), constitutive NOS and nitric oxide (NO) and decreasing malondialdehyde (MDA) content (Zhang et al., 2008a).

Effects on endothelial cells

The structural integrality and normal function of vascular endothelial cells (VECs) are of great importance to maintain the permeability, immune defense and inflammation response of vessels, and VEC injury is the essential ring for genesis and development of atherosclerosis. The contractive response of normal rabbit aortic stripe to phenylephrine (PE) is not affected by PD or asymmetric dimethyl-arginine (ADMA), but can be weaken by PD in a dosage-dependent manner after the stripe is preconditioned by ADMA, indicating that PD dose does not put any impact on the contractive function of normal aortic stripe but noncompetitively antagonizes the contractive response of VECs to PE in the presence of ADMA (Qin et al., 2004).

PD can inhibit inducible cell adhesion molecule-1 (ICAM-1) expression in LPS-stimulated EC and attenuate white blood cell (WBC)-EC adhesion (Zhao et al., 2003). The inhibitory activities of PD on monocyte adhesion to TNF-α-activated endothelial cells are effective. PD could depress the protein and mRNA expression levels of ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) in cultured endothelial cells through inhibition of nuclear factor-kappa B (NF-κB) pathway activation (Deng et al., 2011). Inducible nitric oxide synthase (iNOS) activity significantly increased in experimental hyperlipidemia rats, indicating the production of large amounts of NO, but evidently decreased by PD treatment (Zhu & Jin, 2005).

Hepatoprotective effects

The hepatoprotective effects of PD are closely related to the anti-inflammatory and anti-oxidative activities. Series studies indicate that PD is capable of alleviating liver injury induced by carbon tetrachloride (CCl_4) and high-fat food feeding (HFD). PD (10^{-7}–10^{-4} mol/L) can protect primarily cultured rat hepatocytes against CCl_4 injury *via* reducing glutamic pyruvic transaminase release, MDA formation and glutathione (GSH) content (Huang et al., 1999). PD (0.05–4 mmol/L) decreases NO and MDA contents, inhibits NOS activity, increases SOD, GSH-Px and GSH activities, and suppresses alanine aminotransferase (ALT) release in pyrogallic acid induced hepatocyte culture medium (Mo et al., 1999). The increases in serum aspartate aminotransferase (AST), ALT and hepatic MDA, TNF-α, interleukin (IL)-1β, cyclooxygenase (COX)-2, iNOS and NF-κB in CCl_4-induced liver injury mice are significantly reversed, and the content of GSH, activities of GSH transferase, SOD, catalase (CAT), GSH peroxidase and mRNA and protein expression levels of hepatic transforming growth factor-β1 (TGF-β_1) are also modulated after PD preadministration for 5 continuous days (Zhang et al., 2012a).

PD can alleviate hepatic steatosis and reduce plasma and liver concentrations of TG, total cholesterol (TC) and free fatty acid significantly in HFD-induced chronic liver damage rat. In addition, the levels of TNF-α, MDA and 4-hexanonenal are markedly suppressed by PD in the liver of HFD-fed rats. PD also decreases the gene expression of sterol-regulatory element binding protein and its target genes involved in lipogenesis, including fatty acid synthase and stearoyl-CoA desaturase 1 in HFD-fed rats (Zhang et al., 2012b). Another *in vivo* test reveals that PD obviously reduces serum fasting insulin, fasting blood glucose, insulin resistance index and TNF-α level, and improves the insulin sensitivity index level, whose effects at high dose are better than those of fenofibrate (Zhang & Lv, 2010).

Fulminant hepatic failure (FHF) is a devastating clinical syndrome with extremely poor prognosis and high mortality, which can be induced by LPS in D-galactosamine (D-GalN)-sensitized mice. Pretreatment with PD (10, 30 and 100 mg/kg) exerts the evident protective effects on LPS/D-GalN-induced FHF mice, which reduces serum ALT and AST activities, diminishes liver histopathological injury and decreases mortality in a dose-dependent manner. In addition, pretreatment with PD also suppresses TNF-α production, myeloperoxidase (MPO) activity, intercellular adhesion molecule-1 (ICAM-1) and endothelial cell adhesion molecule-1 expression, caspase-3 activation and NF-κB activity in model mice. PD probably reduces TNF-α production *via* inhibition of NF-κB activation (Wu et al., 2012).

Neuroprotective activity

Previous studies have proved that PD has an obvious neuroprotective activity, especially in the cerebral ischemic pathogenesis. PD protects against the brain damage caused by permanent middle cerebral artery occlusion (MCAO) through up-regulating the expression of glioma-associated oncogene homolog1, patched-1 and SOD1, down-regulating the expression of NF-κB p65, and ameliorating blood–brain barrier permeability (Ji et al., 2012). Intravenous injection of PD can reduce the volume of brain infarction, improve neurological deficits, inhibit the expression of ICAM-1, VCAM-1, E-selectin, L-selectin and integrins after the operation of MCAO for 1 h (Cheng et al., 2006c). PD protects against learning and memory impairments, markedly attenuates cognitive deficits, decreases the production of MDA, meanwhile significantly increases the activities of SOD and CAT in the rat model of vascular dementia induced by chronic cerebral hypoperfusion (Li et al., 2012). PD treatment significantly enhances the cell viability, reduces the levels of LDH, NO, MDA and increases SOD activity of pheochromocytoma cells injured by OGD (Xu et al., 2010) and effectively alleviates OGD-induced neuron injury (Li et al., 2012). Additionally, PD can up-regulate the expression of brain-derived neurotrophic factors in cerebral cortex of neonatal rats (Sun et al., 2012).

PD can improve the abilities of learning and memory in chronic alcoholism mice. Alcohol induces the mRNA expression of cyclin-dependent kinases 5 and *N*-methyl-D-aspartate in the prefrontal cortex of chronic alcoholism mice, but PD markedly reverses these alterations (Xu et al., 2011, 2012). Although the molecular mechanism is not fully understood, PD significantly inhibits cerebral edema and increases the content of Asp and Glu in cerebral hemorrhage rats (Liu et al., 2010). Amyloid-β peptide (Aβ) accumulation is one of the major neurodegenerative processes occurring during the progression of pathogenesis in Alzheimer's disease. Rivière et al. (2010) tested 20 stilbenes derivatives against amyloid-β peptide (Aβ) aggregation *in vitro* by ultraviolet (UV)-visible measurements and electron microscopy. The results indicate that PD effectively and dose-dependently inhibits Aβ polymerization and has the best inhibitory activity among these compounds. The inhibitory rate is 63% and EC_{50} $6 \pm 2\,\mu M$ (Rivière et al., 2007, 2010). PD probably destabilizes fibrils and oligomers to give back monomers induced by $A\beta_{25-35}$ that can open the hydrophobic zipper and shift the reversible equilibrium ''random coil $\leftrightarrow$ β-sheet'' to the disordered structure (Rivière et al., 2009).

Lung protective effects

The protective effects of PD against acute or chronic lung disease are supported by numerous studies. PD has a weak activity in inducing relaxation of isolated pulmonary arteries *in vitro*. Glycosylation markedly diminishes the biological effects of stilbene derivatives possibly because of decreased lipophilicity and/or target accessibility (Waffo-Téquo et al., 2001). The prophylactic and therapeutic effects of PD on acute lung injury in rats with endotoxic shock are carried out by inhibiting phospholipase A2 activity and gene expression of secretory phospholipase A2 type IIA. The mechanism is possibly that PD up-regulates Clara cell secretory protein mRNA expression and down-regulates $cPLA_2$ mRNA expression in lung (Shu et al., 2004, 2011).

On the one hand, PD alleviates lung I/R injury in rabbits by down-regulating TLR4 and NF-κB expression and inhibiting the release of mediators of inflammation as ICAM-1 (Jin et al., 2009). On the other hand, PD also ameliorates SOD activity and injured alveoli rate and reduces MDA content to protect against lung I/R injury (Wang et al., 2008). Moreover, PD regulates the levels of NO, Ang II and ET, which are closely related to pulmonary hypertension remodeling system, and abates the forced activation of PKC signaling by thymeleatoxin (Miao et al., 2012). PD significantly protects against rat pulmonary micro VECs injury *in vitro* induced by hypoxia through preventing the increases of LDH activity and vascular endothelial growth factor (VEGF) expression (Wang et al., 2001). After PD intraperitoneal injection, the activity of PLA_2, the concentration of hydroxyproline in lung homogenate and the levels of prostaglandin E_2 (PGE_2), leukotriene C_4 and TGF-β_1 in bronchoalveolar lavage fluid are significantly reduced. However, PD does not completely block the process of pulmonary fibrosis (Zhang et al., 2011b).

Anti-arteriosclerosis

Zhu and Jin (2006) observed the effect of PD on blood lipids metabolism in the experimental rat model of hyperlipidemia established by HFD. The results show that oral administration of PD for four successive weeks significantly decreases the serum levels of TC, triglyceride (TG), LDL cholesterol (LDL-C) and apolipoprotein A1 (ApoA1) in the model rats but evidently increases the ratios of high-density lipoprotein

cholesterol (HDL-C)/TC and ApoA1/ApoB (Zhu & Jin, 2006). Although there is no statistically significant difference observed in the serum HDL-C levels, the ratios of LDL-C/HDL-C and TC/HDL-C remarkably decrease in PD-treated high-fat/cholesterol hamsters (Du et al., 2009). Similar effects are displayed in rabbits, and administration of PD can significantly reduce the rabbit serum levels of TC, TG and LDL-C in a dose-dependent manner (Xing et al., 2009).

Anti-inflammatory activity

PD has several beneficial effects attributed to its anti-inflammatory properties, such as nephroprotective, hepatoprotective and lung protective activities. Endometriosis, an estrogen-dependent inflammatory disease, is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic inflammatory reaction (Kennedy et al., 2005). PD exhibits anti-hyperuricemic activity through regulating renal organic ion transporters in hyperuricemic mice (Shi et al., 2012).

Numerous studies have reported that PD modulates the expression of inflammatory cytokines and cell adhesion molecules *in vivo* and *in vitro*. PD decreases IL-17 production in activated human peripheral blood mononuclear cells through down-regulation of IL-17 mRNA expression in cells (Lanzilli et al., 2012). The expression of ICAM-1 and TGF-β_1 in glomerular mesangial cells and high glucose-induced production are significantly suppressed by PD *in vitro* (Xie et al., 2012). Additionally, PD downregulates NF-κB p65 activity and expression, blocks the expression of TNF-α, IL-6 and IL-1β at mRNA and protein levels, decreases MPO activity and alleviates inflammatory damage of colitis in mice with ulcerative colitis, suggesting that the anti-inflammation effects of PD can be attributed, at least partially, to the blocking of the NF-κB pathway (Xie et al., 2012; Yao et al., 2011). After intraperitoneal injection of PD (20 mg/kg), NF-κB expression also significantly decreases in renal ischemia-reperfusion injury rats (Fei et al., 2009). PD suppresses the level of serum uric acid *in vivo* and *in vitro* by inhibition of xanthine oxidase activity and ameliorates the renal function in urate nephropathy mice induced by fructose. The nephroprotective activity is attributed to PD inhibition of the involved inflammatory cascade, including the expression of NF-κB p65, COX-2 and iNOS proteins and the production of TNF-α, PGE_2 and IL-1β, which are related to the oxidative stress (Chen et al., 2013).

In many chronic inflammatory diseases, PD can inhibit constitutive bacterial LPS- and interferon-γ (T/I)-induced but not TGF-α-induced extracellular signal regulated kinase (ERK) phosphorylation and suppress NF-κB activity in LPS and T/I-induced primary human keratinocytes (HaCaT). PD activates aryl hydrocarbon receptor machinery in UV-exposed keratinocytes through down-regulating the gene expression of pro-inflammatory cytokines/enzymes, suppressing interferon gamma-inducible protein 10 (IP-10) release, and up-regulating IL-8 level (Potapovich et al., 2011), opposing enhanced monocyte chemotactic protein-1 (MCP-1) and IP-10 transcription/synthesis (Pastore et al., 2012). PD is also able to modulate IL-6, IL-8 and TNF-α gene expression, increase the release of human β-defensin 2 and gene expression of heat shock protein 70B′ in heat-stressed HaCaT (Ravagnan et al., 2013). PD enhances fibroblast proliferation at the concentrations of 10^{-5} and 10^{-4} mol/L but blocks the cellular cycle in S phase at 10^{-3} mol/L, suggesting its bidirectional regulatory effects in fibroblasts (Bian et al., 2012).

Anti-shock effects

Combined with hypotensive resuscitation, bolus infusion of PD (2 mg/kg) evidently prolongs the survival time of pregnant rabbits with uncontrolled hemorrhagic shock by improving capillary perfusion as indicated by increased arteriole diameter and higher functional capillary density (Sheng et al., 2011). PD can activate K_{ATP} channels of vascular smooth muscle cells (VSMC) and decrease pH value and Ca^{2+} of VSMC. PD has multiple effects on VSMC, MC, WBCs and endothelial cells (EC), which are closely related to the enhancement of heart function and improvement of microcirculatory perfusion in shock (Zhao et al., 2003). PD can inhibit mitochondrial swelling, increase mitochondrial membrane potential and improve intracellular adenosine triphosphate (ATP) levels. Furthermore, PD also preserves lysosomal stability, suppresses activation of K_{ATP} channels and arteriolar smooth muscle cell hyperpolarization and reduces vasoresponsiveness to norepinephrine that normally follows severe shock (Wang et al., 2012). Increased lipid peroxides levels, lysosomal injury and mitochondrial permeability transition pore opening cause swollen mitochondria with poorly defined cristae, decreased mitochondrial membrane potential ($\Delta\Psi$) and reduced ATP content in neurons of rats after 2 h of shock, indicating mitochondrial dysfunction. However, PD evidently inhibits these alterations, which increases the ATP level from $44.14 \pm 13.81\%$ to $89.57 \pm 9.21\%$ and prolongs survival time from 6.3 ± 5.9 h to 31.6 ± 13.7 h. PD may be the best choice for protection of neuron against mitochondrial injury in severe shock (Wang et al., 2013).

Anti-tumor activity

PD has the favorable cytotoxic effects on many human tumor cell lines such as human cervical carcinoma HeLa cells, hepatoma cell line SMMC-7721 cells, epidermal carcinoma A-431 cells and nasopharyngeal carcinoma CNE cells. PD can cause mitochondrial disruption, trigger endoplasmic reticulum (ER) stress and down-regulate Akt phosphorylation in CNE cells, while knock-down of CCAAT/enhancer-binding protein homologous protein dramatically abrogates the inactivation of Akt. Furthermore, PD-induced reactive oxygen species (ROS) are an early event that triggers ER stress mitochondrial apoptotic pathways in CNE cells (Liu et al., 2011). Additionally, PD has higher binding affinity to the target G-quadruplex in the proximal VEGF promoter that reduces VEGF expression in PAN-1 cancer cells and NIH3T3 cells (Balasubramanian & Neidle, 2009; Li & Yuan, 2010; Sun et al., 2005). PD inhibits the formation of capillary-like tube networks (angiogenesis) of human umbilical vein endothelial cells (HUVECs) and suppresses DNA synthesis in Lewis lung carcinoma cells (Kimura & Okuda, 2000).

Through hydrophobic stacking and hydrogen bond, PD can interact with neurotensin (NT). The polyphenol–protein complexes seem to affect NT metabolism

(Richard et al., 2005) and diminish the NT-induced metabolic activation of colon carcinoma cells (Briviba et al., 2001). PD significantly inhibits COX-1 activity, with the half maximal inhibitory concentration (IC_{50}) value of 10.6 μM in mouse mammary organ culture (Waffo-Téquo et al., 2001).

Anti-oxidative activity

PD has significant anti-oxidant properties due to its molecular structure of conjugated double bond, which is closely associated with its many pharmacological effects including protecting against I/R injury, improving learning and memory, lowering lipid and extending lifespan. PD is more resistant to enzymatic oxidation than resveratrol owing to the change of molecule structure (Fabris et al., 2008). In fact, the anti-oxidative activity of *trans*-polydatin is stronger than *cis*-PD and *trans*-resveratrol (Mikulski & Molski, 2010).

Free radical scavenging effect is one of PD anti-oxidative properties. Both NADH-PMS-NBT system produced oxygen free radicals (O_2^-) and $EDTANa_2$-Fe(II)-H_2O_2 system produced hydroxyl radicals (·OH) can be reduced by PD *in vitro* (Tian & Yang, 2001), which also scavenges ·OH produced by H_2O_2 to protect HUVECs (ECV304) in a dose-dependent manner (Su et al., 2010). Additionally, PD shows a notable anti-oxidant capacity in fish oil-in-water emulsions (Medina et al., 2010). PD enables the extension of mean lifespan of transgenic strain CL2166 due to its protective effects against oxidative stress (Wen et al., 2012), shows a slower but prolonged protective action against lipid peroxidation in comparison with BHT (2,6-di-tert-butyl-4-methylphenol) and α-tocopherol (vitamin E) and is more efficacious than resveratrol. The susceptible hydroxyl group of PD is located in the lipid region of the bilayer close to the double bonds of polyunsaturated fatty acids, making it particularly suitable for the prevention and control of the lipid peroxidation of the membranes (Fabris et al., 2008).

PD displays no cytotoxicity in HaCaT cells at low concentrations (<100 μg/ml), but reduces HaCaT cell death induced by UVB irradiation. The production of ROS, one of important parameters for an anti-oxidative activity, is apparently increased by UVB irradiation but significantly decreased by PD, which also evidently inhibits COX-2 expression boosted by UVB irradiation in HaCaT cells and the epidermis of BALB/c-nu mice. The mechanism is involved in PD suppressing UVB-induced activation of p38, JNK and ERK1/2 in the cells (He et al., 2012).

Inhibition of thrombus formation

PD shows an antagonistic action on thrombosis, which significantly reduces the fibrinogen content and platelet adhesive rate in acute blood-stasis model rats (Wang et al., 2004), inhibits platelet aggregation and decreases the production of thromboxane B_2 (TXB_2) in platelet-rich plasma induced by arachidonic add or Adenosine diphosphate (Shan et al., 1990). The thrombin-induced platelet neutrophil adhesion and platelet aggregation in nutmeg phorbol-activated neutrophilic granulocyte suspension are markedly inhibited by PD. In addition, PD is also capable of lowering TXB_2 content and elevating 6-keto-PGF1α level in plasma (Chen et al., 2006a,b).

Inhibition of melanogenesis

PD inhibits tyrosinase activity and melanin production in melanocytes better than arbutin, which is well known to inhibit melanin formation. Furthermore, the mRNA and protein expression of tyrosinase, tyrosinase-related proteins 1, 2 and microphthalmia-associated transcription factor is significantly suppressed in melanocytes (Jeong et al., 2010). However, PD displays only weak effects on tyrosinases from mushroom and murine melanoma B-16 *in vitro* with IC_{50} value more than 100 μM (Kim et al., 2002). Presumably different species of cells are responsible for these two diametrically opposed results.

Anti-microbial activity

P. cuspidatum ethyl acetate fraction, including PD, resveratrol, anthraglycoside B and emodin, displays a effective antibacterial activity, which inhibits dental caries-related factors of *Streptococcus mutans* and *Streptococcus sobrinus* and significantly reduces glycolytic acid production at a low level (Ban et al., 2010). PD also has weak inhibitory effects on the acidogenicity of *S. mutans* UA 159 and subsequent dental caries formation (Kwon et al., 2010).

Immunoregulatory effects

The therapeutic effects of PD on passive cutaneous anaphylaxis are carried out by decreasing antigen-stimulated mast cell degranulation. The possible mechanism is that PD suppresses high-affinity IgE receptors-mediated Ca^{2+} mobilization by inhibiting Ca^{2+} entry through Ca^{2+} release-activated Ca^{2+} channel, which are the major contributors to PD-induced mast cell stabilization (Yuan et al., 2012).

Pharmacokinetic studies

Pharmacokinetic studies are often necessary to the clinical use of drugs effectively and safely. The absorption, distribution and metabolism of PD are closely combined with its bioactivity. To date, however, few analytical methods have been used for determination of *trans*-stilbene glycoside in biological samples when its pharmacokinetics profiles are studied (Lv et al., 2011; Ren et al., 2010).

The absorption of some phenols from the diet is enhanced by conjugation with glucose. It seems that PD can be more efficiently conjugated with glucose (Hollman et al., 1995; Hollman, 1997). PD can be absorbed in two different transport systems: passive diffusion and active transport *via* sodium-dependent glucose transporter (SGLT1) mainly existing in the stomach and intestines (Henry et al., 2005). PD, unlike resveratrol that penetrates cell membrane passively, enters the cell *via* an active mechanism using glucose carriers. PD is absorbed at 4 °C, the initial rate of *trans*-PD incorporation is about 1.6-times lower than that estimated at 37 °C, while the content in cells is not much lower (He et al., 2007), suggesting PD active transport by SGLT1. Therefore, PD solution is essential for its uptake in the intestines. Although the accumulation rate and residual amount of resveratrol are higher than PD in Caco-2 cells, the half life time of PD is nearly 4 h, and C_{max} is higher than resveratrol at the same

dosage. In addition, $AUC_{(0-\infty)}$ and $t_{1/2}$ of PD are also increased in a dose-dependent manner (Zhou et al., 2009). Transepithelial transport of PD clearly occurs with the favorable apparent permeability coefficient (Papp) about 10×10^{-6} cm/s for the apical to basolateral flux, suggesting virtually complete absorption of PD in humans (Yee, 1997).

The different tissue concentrations reach maximum values at 10 min postdose, which are 1.53 ± 0.13, 5.22 ± 0.46, 4.59 ± 0.59 and 6.41 ± 0.77 μg/g in heart, liver, lung and kidney, respectively, after intravenous administration of 20 mg/kg PD (Gao et al., 2006). But after oral administration of 50 mg/kg PD to male rats, the maximum concentrations in heart, liver, spleen, lung, kidney, stomach, small intestine, brain and testis are 0.50 ± 0.26, 4.47 ± 2.51, 28.03 ± 13.81, 10.42 ± 3.86, 2.58 ± 1.19, 168.79 ± 77.45, 108.66 ± 29.79, 6.07 ± 2.85 and 5.30 ± 2.40 μg/g, respectively (Lv et al., 2006).

PD is deglycosylated in *trans*-resveratrol through two possible pathways: the first is a cleavage by cytosolic-β-glucosidase, after passing the brush-border membrane by SGLT1. The second is deglycosylation on the luminal side of the epithelium by the membrane-bound enzyme lactase-phlorizin hydrolase, followed by passive diffusion of the released aglycone, which is further metabolized inside the cells into two glucuronoconjugates (Henry-Vitrac et al., 2006). Resveratrol, dihydroresveratrol monosulfate, PD-monosulfate and PD-monoglucuronide are detected in rat urine after oral administration of PD, which can be transformed into resveratrol, dihydropiceid and dihydroresveratrol after incubation with gut microbiota (Wang et al., 2011). Resveratrol, glucuronidated resveratrol and glucuronidated *trans*-PD, the first-pass metabolites of PD in rat small intestine and liver, are detected in plasma after perfusion of *trans*-PD *in situ* rat small intestine and oral administration of PD (Zhang et al., 2008b; Zhou et al., 2009). After oral administration, 98.4% of PD is metabolized in the intestines and liver, and glucuronidated resveratrol is the main metabolite, reaching 84% (Zhou et al., 2009). In addition, the small intestine extracts are more active than the liver extracts (Zhou et al., 2007).

Conclusion

P. cuspidatum, a traditional Chinese medicine, has long been used as analgesic, anti-pyretic, diuretic and expectorant in clinical practice. PD, a monocrystalline compound isolated from *P. cuspidatum*, shows many pharmacological effects confirmed by numerous investigations, including cardiovascular protection, neuroprotection, anti-inflammation, immunoregulation, anti-oxidation, anti-tumour and liver and lung protective effects.

However, further studies are required for PD development. Although various bioactivities of PD are confirmed in laboratory animals, organs or cells, few molecular mechanisms of action are known, and the definitive target proteins bound by PD still remain undetermined, which will make against further clinical applications of PD. When a drug is used in clinical practice, its safety is especially important. Unfortunately, there are also few toxicological evaluations reported on PD.

The documents summarized above strongly support the point of view that PD has favorable therapeutic properties, indicating its potential as an effective material. This review presents and assesses the pharmacological and pharmacokinetic studies of PD in the past 22 years. It may be important for interested readers to easily identify and research further into PD.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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