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Review of the Pharmacology and Pharmacokinetics of Polydatin

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ABSTRACT:

In addition to being found in grape, peanut, hop cones, red wines, hop pellets, cocoa-containing products, chocolate products, and many daily diets, polydatin, also known as piceid (3,40,5-trihydroxystilbene-3-b-D-glucoside, PD), is a monocrystalline compound isolated from Polygonum cuspidatum Sieb. et Zucc. (Polygonaceae). In the past 22 years, there have been many investigations on PD described, however they are typically dispersed across multiple publications, which may hinder future study and clinical use of PD. The article reviews and summarises the scientific literature on the pharmacological effects and pharmacokinetics of PD published since 1990.

Major databases like MEDLINE, Elsevier, Springer, PubMed, Scholar, and CNKI were used to gather the data from the 98 cases that made up this review. Numerous pharmacological studies on PD mostly concentrate on cardiovascular effects, neuroprotection, anti-inflammatory and immunoregulatory effects, anti-oxidation, anti-tumor, and liver and lung protection, among other things. In the past 22 years, numerous pharmacological and pharmacokinetic studies have shown that PD has excellent therapeutic qualities, showing its potential as a useful substance. However, more investigation is required to determine its precise target proteins and molecular mechanisms of action.

Keywords*:* Immune Regulation, Nerve Protection, Plant, Cardiovascular Effect

INTRODUCTION:

For thousands of years, plants have been the primary source of traditional medicines used throughout the world, and they continue to provide humans new treatments. Numerous methods have been used to determine the natural active components found in plants. Polydatin (PD, also known as pieceid, (E)-piceid, (E)-polydatin, trans-polydatin, and [3,40] trihydroxystilbene-3-b-D-glucoside) is a monocrystalline substance that was first isolated from the root and rhizome of Polygonum cuspidatum Sieb. et Zucc. (Polygonaceae), a traditional Chinese medicine that has It is a stilbene phytoalexin glucoside of resveratrol [3,40] trihydroxystilbene), in which the glucoside group linked to position C-3 replaces a hydroxyl group. Trans-polydatin, trans-resveratrol, cis-polydatin, and cis-resveratrol are the

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four primary PD derivatives found in nature. Trans-isomers have greater bioactivity than cis-isomers do (Mikulski & Molski, 2010).

Additionally, PD can be found in many foods that are consumed every day, including grape, peanut, hop cone, red wine, hop pellet, cocoa-containing, and chocolate goods. The most prevalent kind of resveratrol in nature is called PD (Reqev-Shoshani et al., 2003). Previous research has shown that PD has a wide range of biological features, including the ability to prevent platelet aggregation, reduce the oxidative damage caused by low-density lipoprotein (LDL), protect the heart, and control inflammation and the immune system. We attempted to present and evaluate the pharmacological and pharmacokinetic research of PD in this review.

Pharmacological effects

Effects on cardiac muscle cells: According to Luo et al. (1990), PD can prevent damage caused by oxygen and glucose deprivation (OGD) and chlorpromazine, raise Ca2 in MCs, and improve the degree of MC contraction (Zhao et al., 2003). Zhao et al. (2010) studied the impact of Parkinson's disease (PD) on rats with cardiac ultra-structure damage caused by adriamycin and found that PD greatly lowers the toxicity of adriamycin on cardiomyocytes (CMs), clearly acting as a preventative measure. Injection of PD significantly lessens the severity of ischemia, reduces the ischemic and infarcted area, lowers the activities of serum lactate dehydrogenase (LDH), and creatine kinase, which lessens the ischemic injury of CMs in the canine model of myocardial infarction created by coronary left anterior descending branch ligation (Zhang et al., 2006). Through control of Bcl-2 and Bax protein expression, PD can drastically reduce the amount of TdT-mediated dUTP nick end labeling-positive cells (apoptotic cells) and apoptosis rate in ischemia/reperfusion (I/R)-induced cardiac damage in rats (Zhang et al., 2009)

In order to investigate the effects of lipopolysaccharide (LPS) on the b-adrenergic receptor (b-AR) and the prevention/treatment of Parkinson's disease (PD), Zhao et al. (2004) carried out an extra-corporeal experiment. The findings show that LPS directly causes b-AR reduction and down-regulates its affinity in CMs, whereas PD reverses these changes. It might be a key aspect of how PD improves cardiac contraction (Zhao et al., 2004). Another experiment shows that LPS significantly reduces myocardial contraction and causes mitochondrial damage, but that PD reverses these detrimental changes to save CMs by controlling protein kinase C activity and preserving the ultrastructure of myocardial fibres (Xue et al., 2008). When PD (20 mg/kg) is administered intravenously, protein kinase C-ATP-sensitive K+ channel-dependent signalling is activated, which results in a considerable reduction in the release of creatine phosphokinase and LDH from the injured myocardium (Miao et al., 2011, 2012). The electrophysiological explanation is that normal papillary muscles' 50% and 90% repolarization periods are lengthened by PD, but their resting potential, overshoot, action potential amplitude, and maximal rate of depolarization in phase 0 (Vmax) are unaffected. In addition to shortening APD50 and APD90 in partially depolarized papillary muscles, PD (50 mmol/L) significantly reduces OS, APA, and Vmax

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(Zhang et al., 2011a). A follow-up investigation demonstrates that PD somewhat reduces Ca2+ transient through down-regulating L-type Ca2+ channel activity and up-regulating ryanodine receptor activity. Additionally, PD significantly reduces the amplification of Ca2 signalling caused by b-AR stimulation without affecting the inotropic impact of b-AR, which in turn modifies b-AR regulation of excitation-contraction (EC) coupling (Deng et al., 2012).

In isoproterenol-induced mice, PD lowers heart weight indices and the levels of cyclic adenosine monophosphate and angiotensin II (Ang II). In pressure-overload rats, it also reduces ventricular collagen volume, levels of aldosterone (ALD), tumour necrosis factor-a (TNF-a), Ang II, and endothelin-1 (ET-1), and the size of the CM. These findings show that PD, particularly in the renin-angiotensin-ALD system, inhibits neurohormone activation, which is beneficial for attenuating ventricular remodelling (Gao et al., 2010). By increasing the levels of superoxide dismutase (SOD), nitric oxide synthase (NOS), constitutive NOS, and nitric oxide (NO), and lowering the concentration of malondialdehyde (MDA), PD can also protect rats against myocardial I/R injury (Zhang et al., 2008a).

Effects on endothelial cells

Vascular endothelial cells' (VECs') structural integrity and regular operation are crucial for maintaining the permeability, immunological response, and inflammatory response of the arteries, and VEC damage is the key factor in the origin and development of atherosclerosis. Asymmetric dimethyl-arginine (ADMA) and PD have no effect on the normal rabbit aortic stripe's ability to contract in response to phenylephrine (PE), but the stripe can be dosage-dependently weakened by PD after ADMA preconditions it. This indicates that the PD dose has no effect on the normal aortic stripe's ability to contract, but noncompetitively antagonises the contractile response of VECs to (Qin et al., 2004).

PD can lessen white blood cell (WBC)-EC adhesion and reduce inducible cell adhesion molecule-1 (ICAM1) production in LPS-stimulated EC (Zhao et al., 2003). Effectively, PD inhibits the adherence of monocytes to endothelial cells that have been stimulated by TNF-a. Through the regulation of nuclear factor-kappa B (NF-kB) pathway activation, PD might reduce the protein and mRNA expression levels of ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) in cultured endothelial cells (Deng et al., 2011). Rats with experimental hyperlipidemia had much higher induced nitric oxide synthase (iNOS) activity, which showed abundant NO generation, although PD therapy clearly reduced this activity (Zhu & Jin, 2005).

Hepatoprotective effects

The anti-inflammatory and anti-oxidative properties of PD are closely related to its hepatoprotective effects. Numerous studies show that PD can reduce liver damage brought on by the consumption of high-fat foods and carbon tetrachloride (CCl4) (HFD). Rat hepatocytes in culture can be protected from CCl4 injury by PD (107-104 mol/L) by lowering glutamic pyruvic transaminase release, MDA production, and glutathione (GSH) levels

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(Huang et al., 1999). In pyrogallic acid-induced hepatocyte culture media, PD (0.05–4 mmol/L) decreases NO and MDA levels, inhibits NOS activity, boosts SOD, GSH-Px and GSH activities, and suppresses alanine aminotransferase (ALT) release (Mo et al., 1999). The CCl4-induced liver injury in mice is 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-b1 (TGF-b1) are also modulated after PD preadministration for 5 continuous days. These increases in serum aspartate aminotransferase (AST), ALT, and hepatic (Zhang et al., 2012a).

In HFD-induced chronic liver damage rats, PD can considerably improve hepatic steatosis and lower plasma and liver concentrations of TG, total cholesterol (TC), and free fatty acids. Additionally, PD significantly reduces the levels of TNF-a, MDA, and 4-hexanonenal in the liver of rats on an HFD.

In HFD-fed rats, PD also lowers the expression of the lipogenesis-related genes sterol-regulatory element binding protein and its targets, such as fatty acid synthase and stearoyl-CoA desaturase 1. (Zhang et al., 2012b). Another in vivo test shows that PD clearly lowers serum fasting insulin, fasting blood glucose, the insulin resistance index, and TNF-a levels while raising the insulin sensitivity index, with higher doses having superior effects than fenofibrate (Zhang & Lv, 2010). In mice that have been sensitised to D-galactosamine (D-GalN), LPS can cause the terrible clinical state known as fulminant hepatic failure (FHF), which has a very poor prognosis and a high mortality rate. On LPS/D-GalN-induced FHF mice, pretreatment with PD (10, 30 and 100 mg/kg) exerts the clear protective effects, reducing serum ALT and AST activity, reducing liver histological injury, and decreasing mortality in a dose-dependent way. Pretreatment with PD also inhibits the synthesis of TNF-a, myeloperoxidase (MPO) activity, intercellular adhesion molecule-1 (ICAM-1) and endothelial cell adhesion molecule-1 expression, caspase3 activation, and NF-kB activity in model mice. Through preventing NF-kB activation, PD likely lowers TNF-a production (Wu et al., 2012).

Neuroprotective activity

Previous research has demonstrated that PD has a clear neuroprotective effect, particularly when it comes to the pathophysiology of cerebral ischemia. Through enhancing the expression of glioma-associated oncogene homolog 1, patched-1, and SOD1, decreasing the expression of NF-kB p65, and improving blood-brain barrier permeability, PD guards against the brain damage brought on by persistent middle cerebral artery occlusion (MCAO) (Ji et al., 2012). After performing MCAO for one hour, an intravenous injection of PD can decrease the size of brain infarction, ameliorate neurological impairments, and block the production of integrins, ICAM-1, VCAM-1, E-selectin, and L-selectin (Cheng et al., 2006c). In the rat model of vascular dementia generated by chronic cerebral hypoperfusion, PD protects against learning and memory impairments, greatly attenuates cognitive deficits, reduces the formation of MDA, and significantly boosts the activities of SOD and CAT (Li et al., 2012).

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OGD-induced neuron injury is efficiently treated by PD therapy, which greatly boosts cell survival, lowers levels of LDH, NO, MDA, and raises SOD activity in pheochromocytoma cells (Li et al., 2012). Additionally, in the cerebral cortex of newborn rats, PD can increase the expression of brain-derived neurotrophic factors (Sun et al., 2012).

In chronically drunk mice, PD can enhance learning and memory skills. Alcohol increases cyclin-dependent kinase 5 and N-methyl-D-aspartate mRNA expression in the prefrontal brain of chronic alcoholic rats, while PD dramatically counteracts these changes (Xu et al., 2011, 2012). In cerebral haemorrhage rats, PD dramatically reduces cerebral edoema and raises the amount of Asp and Glu, albeit the chemical mechanism is not entirely understood (Liu et al., 2010). One of the main neurodegenerative processes taking place as Alzheimer's disease pathogenesis progresses is amyloid-b peptide (Ab) buildup. In vitro amyloid-b peptide (Ab) aggregation was examined by Rivie're et al. (2010) using electron microscopy and ultraviolet (UV)-visible measurements on 20 derivatives of stilbenes. The findings show that PD has the best inhibitory efficacy of these drugs, efficiently and dose-dependently inhibiting Ab polymerization. The EC50 is 6.2 mM, and the inhibitory rate is 63% (Rivie're et al., 2007, 2010). According to Riviere et al. (2009), PD destabilises fibrils and oligomers to release the Ab25-35-induced monomers that can open the hydrophobic zipper and shift the reversible equilibrium "random coil$ b-sheet" to the disordered structure.

Lung protective effects

Numerous studies demonstrate the preventive effects of PD against acute or chronic pulmonary illness. In vitro, PD has a negligible effect on relaxing isolated pulmonary arteries. Due to decreased lipophilicity and/or target accessibility, glycosylation significantly reduces the biological effects of stilbene derivatives (Waffo-Te'quo et al., 2001). By reducing phospholipase A2 activity and secretory phospholipase A2 type IIA gene expression, PD has both preventative and curative effects on acute lung injury in rats with endotoxic shock. The mechanism may be that PD increases the expression of Clara cell secretory protein and decreases the expression of cPLA2 in the lung (Shu et al., 2004, 2011).

On the one hand, PD reduces lung I/R injury in rabbits by suppressing the expression of TLR4 and NF-kB and preventing the release of inflammatory mediators like ICAM-1 (Jin et al., 2009). To counteract lung I/R injury, PD, however, also improves SOD activity, injured alveoli rate, and reduces MDA content (Wang et al., 2008). Additionally, PD controls the levels of NO, Ang II, and ET, all of which are strongly associated to the remodelling system for pulmonary hypertension, and it inhibits the forced activation of PKC signalling by thymeleatoxin (Miao et al., 2012). Through preventing increases in LDH activity and vascular endothelial growth factor (VEGF) production, PD effectively protects against rat lung micro VECs injury in vitro caused by hypoxia (Wang et al., 2001). Prostaglandin E2 (PGE2), leukotriene C4, and TGFb1 levels in bronchoalveolar lavage fluid, as well as the activity of PLA2 and the concentration of hydroxyproline in lung homogenate, are all

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considerably decreased after PD intraperitoneal injection. PD does not entirely stop the development of pulmonary fibrosis, though (Zhang et al., 2011b).

Anti-arteriosclerosis

In the experimental rat model of hyperlipidemia created by HFD, Zhu and Jin (2006) discovered the impact of PD on blood lipid metabolism. The findings demonstrate that oral administration of PD for four consecutive weeks significantly lowers serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein A1 (ApoA1) in model rats but clearly raises the ratios of high-density lipoprotein cholesterol (HDL-C)/TC and ApoA1/ApoB. Although there is no statistically significant difference in the blood HDL-C levels, PD-treated high-fat/cholesterol hamsters show a striking reduction in the ratios of LDLC/HDL-C and TC/HDL-C. (Du et al., 2009). Rabbits exhibit similar effects, and treatment of PD can considerably lower the levels of TC, TG, and LDL-C in the serum of rabbits in a dose-dependent way (Xing et al., 2009).

Anti-inflammatory activity

Due to its anti-inflammatory characteristics, PD has a number of positive effects, including nephroprotective, hepatoprotective, and lung protective activities. A chronic inflammatory response brought on by the presence of endometrial-like tissue outside the uterus is known as endometriosis, an estrogen-dependent inflammatory illness (Kennedy et al., 2005). In hyperuricemic mice, PD controls renal organic ion transporters to produce anti-hyperuricemic effects (Shi et al., 2012).

According to numerous studies, both in vivo and in vitro, PD influences the production of inflammatory cytokines and cell adhesion molecules. Human peripheral blood mononuclear cells that have been stimulated produce less IL-17 thanks to PD's ability to suppress the expression of IL-17 mRNA in the cells (Lanzilli et al., 2012). PD in vitro dramatically reduces the synthesis of high glucose-induced ICAM-1 and TGF-b1 in glomerular mesangial cells (Xie et al., 2012). Additionally, PD reduces NF-kB p65 activity and expression, inhibits TNF-a, IL-6, and IL-1b expression at the mRNA and protein levels, decreases MPO activity, and reduces inflammatory damage of colitis in mice with ulcerative colitis, suggesting that the anti-inflammation effects of PD can be attributed, at least in part, to the blocking of the NF-kB pathway. In renal ischemia-reperfusion injury rats, NF-kB expression also sharply declines following intraperitoneal injection of PD (20 mg/kg) (Fei et al., 2009). By inhibiting xanthine oxidase activity, PD lowers the level of blood uric acid both in vivo and in vitro. It also improves renal function in animals with fructose-induced urate nephropathy.

The nephroprotective action is linked to PD suppression of the implicated inflammatory cascade, which includes the expression of NF-kB p65, COX-2, and iNOS proteins as well as the creation of TNF-a, PGE2, and IL-1b, which are connected to oxidative stress (Chen et al., 2013). PD can limit NF-kB activity in LPS and T/I-induced primary human keratinocytes and inhibit constitutive bacterial LPS and interferon-g (T/I)-induced but not TGF-a-induced ERK

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phosphorylation in various chronic inflammatory disorders (HaCaT). According to Potapovich et al. (2011), PD inhibits increased monocyte chemotactic protein-1 (MCP-1) and IP-10 transcription/synthesis, suppresses interferon gamma-inducible protein 10 (IP-10) release, and increases IL-8 levels in order to activate aryl hydrocarbon receptor machinery in UV-exposed keratinocytes (Pastore et al., 2012). In heat-stressed HaCaT, PD is also able to modify the gene expression of IL-6, IL-8, and TNF-a, as well as to increase the release of human b-defensin 2 and the gene expression of heat shock protein 70B0 (Ravagnan et al., 2013). At doses of 10-5 and 104 mol/L, PD promotes fibroblast proliferation, but at concentrations of 103 mol/L, it inhibits the biological cycle in S phase, indicating that it has bidirectional regulatory effects on fibroblasts (Bian et al., 2012).

Anti-shock effects

The survival time of pregnant rabbits with uncontrolled hemorrhagic shock is evidently extended by bolus infusion of PD (2 mg/kg) when combined with hypotensive resuscitation. This improvement in capillary perfusion is demonstrated by an increase in arteriole diameter and a rise in functional capillary density (Sheng et al., 2011). Vascular smooth muscle cells (VSMC) can have their pH and Ca2 levels decreased by PD while also having their KATP channels activated. Multiple effects of PD on VSMC, MC, WBCs, and endothelial cells (EC) are intimately associated to improvement of microcirculatory perfusion in shock and restoration of heart function (Zhao et al., 2003). Increased mitochondrial membrane potential, decreased swelling of the mitochondria, and higher intracellular adenosine triphosphate (ATP) levels are all effects of PD. Additionally, PD prevents the typical vasoresponsiveness to norepinephrine that occurs after a severe shock, inhibits the activation of KATP channels, arteriolar smooth muscle cell hyperpolarization, and retains lysosomal stability (Wang et al., 2012). After 2 hours of shock, rat neurons exhibit swollen mitochondria with poorly defined cristae, decreased mitochondrial membrane potential (D), and decreased ATP content, all of which are signs of mitochondrial dysfunction due to increased lipid peroxide levels, lysosomal damage, and mitochondrial permeability transition pore opening. However, it is clear that PD prevents these modifications, which raises the level of ATP from 44.14 13.81% to 89.57 9.21% and lengthens the survival time from 6.3 5.9 h to 31.6 13.7 h. In cases of severe shock, PD might be the best option for protecting neurons from mitochondrial damage (Wang et al., 2013).

Anti-tumor activity

Many human tumour cell lines, including human cervical carcinoma HeLa cells, hepatoma cell line SMMC-7721 cells, epidermal carcinoma A-431 cells, and nasopharyngeal carcinoma CNE cells, are positively affected by PD's cytotoxic actions. In CNE cells, PD can damage the mitochondria, lead to ER stress, and down-regulate Akt phosphorylation, whereas CCAAT/enhancer-binding protein homologous protein knockdown substantially reverses the inactivation of Akt. Additionally, according to Liu et al. (2011), PD-induced reactive oxygen species (ROS) are an early event that set off the mitochondrial apoptotic pathways in CNE

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cells under ER stress. Additionally, PD lowers VEGF expression in NIH3T3 cells and PAN-1 cancer cells by binding more strongly to the target G-quadruplex in the proximal VEGF promoter (Balasubramanian & Neidle, 2009; Li & Yuan, 2010; Sun et al., 2005). Human umbilical vein endothelial cells' (HUVECs') ability to construct capillary-like tube networks is inhibited by PD, and Lewis lung carcinoma cells' ability to synthesise DNA is also suppressed by PD (Kimura & Okuda, 2000).

PD can interact with neurotensin via hydrogen bonds and hydrophobic stacking (NT). According to Richard et al. (2005), the polyphenol-protein complexes appear to influence NT metabolism and reduce the metabolic activation of colon cancer cells caused by NT (Briviba et al., 2001). In mouse mammary organ culture, PD strongly suppresses COX-1 activity, with a half maximum inhibitory concentration (IC50) value of 10.6 mM (Waffo-Te'quo et al., 2001).

Anti-oxidative activity

Due to its molecular structure, which contains a conjugated double bond, PD has strong anti-oxidant properties. These properties are closely related to its numerous pharmacological effects, which include preventing I/R injury, enhancing learning and memory, lowering lipid levels, and lengthening lifespan. Due to the altered molecular structure, PD is more resistant to enzymatic oxidation than resveratrol (Fabris et al., 2008). Trans-polydatin really has more potent antioxidative properties than cis-PD and trans-resveratrol (Mikulski & Molski, 2010).

One of the anti-oxidative features of PD is its ability to scavenge free radicals. Both oxygen free radicals (O 2) and hydroxyl radicals (OH) produced by the EDTANa2-Fe(II)-H2O2 system and oxygen free radicals (O 2) produced by the NADH-PMS-NBT system can be reduced in vitro by PD (Tian & Yang, 2001). PD also scavenges OH produced by H2O2 to protect HUVECs (ECV304) in a dose-dependent manner (Su et al., 2010). Additionally, fish oil-in-water emulsions with PD exhibit a substantial anti-oxidant capacity (Medina et al., 2010). In contrast to BHT (2,6-di-tert-butyl-4-methylphenol) and a-tocopherol (vitamin E), PD exhibits a slower but more sustained protective action against lipid peroxidation and is more effective than resveratrol in extending the mean lifetime of transgenic strain CL2166 (Wen et al., 2012). It is especially well suited for the prevention and control of the lipid peroxidation of the membranes because the vulnerable hydroxyl group of PD is situated in the lipid area of the bilayer adjacent to the double bonds of polyunsaturated fatty acids (Fabris et al., 2008).

Low doses of PD (5100 mg/ml) have no cytotoxic effects on HaCaT cells, but they do lessen UVB-induced HaCaT cell death. In HaCaT cells and the epidermis of BALB/c-nu mice, UVB irradiation appears to increase the production of ROS, one of the crucial parameters for an anti-oxidative activity, which is then significantly decreased by PD. PD also appears to inhibit COX-2 expression, which has been amplified by UVB irradiation. The process

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involves PD inhibiting UVB-induced cell activation of p38, JNK, and ERK1/2 (He et al., 2012).

Inhibition of thrombus formation

According to Wang et al. (2004), PD inhibits platelet aggregation and lowers the production of thromboxane B2 (TXB2) in platelet-rich plasma induced by arachidonic acid or adenosine diphosphate. PD also significantly lowers the fibrinogen content and platelet adhesive rate in acute blood-stasis model rats. In nutmeg phorbolactivated neutrophilic granulocyte suspension, thrombin-induced platelet neutrophil adhesion and platelet aggregation are substantially reduced by PD. Additionally, PD can increase plasma levels of 6-keto-PGF1a while decreasing TXB2 concentration (Chen et al., 2006a,b).

Inhibition of melanogenesis

Arbutin, which is well known to prevent melanin creation, is not as effective at inhibiting tyrosinase activity and melanin production in melanocytes as PD. Additionally, melanocytes exhibit a substantial suppression of the mRNA and protein expression of tyrosinase, tyrosinase-related proteins 1, 2, and microphthalmia-associated transcription factor (Jeong et al., 2010).

But in vitro, PD has only marginal effects on the tyrosinases from murine melanoma B-16 and mushroom, with an IC50 value greater than 100 mM. (Kim et al., 2002). These two completely distinct outcomes are most likely the result of various cell kinds.

Anti-microbial activity

Streptococcus mutans and Streptococcus sobrinus have dental caries-related factors that are inhibited by P. cuspidatum ethyl acetate fraction, which also contains PD, resveratrol, anthraglycoside B, and emodin. This fraction also dramatically lowers glycolytic acid production at a low level (Ban et al., 2010). Additionally, S. mutans UA 159's acidogenicity and consequent dental caries development are weakly inhibited by PD (Kwon et al., 2010).

Immunoregulatory effects

Decreases in antigen-stimulated mast cell degranulation are what PD uses to treat passive cutaneous anaphylaxis. According to Yuan et al. (2012), one potential mechanism for how PD causes mast cell stability is by limiting Ca2 entry through Ca2 release-activated Ca2 channels, which are the principal drivers of high-affinity IgE receptor-mediated Ca2+ mobilisation.

Pharmacokinetic studies

Pharmacokinetic studies are frequently required for the clinically effective and secure administration of medications. The bioactivity of PD and its absorption, distribution, and metabolism are intimately related. However, there haven't been many analytical techniques

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employed to date to analyse the pharmacokinetic profiles of trans-stilbene glycoside in biological samples (Lv et al., 2011; Ren et al., 2010).

By conjugating with glucose, several phenols in the diet are more readily absorbed. According to Hollman et al. (1995; Hollman, 1997), glucose appears to be a more effective conjugation partner for PD. Passive diffusion and active transfer via the sodium-dependent glucose transporter (SGLT1), which is mostly found in the stomach and intestines, are the two primary transport mechanisms by which PD can be absorbed (Henry et al., 2005). Unlike resveratrol, which enters the cell passively through the cell membrane, PD enters the cell by an active method involving glucose transporters.

The initial rate of trans-PD incorporation is about 1.6 times lower at 4 C than it is at 37 C, although the content in cells is not significantly decreased (He et al., 2007), supporting PD active transport by SGLT1. PD solution is therefore necessary for its absorption in the intestines. Resveratrol accumulates at a faster pace and leaves behind more material than PD in Caco-2 cells, whereas PD has a half-life of over 4 hours and a greater Cmax than resveratrol at the same dosage. AUC(0-1) and t1/2 of PD are likewise elevated in a dose-dependent manner in addition (Zhou et al., 2009).

With a positive apparent permeability coefficient (Papp) of roughly 10 106 cm/s for the apical to basolateral flux, transepithelial transport of PD is obviously present, indicating nearly full absorption of PD in humans (Yee, 1997).

Following intravenous injection of 20 mg/kg PD, the various tissue concentrations attain their maximum levels at 10 min postdose, which are 1.53 ± 0.13, 5.22± 0.46, 4.59± 0.59, and 6.41 ±0.77 mg/g in the heart, liver, lung, and kidney, respectively (Gao et al., 2006). The maximum concentrations in the heart, liver, spleen, lung, kidney, stomach, small intestine, brain, and testis, however, after oral administration of 50 mg/kg PD to male rats, 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 mg/g, respectively (Lv et al., 2006).

There are two ways that PD can be deglycosylated in trans-resveratrol. The first is a cleavage by cytosolic b-glucosidase after it has passed the brush-border membrane by SGLT1. The second involves passive diffusion of the released aglycone, which is then further converted inside the cells into two glucuronoconjugates by the membrane-bound enzyme lactasephlorizin hydrolase on the luminal side of the epithelium (Henry-Vitrac et al., 2006). After oral administration of PD, which can be converted into resveratrol, dihydropiceid, and dihydroresveratrol after being incubated with gut bacteria, rat urine contains resveratrol, dihydroresveratrol monosulfate, PDmonosulfate, and PD-monoglucuronide (Wang et al., 2011).

After oral administration of PD and perfusion of trans-PD in situ in the rat small intestine, resveratrol, glucuronidated resveratrol, and glucuronidated trans-PD, the first-pass metabolites of PD in the rat liver, are found in plasma (Zhang et al., 2008b; Zhou et al.,

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2009). Glucuronidated resveratrol is the primary metabolite of PD, reaching 84% of the total amount after oral treatment in the liver and intestines (Zhou et al., 2009). The tiny intestinal extracts are also more potent than liver extracts (Zhou et al., 2007).

CONCLUSION:

Traditional Chinese medicine's P. cuspidatum has long been employed in therapeutic settings as an analgesic, antipyretic, diuretic, and expectorant. PD, a monocrystalline substance isolated from P. cuspidatum, has a wide range of pharmacological actions that have been verified by various studies, including liver and lung protection, cardiovascular protection, neuroprotection, anti-inflammation, immunoregulation, and anti-tumor properties.

However, further research is needed to understand PD development. Even though many bioactivities of PD have been demonstrated in lab animals, organs, or cells, few molecular mechanisms of action are understood, and the specific proteins that PD binds to are still unknown, which will prevent further clinical applications of PD. The safety of a medicine is particularly crucial when it is used in clinical settings. Sadly, there aren't many toxicological analyses of PD reported. The documents reviewed above provide significant evidence in favour of the idea that PD has beneficial therapeutic qualities, suggesting that it has the potential to be a useful substance. The pharmacological and pharmacokinetic studies of PD conducted over the previous 22 years are presented and evaluated in this review. It might be crucial for interested readers to quickly identify and further explore PD.

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