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A Comprehensive Review on the Bioactivities, Mechanism, and Translational Potential of Platycodin D

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ABSTRACT: Platycodin D (PD) as the main triterpene saponins in *Platycodon grandiflorum* (Jacq.) A. DC. (PG), has both food and medicinal value, and has shown broad application prospects in functional food and health products. This article systematically reviews the pharmacological activities, mechanisms of action and pharmacokinetic characteristics of PD. Some studies have shown that PD has various biological activities such as anti-cancer, anti-inflammatory, anti-oxidation, metabolic regulation and organ protection by regulating phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), nuclear factor- κ B (NF- κ B) and nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathways. For example, it can induce tumor cell apoptosis, arrest cell cycle, alleviate airway inflammation through inhibiting toll-like receptor 4 (TLR4)/NF- κ B pathway, and improve metabolic syndrome by activating AMP-activated protein kinase (AMPK) pathway. In terms of preparation, enzymatic conversion methods (such as β -glucosidase catalysis) and response surface method can significantly improve the extraction process of PD. Dehydroxylation and deglycosylation are the primary metabolic pathways of PD *in vivo*. However, its oral bioavailability in rats is relatively low (absolute bioavailability 1.89%), necessitating the use of nanodelivery systems or other technologies to enhance absorption. Safety evaluation showed that PD has low toxicity at therapeutic doses, but its hemolytic activity and concentration-dependent cytotoxicity still need attention. Future research should concentrate on the development of novel delivery systems, analysis of multi-target action networks and clinical translation to promote the application of PD in functional foods and innovative drugs.

Keywords: Platycodin D, Bioactivities, Anticancer activity, Pharmacokinetics, Safety evaluation, Signaling pathways, Clinical translation

1. Introduction

Platycodon grandiflorum (Jacq.) A. DC. (PG) is widely utilized as a food in Korea, South Korea and Japan, and as a medicinal and edible Chinese herbal medicine in China. PG contains a large amount of

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unsaturated fatty acids, such as linoleic acid, which has the effects of reducing blood pressure, lipid and anti-atherosclerosis. PG is also used as a food product, such as pickles, and the saponins extracted from PG are used in food, agriculture, cosmetics, and pharmaceuticals [1]. Platycodin D (PD) is the most representative triterpenoid saponin isolated from PG, and it is also the first apiose-containing saponin obtained from plants [2]. PD, as an oleanane triterpenoid saponin, has two sugar chains, which are connected at C-3 and C-28, respectively (**Fig. 1A**).

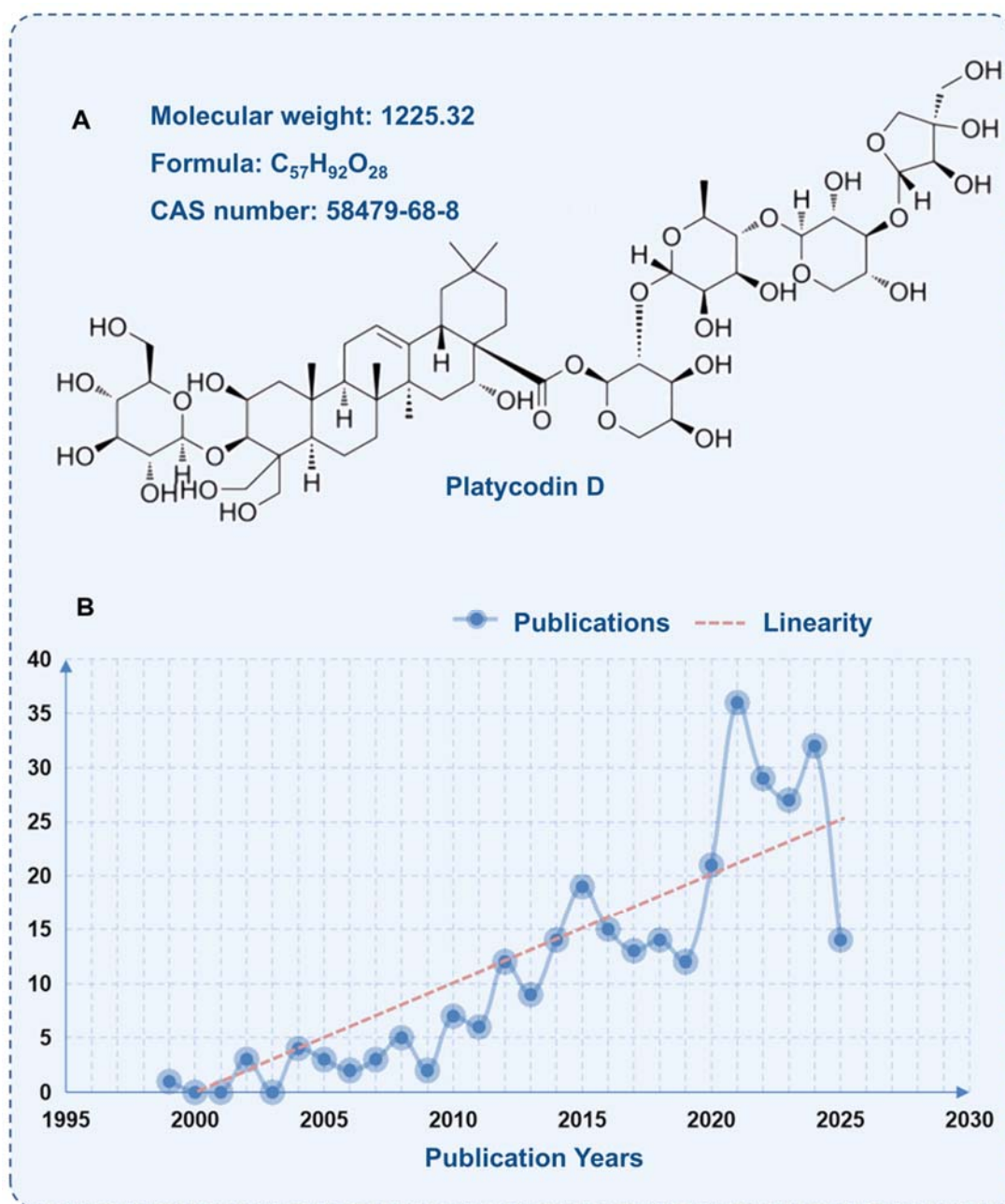


Figure 1. Chemical structure and publication trend of Platycodin D. (A) The chemical structures of platycodin D. (B) Current status of research literature on PD (1999–2025). Temporal trend of publications related to Platycodin D from 1999 to 2025. Blue dots represent the number of annual publications, and the red dashed line indicates the linear fit of publication growth over the years, illustrating the research interest evolution in Platycodin D.

PD can be widely used in medical products, functional food and health-promoting products due to its high medicinal value. In recent years, PD, as an important active triterpenoid saponin in PG, has attracted much attention due to its excellent and diverse pharmacological activities, such as anticancer, antitussive and

expectorant, anti-inflammatory, antioxidant, hypoglycemic and lipid-lowering, immune regulation, neuroprotection, cardiovascular protection, liver protection, anti-obesity and anti-allergy [3-5], which has been clinically utilized in treating lung diseases, tumors, cerebrovascular and cardiovascular diseases, and liver diseases. To analyze the current state and recent advances in PD research, this review synthesizes literature from the Web of Science (WOS) core collection, focusing on PD as the subject and restricting document types to original articles and reviews, with the date range set from January 1999 to June 2025. Following title and abstract screening to exclude irrelevant and duplicate records, 303 publications were identified (**Fig. 1B**). As illustrated, PD research remained limited before 2010, laying foundational groundwork, but has since expanded markedly, underscoring its scientific significance and untapped potential. Furthermore, 119 publications closely related to the theme of this review were selected for subsequent analysis.

Despite of multiple studies have focused on PD, comprehensive analysis of multi-target networks, clinical translation evidence, and systematic safety profiles remains insufficient. The safety evaluation, challenges and future directions of PD are also rarely systematically discussed. Hence, this review systematically summarized and discussed the recent advances in PD, including its chemical properties, plant sources, pharmacological activities and potential mechanisms, preparation and metabolism, safety evaluation and other related research results by integrating multiple online databases, aiming to provide new perspectives for further in-depth development and applications of PD. Additionally, many expectations for challenges, future study and development were prospectively proposed according to the previous publications in this field.

2. Pharmacological activities of PD

As an important active triterpenoid saponin in PG, PD is used to fight various diseases. Numerous studies have shown that PD has multiple biological activities, including anticancer, anti-inflammatory, immune regulation, metabolic regulation, anti-obesity, organ protection, antimicrobial, *etc.*

2.1. Anticancer activity

Many studies have corroborated that PD had multiple anticancer activities, significantly inhibiting cell proliferation, inducing apoptosis, causing cell cycle arrest, regulating autophagy, anti-angiogenesis, and inhibiting metastasis in several cancers. A summary of studies on the anticancer activity of Platycodin D is presented in **Table 1** and **Fig. 2**.

Table 1. The pharmacological activities of platycodin D in the treatment of cancer diseases.

Cancer risk factors	Type of tumor	Dosages	Cellular/animal models	Mechanisms	Ref.
Inducing apoptosis	Hepatocellular carcinoma	5, 10, 20 μ M	SMMC-7721/HepG2/MCF-7/A549/HeLa/H226 cells	Via inhibition of the AKT and ERK1/2 signaling pathways and activation of the JNK and p38 MAPK signaling pathways	[8]
	Hepatocellular carcinoma	10, 20 μ M	HepG2/Hep3B cells	By inducing cell apoptosis	[9]
	Hepatocellular carcinoma	12.5, 25, 50 mg/kg	H22 tumor-bearing mice model	By improving immune function, inducing apoptosis and inhibiting angiogenesis	[18]
	Hepatocellular carcinoma	24000, 36000, 48000 μ M	HepG2 cells	By inhibiting PI3K/Akt pathway	[10]
	Lung Cancer	5, 10, 20 μ M	The lung cancer cell models: NCL-H1299/PC-9/A549 Cells	By targeting the TGF- β pathway	[12]
	Lung Cancer	0.25, 0.5, 1 μ M	A549 cells	By activating caspase-3 and regulating the p53/VEGF/MMP2 pathway regulated by RRM1	[11]
	Lung Cancer	5, 10, 15 μ M	NOD nude mice; NSCLC cells: H1299/H2030/A549 cells	By upregulating PUMA through the JNK1/AP-1 pathway, impairing mitochondrial function	[13]
	gastric cancer	2.5, 10, 15 μ M	AZ521/NUGC3 cells	Via suppression of c-Myc protein expression	[15]
	Colon cancer	10,20 μ M	HT-29 colon cancer cells	By up-regulating the expression of Bax and p38-JNK, down-regulating the expression of Bcl-2 and the expression of ERK in the MAPK pathway	[7]
	Diffuse large B-cell lymphoma	<i>In vivo</i> : 5 mg/kg; <i>In vitro</i> : 5, 10, 20, 40 μ M	Xenograft Mouse Model; Pfeiffer, DB/Farage/OCI-Ly3/U2932, SUDHL-16/OCI-Ly10, SUDHL-4	By regulating the balance between BCL-2 family proteins	[17]
Inducing cell cycle arrest	Acute myeloid leukemia	10, 20, 40 μ M	MV4-11/MOLM-13/THP-1/U937 human AML cells	By the mitochondria-dependent pathway	[6]
	Prostate cancer	<i>In vivo</i> : 2.5 mg/kg; <i>In vitro</i> : 2.5, 5, 10 μ M	PC3 human prostate cancer xenograft tumors mouse model; Prostate cancer cell lines: PC3/DU145/LNCaP cells	By MDM2-FOXO3a-mediated apoptosis	[21]
	Gastric cancer	2, 5, 10, 15 μ M	AZ521/NUGC3 cells	Via suppression of c-Myc protein expression	[15]
	Breast cancer	<i>In vivo</i> : 1, 2.5 mg/kg; <i>In vitro</i> : 5, 10, 20 μ M	MDA-MB-231 xenograft model in BALB/c nude mice; MDA-MB-231 cells	By targeting the MDM2 oncogene	[20]
	Prostate cancer	<i>In vivo</i> : 2.5 mg/kg; <i>In vitro</i> : 2.5, 5, 10 μ M	PC3 human prostate cancer xenograft tumors mouse model; Prostate cancer cell lines: PC3/DU145/LNCaP cells	By activating FOXO3a expression	[21]
	Hepatocellular carcinoma	24000, 36000, 48000 μ M	HepG2 cells	By inhibiting PI3K/Akt pathway	[10]

Regulating autophagy	Hepatocellular carcinoma	<i>In vivo</i> : 10 mg/kg; <i>In vitro</i> : 5, 10, 20 μ M	BEL-7402-bearing mice; BEL-7402 cells	By activating the ERK and JNK signaling pathways	[22]
	Hepatocellular carcinoma	20 μ M	Human hepatocellular carcinoma HepG2/Hep3B cells, human breast cancer MCF-7/MDA-MB-231 cells, human lung cancer A549 cells/lung cancer 95D cell line	By activating the ERK pathway	[23]
	GBM	10 μ M	Cancer cell lines : U87MG/U373MG/A549/H358/MCF-7/HT-29/HepG2; normal human astrocyte; primary GBM cells	By inhibiting autophagosome-lysosome fusion and lysosomal degradation	[24]
	cancer	<i>In vivo</i> : 6 mg/kg; <i>In vitro</i> : 0.3-30 μ M (cells)	BALB/c nude mice; Human colorectal adenocarcinoma cell line HCT-15/Human umbilical vein endothelial cells (HUVECs)	Via blockade of the VEGFR2-mediated signaling pathway	[27]
Inhibiting angiogenesis	cancer	<i>In vivo</i> : 5, 10 μ M (subcutaneous injection), 0.5, 1 mg/kg (Intragastric administration); <i>In vitro</i> : 1, 3, 5 μ M	C57BL/6 male mice (25 $\pm$ 5 g, 7 weeks of age) and BALB/c female nude mice (20 $\pm$ 5 g, 5 weeks of age); HUVECs/MDA-MB-231 breast cancer cells	Via inhibition of MAPK activation	[26]
Inhibiting migration	Non-small cell lung cancer	<i>In vivo</i> : 5, 7.5 mg/kg; <i>In vitro</i> : 4, 8, 16 μ M	NSCLC Mice; A549 cells/human umbilical vein endothelial (HUVEC) cells	By modulating the lncRNA/eIF4E/EGFR axis	[29]
	Lung Cancer	<i>In vivo</i> : 7.5, 15 mg/kg; <i>In vitro</i> : 4, 8 μ M (A549) or 7.5, 15 μ M (PC-9)	BALB/c nude mice (male, 4–5 weeks old); A549/PC-9 cells	By modulating the Hsa-miR-1246/FUT 9/GSK 3 β pathway	[30]
	Breast cancer lung metastasis	<i>In vivo</i> : 10, 20 mg/kg; <i>In vitro</i> : 4,8,12 μ M	4 T1 breast cancer Balb/c mouse model; dHL-60 cells	By downregulating PD-L1 expression to inhibit the PI3K/Akt signaling pathway	[32]
	Breast cancer	<i>In vivo</i> : 1, 2.5 mg/kg; <i>In vitro</i> : 5, 10, 20 μ M	MDA-MB-231 xenograft model in BALB/c nude mice; MDA-MB-231 cells	By targeting the MDM2 oncogene	[20]
	Colorectal cancer	<i>In vivo</i> : 2.5 mg/kg; <i>In vitro</i> : 5.55 μ M (CaCo2), 5.88 μ M (HT29)	HT29 and CaCo2 in nu/nu nude mice; HT29 and CaCo2 cells	By inhibiting β -catenin	[33]

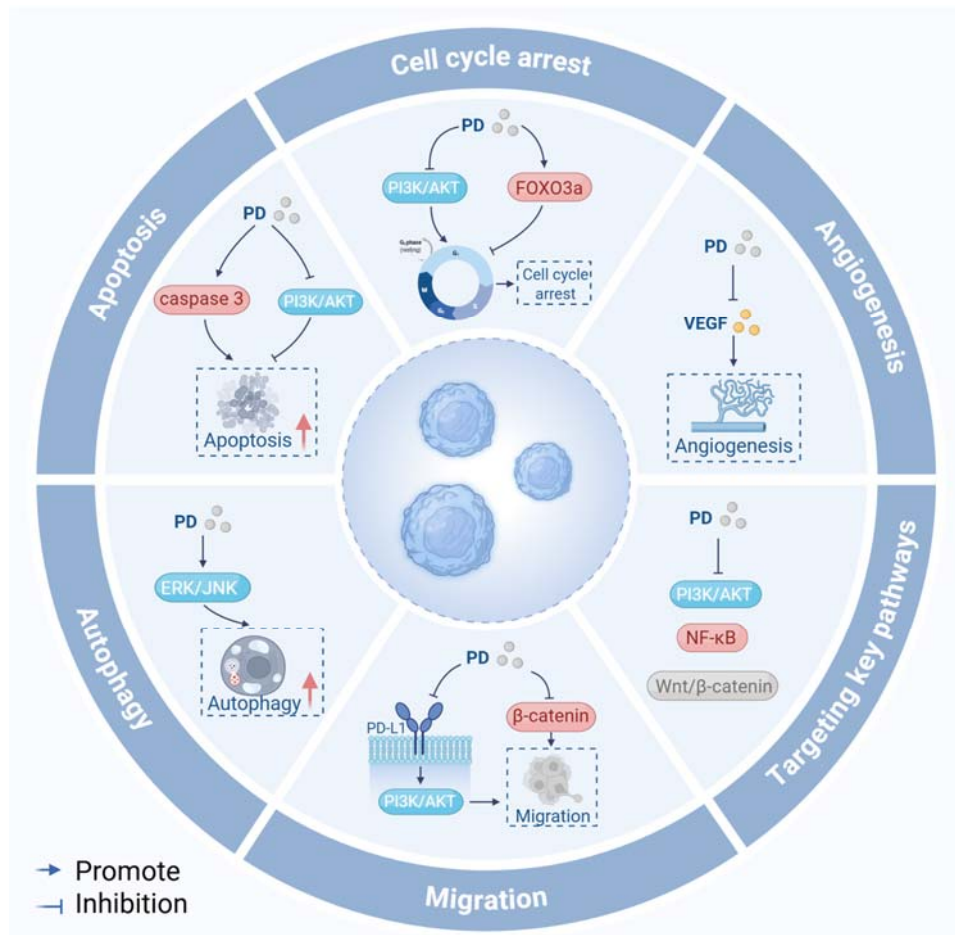


Figure 2. An overview of the role of PD in cancer regulation. The central cancer cells are surrounded by pathways through which PD exerts its actions: inducing apoptosis (via caspase 3, PI3K/AKT signaling), causing cell cycle arrest (modulating PI3K/AKT-FOXO3a axis), suppressing angiogenesis (targeting VEGF), regulating autophagy (via ERK/JNK pathways), inhibiting migration (impacting PD-L1, PI3K/AKT, and β -catenin related processes), and interfering with key oncogenic pathways (PI3K/AKT, NF- κ B, Wnt/ β -catenin). This integrated network depicts how PD modulates diverse cancer - associated cellular functions.

2.1.1 Apoptotic induction

Apoptosis is a carefully controlled process of cell death. It is preserved through evolution and is a mechanism for inhibiting tumors. It is generally believed that the obtained anti-span toe is a characteristic of cancer cells, which promotes its growth and development and leads to treatment failure. Acute myeloid leukemia (AML), as an invasive and heterogeneous hematologic malignancy characterized by frequent relapse and variable prognosis. Notably, PD can induce apoptosis through a mitochondrial-dependent pathway to inhibit AML cell viability [6].

Recent report revealed that treatment with PD promoted apoptosis of HT-29 by up-regulating Bcl-2-associated X (Bax) and p38 c-Jun N-terminal kinase (JNK), down-regulating Bcl-2 and extracellular signal-regulated kinase (ERK) in Mitogen-Activated Protein Kinase (MAPK) pathway, thereby exerting anti-tumor effects[7]. PD can promote the endosomal escape of endocytic protein without affecting plasma membrane integrity, and act in concert with MHBP, a fusion protein of MAP30 and HBP (human derived cell membrane penetrating peptide), activate JNK and p38 MAPK signaling pathways, induce caspase-dependent apoptosis in hepatocellular carcinoma cells by inhibiting protein kinase B (AKT) and

ERK1/2 signaling pathway^[8]. PD exhibits anticancer potential in hepatoma cells by inducing apoptosis of HepG2 hepatoma cells and inhibiting cell adhesion, migration and invasion ^[9]. PD induces apoptosis of HepG2 cells through inhibiting the phosphoinositide 3-kinase (PI3K)/Akt pathway^[10].

Lung cancer is currently the cancer with the highest morbidity and mortality in the world, ranking first in the world for ten consecutive years. In a previous study, PD inhibited the proliferation and induced apoptosis in A549 cells by activating caspase-3 and regulating p53/VEGF/MMP2 pathway regulated by RRM1, thereby inhibiting the growth of non-small-cell lung carcinoma (NSCLC) A549 cells ^[11]. Transcriptomic and bioinformatic analyses showed that PD exerts anti-tumor effects by specifically targeting the transforming growth factor β (TGF- β) pathway, significantly downregulating both TGF- β and p-SMAD3 proteins expression, thereby inducing apoptosis and suppressing proliferation in A549, NCI-H1299, and PC-9 lung cancer cell lines ^[12]. PD up-regulated the expression of PUMA (p53 upregulated modulator of apoptosis) via JNK1/AP-1 pathway to inhibit cell viability and colony formation, destroy mitochondrial function, induce apoptosis of NSCLC cells, and reduce the growth of xenograft tumors ^[13]. PD exerted dose-dependent antitumor activity through direct cytotoxicity, increased tumor cell apoptosis and immune stimulation in H520 tumor cell-bearing athymic nude mice, and can control cancer-related cachexia ^[14].

To explore the anti-gastric cancer (GC) effect of PD, it was found that PD promoted the degradation and ubiquitination of c-Myc protein by destroying the stability of c-Myc protein, significantly arrested the cell cycle, caused subsequent apoptosis, and inhibited the proliferation and growth of GC cells ^[15]. Recent studies have shown that PD can suppress the proliferation of GC cells and trigger apoptosis. Additionally, miR-34a has been found to increase GC sensitivity to PD by targeting survivin ^[16]. Diffuse large B-cell lymphoma (DLBCL), known for its high invasiveness and heterogeneity, is the most prevalent subtype of malignant lymphoma. The treatment effect is not ideal, especially when recurrence occurs after initial chemotherapy. Researchers have shown that PD has the potential to treat DLBCL by regulating the balance of BCL-2 family proteins, inducing mitochondrial-dependent apoptosis, and inhibiting proliferation in *in vivo* cell lines and *in vitro* xenograft mouse models ^[17]. PD increased the expression of Bax, reduced the expression of Bcl-2 and VEGF in H22 tumor tissues, and effectively hindered tumor growth of H22 xenografts *in vivo*, partly by enhancing immune function, promoting apoptosis, and suppressing angiogenesis ^[18]. PD decreased the expression of Bcl-2 and Bcl-x, increased the expression of Bid, and triggered apoptosis in PC-12 cells by affecting the mitochondrial dysfunction pathway ^[19].

2.1.2. Cell cycle regulatory

The complete cell cycle includes first gap phase (G1 phase), synthesis (S phase), second gap phase (G2 phase), mitosis (M phase) and stationary phase (G0 phase). Cell cycle disorder represents one of the hallmark characteristics of cancer pathogenesis. Dysregulation of cell cycle monitoring and driving mechanisms constitutes the fundamental cause of uncontrolled proliferative growth in tumor cells. PD significantly inhibited AML cells proliferation via inducing cell cycle arrest at the G0/G1 phase ^[6]. PD can

also induce G0/G1 phase cell cycle arrest in PC-12 cells, accompanied by the activation of both apoptosis and autophagy ^[19]. PD inhibited MDA-MB-231 cell growth in a concentration-dependent manner, exerted anti-proliferative effects, and induced G0/G1 phase cell cycle arrest ^[20]. PD activated forkhead box O3 (FOXO3a) expression in prostate cancer cells, leading to growth arrest both *in vitro* and *in vivo*. It effectively halted cell proliferation by promoting apoptosis through the MDM2-FOXO3a pathway and regulating cell cycle progression ^[21]. Additionally, PD induced G2/M phase arrest and caused apoptosis in HepG2 cells by targeting the PI3K/Akt signaling pathway ^[10].

2.1.3. Autophagy induction

Autophagy plays a crucial role in regulating cellular processes by removing unnecessary or damaged components and recycling metabolic resources to keep the cell in balance. The autophagy pathway plays a dual role in tumor biology, functioning as a critical survival mechanism for cancer cells while exhibiting context-dependent therapeutic implications, where both its induction and inhibition may potentiate anticancer drug efficacy. Therefore, targeting autophagy represents a complex yet promising therapeutic strategy in cancer treatment. Autophagy in BEL-7402 cells triggered by PD may be enhanced by the activation of the ERK and JNK signaling pathways, while inhibiting autophagy can prevent the activation of these pathways. In turn, suppressing PD-induced autophagy can promote apoptosis and inhibit cell proliferation. These findings suggest that autophagy plays a crucial role as a defense mechanism in PD-treated BEL-7402 cells^[22]. PD stimulated hepatocellular carcinoma HepG2 cells autophagy by activating the ERK pathway, and pretreatment with autophagy inhibitors enhanced PD-induced inhibition of proliferation and apoptosis ^[23]. This combination treatment may represent a promising therapeutic strategy for hepatocellular carcinoma. PD enhanced exogenous cholesterol uptake by upregulating low-density lipoprotein receptor (LDLR) expression, subsequent accumulation of cholesterol within lysosomes impaired autophagic flux, ultimately leading to cell death in glioblastoma multiforme (GBM) cells, PD could be a potent anti-GBM drug by autophagy and disrupting cholesterol trafficking ^[24]. PD reduced cellular energy levels, thereby activating AMPK to induce cancer cell death, which was associated with cytoplasmic endocytosis and autophagic vacuolation ^[25].

2.1.4. Anti-angiogenesis

Angiogenesis is crucial for the advancement of tumors. Vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) are key factors in promoting tumor angiogenesis. PD effectively blocked VEGF and IL-8 mediated angiogenesis by inhibiting MAPK activation ^[26]. Study has demonstrated that PD suppressed tumor growth by exerting anti-angiogenic activity through blockade of the VEGFR2-mediated signaling pathway ^[27]. In a mouse model of experimental lung metastasis, PD suppressed B16F10 melanoma metastasis and tumor angiogenesis, thereby inhibiting melanoma dissemination through its anti-angiogenic activity ^[28]. PD exerts anti-tumor effects in NSCLC through non-coding RNA regulation. More analysis showed that PD inhibited vascular mimicry (VM) in NSCLC by affecting the lncRNA/eIF4E/EGFR axis, leading to significant reductions in microvessels, VM, and the levels of vascular endothelial growth factor A

(VEGFA)/VEGFR in the lungs and liver [29]. These results emphasize the potential of PD as a therapy for VM in NSCLC patients

2.1.5. Metastasis inhibition

Cancer metastasis represents one of the most formidable challenges in oncology, accounting for up to 90% of cancer-related mortality. Once cancer cells metastasize, it means that they are separated from primary tumor sites and spread to other organs of the body via hematogenous or lymphatic routes, which not only increases therapeutic complexity, but also significantly diminishes patient overall survival. Consequently, developing metastasis-suppressive therapeutic strategies remains a persistent research focus in oncology. Single-cell sequencing identified Fucosyltransferase 9 (FUT9) was an oncogene in metastatic NSCLC progression, while hsa-miR-1246 suppressed cellular growth, migration, and invasion by downregulating FUT9; PD treatment upregulated hsa-miR-1246 and downregulated FUT9, consequently inhibiting tumor growth and metastatic dissemination in metastatic NSCLC mice [30].

Programmed death-ligand 1 (PD-L1) is a crucial immune checkpoint in clinical cancer treatment. Research showed that PD decreased levels of PD-L1 proteins in lung cancer cells by promoting their release into the extracellular environment. Additionally, lung cancer cells treated with PD were able to reactivate Jurkat T cells in co-culture systems, demonstrating its effectiveness in anti-tumor immunotherapy [31]. PD suppressed PI3K/Akt signaling pathway and induced neutrophil apoptosis through down-regulating PD-L1 expression in neutrophils, thereby inhibiting pre-metastatic niche formation and ultimately blocking breast cancer lung metastasis development [32]. PD was able to inhibit the growth and proliferation of highly metastatic MDA-MB-231 breast cancer cells both *in vitro* and *in vivo* by targeting the MDM2 oncogene [20]. Additionally, PD was found to inhibit the metastasis of cetuximab-treated KRAS wild-type colorectal cancer cells by inhibiting β -catenin [33].

Taken together, the evidence presented highlights PD as a versatile anticancer agent that targets multiple hallmarks of cancer through interconnected molecular mechanisms. Its ability to induce apoptosis, via mitochondrial pathways, modulation of BCL-2 family proteins, and regulation of key signaling cascades, underscores its potential across hematologic malignancies (e.g., AML, DLBCL) and solid tumors (e.g., lung, colon, gastric cancer). PD further restrains tumor growth by arresting cell cycles at G0/G1 or G2/M phases, with context-dependent regulation of FOXO3a and PI3K/Akt signaling dictating its effects on proliferation. Notably, PD serves dual functions in autophagy, which include promoting the process to be a cytotoxic mechanism and exploiting its inhibition to enhance apoptosis. This dual function allows for the development of a more complex therapeutic profile. Additionally, it is recommended that the combination strategies with autophagy modulators may augment efficacy, especially for hepatocellular carcinoma and GBM. Its anti-angiogenic activity, mediated by suppression of VEGF/VEGFR2 and MAPK pathways, and capacity to block metastasis through non-coding RNA regulation, PD-L1 modulation, and β -catenin inhibition, extend its utility to advanced-stage cancers.

2.2. Anti-inflammatory and immunomodulatory activities

Inflammation, a natural physiological response to tissue damage and infection, is intimately linked to the immune system, which defends the body against pathogenic invasion. In acute murine asthma models, PD reduced airway inflammation by inhibiting the production of Th2-related cytokines (such as IL-4, IL-5, IL-13), indicating a possible treatment for allergic asthma [34]. PD alleviated airway inflammation in ovalbumin (OVA)-induced allergic asthmatic mice by inhibiting nuclear factor- κ B (NF- κ B) pathway, which can effectively improve the progression of asthma [35]. By inhibiting the DPP4/JAK2/STAT3 pathway, PD markedly ameliorated nasal symptoms and histopathological alterations in the nasal mucosa of AR mice, increased the level of IFN- γ , decreased the levels of IgE and IL-4 in serum, thereby ameliorating allergic rhinitis in the murine model [36]. PD inhibited the activation of NF- κ B and MAPK signaling pathways, leading to a decrease in inflammatory mediators and mucus hypersecretion in nasal mucosal epithelial cells induced by IL-13 [37]. Researchers demonstrated that PD significantly alleviated histopathological alterations in lung tissues of lipopolysaccharide (LPS)-induced ALI mice by disrupting toll-like receptor 4 (TLR4)-containing lipid rafts, thereby suppressing NF- κ B pathway activation and reducing pulmonary inflammation [38]. PD attenuated acute lung injury (ALI) *in vitro* and *in vivo* by inhibiting apoptosis and inflammation [39]. The extracellular matrix (ECM) -receptor interaction pathway is considered to be an important pathway for PD to exert anti-fibrotic effects. Based on ammonia-induced mouse models and NH₄Cl-treated BEAS-2B cells, it was confirmed that PD alleviated ammonia-induced lung inflammation and fibrosis by inhibiting TGF- β 1-mediated ECM remodeling [40]. PD suppressed TGF- β 1-induced proliferation, inflammatory cytokine secretion, and ECM accumulation in pulmonary fibroblasts [41]. Additionally, PD was found to greatly reduce collagen production and the formation of hypertrophic scars, partly by blocking the TGF- β /Smad pathway and inducing cell death in fibroblasts [42].

The transformation of inflammatory macrophages from the M1 to the M2 phenotype by PD was observed both *in vivo* and *in vitro*, resulting in the suppression of inflammation. As a result, PD effectively alleviated dextran sulfate sodium (DSS)-induced colitis and LPS-induced inflammation [43]. PD suppressed NF- κ B activation and decreased inflammatory response in osteoarthritis chondrocytes stimulated by IL-1 β through the activation of LXR α [44]. Rheumatoid arthritis (RA) is a systemic, chronic, inflammatory autoimmune disorder characterized primarily by proliferative synovitis. Apoptosis represents a key therapeutic target for PD. Research demonstrates that PD significantly ameliorated synovial inflammation, synovial hyperplasia, and apoptosis in collagen-induced arthritis (CIA) rats, potentially by modulating mitochondrial apoptosis via the Hedgehog signaling pathway, thereby alleviating RA pathology [45]. Studies report that PD exerts potent anti-inflammatory and immunomodulatory effects, along with antioxidant activity via suppression of malondialdehyde (MDA) production in mice, suggesting its potential as a promising therapeutic agent for RA [46]. Atopic dermatitis (AD) significantly reduces quality of life due to its chronic inflammatory nature, frequent flare-ups, prolonged course, and severe itching. PD reduced the occurrence of AD-like skin lesions by inhibiting NF- κ B and STAT1 activation, while also promoting

activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/ARE pathway to stimulate heme oxygenase-1 (HO-1) expression, thereby adjusting cytokine mediators ^[47].

PD has the ability to modulate the immune system. Immunotherapy is now a leading treatment option for solid tumors such as lung and kidney cancers, as well as some types of breast cancer. The PD-1/PD-L1 pathway is a crucial checkpoint in preventing cancer cells from evading the immune system's attack. PD, which relies on cholesterol for lipid raft modulation, can help create extracellular vesicles with PD-L1 and release PD-L1 immune checkpoint glycoproteins into the surrounding environment ^[48]. Chronic periodontitis is a common chronic inflammation of periodontal support tissue, which can lead to the gradual destruction and loss of periodontal tissue. The involvement of the PD-1/PD-L1 immune checkpoint in chronic periodontitis presents a promising new option for natural product treatment. PD was found to suppress the growth of *P.gingivalis*, the bacteria responsible for periodontitis, and promote the release of soluble PD-L1 outside cells, leading to the restoration of T cell function and improvement in chronic periodontitis ^[49]. Resistance to PD-1/PD-L1 checkpoint inhibitors is prevalent in most tumors, potentially stemming from impaired antigen presentation due to downregulation of major histocompatibility complex class I (MHC-I) molecules on tumor cells. PD significantly reduced PD-L1 levels by inhibiting liver X receptor β (LXR- β) activity, and its combination with nintedanib synergistically upregulated MHC-I expression, thereby enhancing T-cell-mediated tumor recognition and cytotoxicity ^[50].

Influenza virus infection represents a global challenge. Mortality in severe influenza cases is frequently associated with hyperactive immune dysregulation characterized by hypercytokinemia, underscoring an urgent need for the development of host-directed immunomodulatory therapeutics. PD suppressed activation of transforming growth factor- β -activating kinase 1(TAK1)/I κ B kinase (IKK)/NF- κ B and MAPK pathways and, by binding TNF receptor-associated factor 6 (TRAF6) and reducing its K63-linked ubiquitination levels, further inhibited cytokine storm, thereby promoting antiviral immunity ^[51]. Utilizing network pharmacology and experimental validation, it has been discovered that PD may reduce inflammation in influenza viral pneumonia by targeting the IL-17 signaling pathway ^[52]. Th17/Treg imbalance contributes to immune-related disorders including liver injury. PD improved diabetic liver injury in mice caused by alloxan by restoring the balance between Th17 and Treg cells ^[53]. Furthermore, in tilapia lake virus (TiLV)-infected tilapia, PD enhanced the expression of antiviral genes like type I interferon (IFN-I) and C-C motif chemokine ligand 2 (CCL2) in the spleen and kidney, while inhibiting the expression of pro-inflammatory cytokines (TNF- α , IL-1 β) and TLR2. As a result, PD demonstrates potential anti-TiLV effects by alleviating oxidative stress and inflammation in the fish ^[54]. In summary, PD exhibits robust anti-inflammatory and immunomodulatory activities across a spectrum of pathological contexts, mediated by its ability to orchestrate key signaling pathways and immune cell functions. A summary of studies on the anti-inflammatory and immunomodulatory activities of PD was presented in **Table 2** and **Fig. 3**.

Table 2. The anti-inflammatory and immunomodulatory activities of Platycodin D.

Type of disease	Dosages	Cellular/animal models	Mechanisms	Ref.
Airway inflammation in asthma	40, 80 mg/kg	OVA-induced mouse model of asthma	By inhibiting NF- κ B pathway	[35]
Asthma	40 mg/kg	OVA (20 ng/50 μ L in PBS)-stimulated mouse model of allergic asthma 100 μ L of saline containing 50 μ g	Via suppression Th2 transcription factor	[34]
Allergic Rhinitis (AR)	20, 40 mg/kg	OVA-sensitized AR mouse model; human nasal mucosa cells (HNEpC)	Through DPP4/JAK2/STAT3 Pathway Inhibition	[36]
Allergic Rhinitis (AR)	10, 50 μ M	10 ng/mL IL-13-induced RPMI2650 cells	By inhibiting the activation of NF- κ B and MAPK signaling pathways	[37]
Acute Lung Injury (ALI)	<i>In vivo</i> : 20, 40, 80 mg/kg; <i>In vitro</i> : 5, 10, 20 μ M	200 μ g/mL LPS-induced ALI mice; 1 μ g/mL LPS-induced A549 lung epithelial cells	By activating LXR α -ABCA1 signaling pathway	[38]
Colitis, Inflammation	<i>In vivo</i> : 10 mg/kg; <i>In vitro</i> : 2.5, 5 μ M	3% DSS-induced colitis mouse model; 1 μ g/mL LPS- stimulated RAW 264.7 cell model	Via activation of AMPK	[43]
Osteoarthritis	5, 10, 20 μ M	IL-1 β -stimulated chondrocytes	By activating LXR α	[44]
Rheumatoid arthritis (RA)	<i>In vivo</i> : 50, 150 mg/kg; <i>In vitro</i> : 4.08, 8.16, 12.24 μ M	2 mg/mL collagen-induced arthritis (CIA) rats; RA-FLS cells	By promoting apoptosis of mitochondria to inhibit activation of hedgehog pathway	[45]
Arthritis (CIA)	50, 100, 200 mg/kg	Collagen-Induced DBA/1J Mouse	Direct antiinflammatory effects, antioxidant effect by inhibiting MDA, some immunomodulatory effects	[46]
Atopic dermatitis (AD)	0.5, 1, 2 μ M	HaCaT cells	Via up-regulation of Nrf2/ARE-mediated HO-1 expression and down-regulation of NF- κ B and STAT1 activation	[47]
Tumor	<i>In vivo</i> : 5 mg/kg; <i>In vitro</i> : 10 μ M <i>In vivo</i> : 1, 2, and 4 mg/kg (survival experiments), 2 mg/kg (inflammation studies);	Tumor-bearing mice; H460 cells or H226 cells	By inhibiting LXR- β activity and combines with nintedanib	[50]
Influenza virus infection	<i>In vitro</i> : 1.25, 2.5, 5 (A549), 0.625, 1.25, 2.5, 5 μ M (RAW264.7 cells)	PR8-infected mice; PR8-infected human lung epithelial cells (A549), R837 or PR8-stimulated RAW264.7 cells	Via targeting K63-linked TRAF6 ubiquitination	[51]
Influenza Virus Pneumonia	2.04 μ M	Influenza A virus-induced MLE- 12 cells	By modulating the IL-17 signaling pathway	[52]
Tilapia lake virus	<i>In vivo</i> : 5, 10 mg/kg; <i>In vitro</i> : 20, 40, 60 μ M	TiLV infection Oreochromis niloticus; CIK cells	By inducing IFN-I expression	[54]

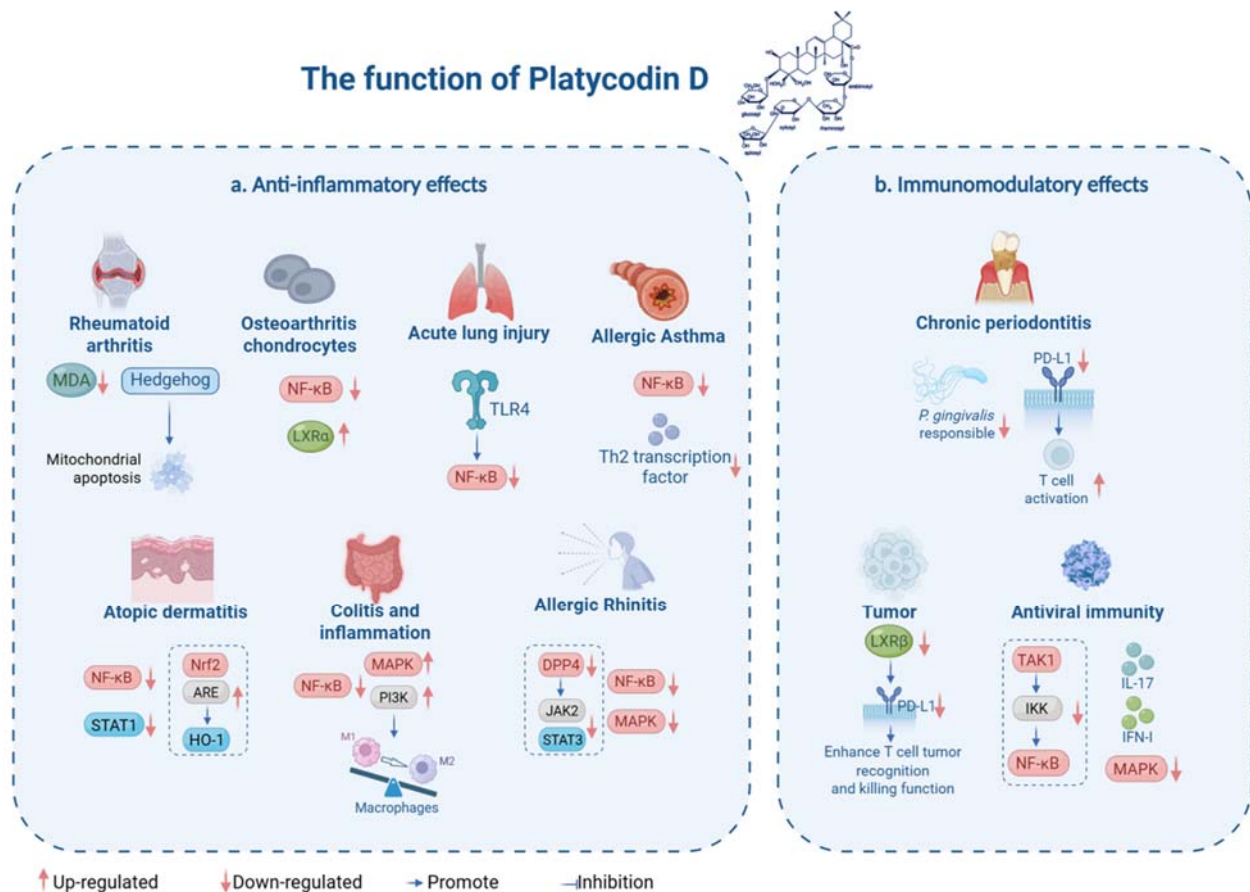


Figure 3. Schematic summary of PD-mediated effects on inflammatory and immunomodulatory processes. In the anti-inflammatory arm (A), PD modulates signaling in diverse disease contexts: in rheumatoid arthritis, it impacts mitochondrial apoptosis via MDA and Hedgehog; in osteoarthritis chondrocytes, it regulates NF-κB and LXRα; in acute lung injury, it targets TLR4-NF-κB; in allergic asthma, it affects NF-κB and Th2 transcription factors; in atopic dermatitis, it influences NF-κB, STAT1, Nrf2-ARE-HO-1; in colitis and inflammation, it acts on NF-κB, MAPK, PI3K, and macrophage polarization (M1/M2); and in allergic rhinitis, it modulates DPP4, JAK2, STAT3, NF-κB, and MAPK. In the immunomodulatory arm (B), PD exerts effects in chronic periodontitis (regulating PD-L1, *P. gingivalis* related responses, and T cell activation), tumor immunity (via LXRβ-PD-L1 to enhance T cell tumor recognition/killing), and antiviral immunity (modulating TAK1, IKK, NF-κB, MAPK, IL-17, and IFN-I).

2.3. Metabolic regulation and anti-obesity activities

PD can maintain glucose homeostasis, regulate hepatic gluconeogenesis pathway by enhancing AMPK phosphorylation/expression while diminishing PCK1 and G6Pase expression; it concurrently reduced systemic lipid levels and attenuates hepatic fat accumulation induced by T2D, primarily via the AMPK/ACC/CPT-1 fatty acid anabolic pathway, ultimately ameliorating hyperglycemia and hepatic metabolic disorders in high-fat diet (HFD)/streptozotocin (STZ)-induced type 2 diabetic mice [55]. Diabetic kidney disease (DKD) is a crucial complication of diabetes and a leading cause of end-stage renal disease. Ferroptosis, a newly identified form of cell death tied to iron ions, is closely linked to kidney damage. High glucose levels decreased glutathione peroxidase 4 (GPX4) expression in HK-2 cells, but PD countered this effect by increasing GPX4 levels and preventing cell death, suggesting that PD could be an effective treatment for DKD [56]. Recent evidence has demonstrated that PD effectively suppressed type 2 diabetes induced by cardiac injury in mice via activating AMPK pathway, and enhances the energy metabolism of

H9C2 cells stimulated by glucose (HG-PA) and palmitic acid, revealing its potential cardioprotective effect by regulating AMPK signaling pathway [57]. PD conferred cardioprotection in spontaneously hypertensive rats by attenuating two key pathological responses to hypertension: myocardial hypertrophy and fibrosis [58]. PD enhanced LDLR expression and LDL uptake by downregulating IDOL mRNA expression in hepatocytes, confirming the anti-hypercholesterolemia activity of PD and demonstrating that PD alone or in combination with statins may be a potential therapeutic option for the treatment of atherosclerotic cardiovascular disease [59]. PD exerts a significant therapeutic or preventive effect against HFD-induced metabolic syndrome and fatty liver disease. PD ameliorated HFD-induced obesity and non-alcoholic fatty liver disease (NAFLD) by activating intestinal AMPK to inhibit lipid absorption, an effect likely mediated by suppressed gene expression of key intestinal lipid absorption genes (CD36, NPC1L1, Apo B) [60]. PD has been shown to have anti-obesity qualities, exerting anti-lipogenesis and thermogenesis by activating the AMPK pathway, and reducing adipogenic markers (PPAR γ and C/EBP α) to improve obesity in db/db mice [61]. Metabolic dysfunction-associated steatotic liver disease, also known as NAFLD, has rapidly emerged as the most prevalent chronic liver disorder globally affecting 1/3 of the adult population. NAFLD poses a serious public health challenge not only as a major contributor to liver-related disability and mortality, but also due to its strong association with increased incidence of extrahepatic conditions, including cardiovascular-kidney-metabolic syndrome and malignancies. *In vitro* model induced by palmitic acid (PA), PD demonstrated protective effects by ameliorating NAFLD pathology through attenuation of oxidative stress and stimulation of autophagy [62].

2.4. Other activities

PD ameliorates osteoporosis by stimulating osteoblast differentiation and promoting bone mineralization via the SIRT1/ β -catenin pathway, achieved through upregulation of alkaline phosphatase (ALP) levels, induction of β -catenin nuclear accumulation by enhancing GSK3 β phosphorylation, and elevation of osteogenic markers and transcription factors [63]. PD inhibited osteoclast differentiation by inhibiting the activation of ERK, NF- κ B, and p38 MAPK induced by Receptor Activator of NF- κ B Ligand (RANKL), positioning it as a promising anti-osteoporotic drug candidate [64]. PD blocks breast cancer-induced bone loss by suppressing osteoclast activity, formation, and survival, concurrently inhibiting the metastatic breast cancer cells growth [65]. *Mycoplasma pneumoniae* is a pathogenic microorganism between bacteria and viruses, which is considered to be a major cause of community-acquired pneumonia. PD prevented *M. pneumoniae* infection and exhibited anti-mycoplasma effects by inhibiting the adhesion proteins P1 and P30 expression in model cells [66]. PD significantly inhibited *Mycoplasma pneumoniae* proliferation in infected cells or mice while promoting cell growth following anti-mycoplasma treatment [67]. Key pathogenic factors in acne include excessive sebum production and inflammatory response. PD ameliorated acne and prevented scar formation by downregulating the expression of sterol regulatory element binding protein-1 (SREBP-1) through inhibiting the IGF-1R/PI3K/Akt signaling pathway to suppress sebum production, and by increasing fibroblast collagen levels and modulating inflammation

through suppression of NF- κ B and matrix metalloproteinase (MMP) activity [68]. PD protected human dermal fibroblasts from H₂O₂-induced premature senescence via enhancing mitochondrial biogenesis and attenuating age-dependent endogenous oxidative damage, demonstrating its antioxidant and anti-senescence potential against H₂O₂-induced aging [69]. PD exhibited potent spermicidal activity by breaking the sperm plasma membrane to induce its contraceptive effect, without causing DNA damage or injury to rat vaginal tissue [70]. The combination of polyanionic carbosilane dendrimers (G1-S4 or G2-S16) with PD can produce dual antiviral and spermicidal activities, positioning this combination as a candidate vaginal microbicide with contraceptive activity [71]. PD inhibits platelet activation, aggregation, hemostasis *in vivo*, and arterial thrombus formation by inducing the internalization of platelet glycoprotein receptors α IIB β 3, GPIb α , and GPVI, and this suppression of platelet function and thrombosis is independent of platelet apoptosis, suggesting PD may also represent a potential antithrombotic agent [72]. PD significantly reduced the damage caused by cisplatin in human embryonic kidney 293 (HEK-293) by inhibiting reactive oxygen species (ROS)-induced oxidative harm, apoptosis, and inflammation [73]. Study has demonstrated that PD conferred hepatoprotection through modulating the MAPK signaling pathway, effectively protecting hepatocytes from acetaminophen (APAP)-induced hepatotoxicity in mice by reducing oxidative stress, suppressing inflammatory responses, and inhibiting hepatocellular apoptosis [74]. Similarly, PD lessens liver fibrosis and the activation of hepatic stellate cells (HSCs) by controlling the JNK/c-Jun signaling pathway, which in turn alters the processes of autophagy and apoptosis in HSCs [75]. PD reduced serum biochemical markers, enhanced hepatic enzymatic antioxidants, suppressed pro-inflammatory cytokines, and inhibition of hepatocyte apoptosis and steatosis in mice, which may play a protective role in alcohol-induced hepatic oxidative injury by alleviating oxidative stress and inflammatory response [76]. PD demonstrated therapeutic efficacy against esophageal and gastric mucosal injury in rats with reflux esophagitis, inhibiting histamine and gastric acid secretion while enhancing gastrointestinal antioxidant function [77]. PD conferred intestinal protection by ameliorating small intestinal pathological alterations in cisplatin (CP)-induced injury models and restoring the mechanical barrier through suppression of endoplasmic reticulum stress-mediated apoptosis in both CP-treated mice and IEC-6 cells [78].

3. Pharmacological mechanisms of PD

3.1. Signaling pathway regulation

3.1.1. Targeting PI3K/Akt/mammalian target of rapamycin (mTOR) pathway

The PI3K/Akt/mTOR pathway is a crucial signal transduction network involved in cell growth, protein synthesis, lipid biosynthesis, and autophagy regulation [79]. PI3K/AKT/mTOR pathway is one of the most frequently hyperactivated pathways in cancers, connecting receptor tyrosine kinase (RTK) signaling to the control of cell growth and survival. Increased activity in this pathway promotes cell proliferation, blocks apoptosis, disrupts normal differentiation and autophagy processes, which all play a role in tumor development and spread. Overactivation of this pathway enhances proliferation, inhibits apoptosis, undermines normal differentiation and autophagy, contributing to tumor formation and metastasis [80]. PD

caused DNA damage and apoptosis in PC-3 cells through ROS-dependent inactivation of PI3K/AKT/mTOR pathway, suggesting its potential as a treatment for inhibiting the cell proliferation of human prostate cancer (PCa) [81]. Cetuximab blocks the PI3K/Akt pathway to stop tumor cell growth and induce cancer cell death. However, constant activation of this pathway can lead to resistance to cetuximab. PD increased the effectiveness of cetuximab on KRAS-mutant colorectal cancer cells by inhibiting the PI3K/Akt pathway, as shown by reduced PI3K and Akt phosphorylation *in vitro* and *in vivo* in HCT116 and LoVo cells, leading to reduced tumor cell proliferation, migration, and invasion [82]. AML is a hematologic malignancy that is aggressive and heterogeneous, causing bone marrow hematopoiesis to be disrupted and leading to cytopenias in the peripheral blood. Research indicated that PD inhibited activation of both the PI3K/AKT and MAPK/ERK signaling pathways, inducing apoptosis in AML cells and synergistically potentiating the activity of venetoclax [6]. PD exerts protective effects against oxygen-glucose deprivation/reperfusion (OGD/R) injury in primary cortical neurons derived from neonatal rats with hypoxic-ischemic encephalopathy by modulating the PI3K/Akt/mTOR signaling pathway [83]. PD reduced oxidative stress, improved mitochondrial dysfunction, and inhibited neuronal apoptosis in Type 2 Diabetes Mellitus (T2DM) mice by regulating the PI3K/Akt/GSK3 β pathway, ultimately attenuating cognitive dysfunction [2]. By inhibiting the activation of the PI3K/mTOR pathway, PD may prevent the release of pro-inflammatory cytokines and reduce the inflammatory response in oral mucosal cells affected by high glucose levels, potentially offering therapeutic benefits for oral mucosal diseases [84]. As an Hsp90 inhibitor disrupting the Hsp90/Cdc37 complex, PD abrogates mTOR inhibition-induced survival signals through feedback blockade, and synergistically enhances anti-tumor efficacy against NSCLC when combined with mTOR inhibitors [85].

3.1.2. Targeting NF- κ B pathway

NF- κ B is a critically important signaling pathway involved in regulating diverse physiological processes, including inflammation, immune responses, cell proliferation, cell growth, and apoptosis. Acting as the master regulator of inflammation in humans, the NF- κ B pathway rapidly initiates inflammatory responses. Upon binding of external ligands to cell surface receptors (e.g., TLR, IL-1R, TNFR), downstream IKK is activated, leading to phosphorylation and subsequent ubiquitin-mediated degradation of I κ B proteins. This release of NF- κ B dimers allows them to move into the nucleus and increase the transcription of pro-inflammatory cytokine genes (IL-1 β , IL-6, and TNF- α), thus initiating acute and chronic inflammatory reactions in humans [86].

ALI is a serious condition caused by some inflammatory process. Due to abnormal activation of macrophages, it will require new pharmacological targets and drugs. NLRP3 inflammasome and NF- κ B signaling pathway are key players in the inflammatory response. PD attenuates LPS-induced ALI in rats by suppressing NLRP3 inflammasome activation via the TLR4/MyD88/NF- κ B pathway, conferring significant protection [87]. PD ameliorates alcohol-induced fatty liver (AFL) in rats by exerting anti-inflammatory and endotoxin-antagonizing effects through the TLR4/MyD88/NF- κ B signaling pathway, thereby effectively suppressing AFL progression and improving hepatic function [88]. PD effectively inhibited PTC progression

by suppressing the NF- κ B pathway, concomitantly enhancing apoptosis and cell cycle arrest, suppressing tumor cell growth, and thereby exerting potent anti-tumor effects [89]. PD can also reduce the abnormal increase of serum inflammatory factors (TNF- α and IL-1 β) via regulating NF- κ B and apoptotic pathways, repair renal cell apoptosis, and thus significantly inhibit the development of diabetic nephropathy in mice [90].

3.1.3. Targeting Nrf2/HO-1 signaling pathway

The Nrf2/HO-1 signaling pathway is essential in responding to oxidative stress, playing a crucial role in anti-inflammatory, antioxidant, and apoptosis processes. It is a key therapeutic target for intervening in disease [91]. Diabetes constitutes a cluster of physiological issues related to hyperglycemia-mediated oxidative stress and pancreatic β -cell apoptosis. PD protected these pancreatic β -cells against STZ-induced oxidative stress and apoptosis by suppressing STZ-triggered p38 pathway activation in INS-1 cells while concurrently enhancing Nrf2/HO-1 pathway activation [92]. PD suppressed the TLR4/MyD88/NF- κ B signaling pathway and activated the Nrf2/HO-1 signaling pathway to inhibit inflammation and oxidative stress induced by high glucose in diabetic retinopathy, thus improving the pathological progression [93]. PD protected mouse-derived C2C12 myoblasts from oxidative stress damage by activating the Nrf2/HO-1 pathway, thereby suppressing aberrant ROS generation, inhibiting hydrogen peroxide (H₂O₂)-induced cytotoxicity and DNA damage, and shielding cells from mitochondria-mediated apoptosis, ultimately ameliorating muscular and skeletal muscle injury [94]. Myocardial ischemia/reperfusion (I/R) injury as a complex pathophysiological process implicated in myocardial infarction (MI). PD was able to inhibit oxidative stress and apoptosis in H9C2 cardiomyocytes after exposure to hypoxia/reoxygenation (H/R) injury by activating the Akt/Nrf2/HO-1 signaling pathway, ultimately contributing to its therapeutic benefits in myocardial I/R injury [95]. PD exerted protective effects against cigarette smoke (CS)-induced pulmonary inflammation in mice by upregulating Nrf2 and HO-1 expression via activating the Nrf2 signaling pathway, suppressing CS-induced NF- κ B activation, and thereby mitigating inflammatory and oxidative responses, ultimately preventing CS-driven lung inflammation [96]. A summary of studies on mechanism of the pharmacological activities of Platycodin D is presented in **Fig. 4**.

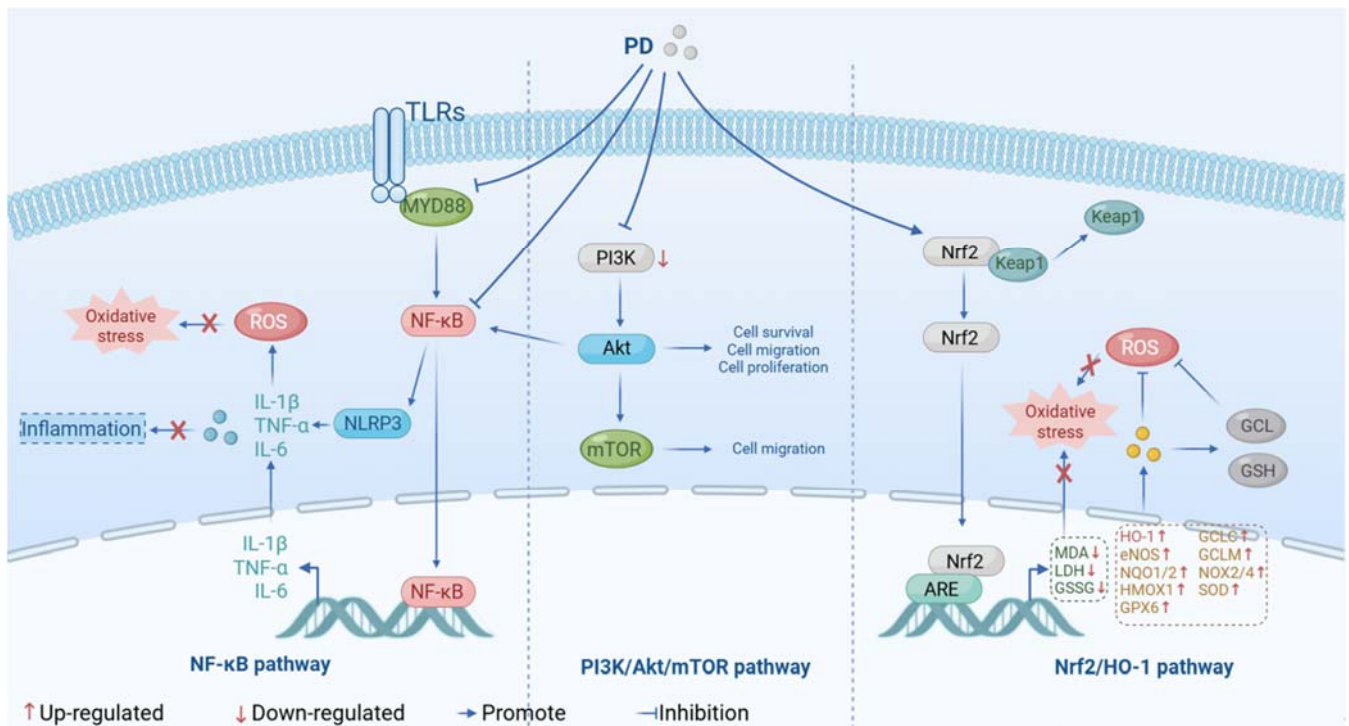


Figure 4. Schematic depiction of PD mediated regulation of key signaling pathways. PD acts on the NF- κ B pathway (left), influencing TLRs-MYD88 signaling to modulate NF- κ B activation, and downstream pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6) and NLRP3. In the PI3K/Akt/mTOR pathway (middle), PD targets PI3K (down-regulated), affecting Akt and mTOR to control cell survival, migration, and proliferation. For the Nrf2/HO-1 pathway (right), PD modulates Nrf2-Keap1 interactions, countering oxidative stress via ROS regulation and up-regulating antioxidant-related effectors (e.g., HO-1, NQO1).

3.2. Epigenetics and Metabolic Regulation

Beyond its modulation of canonical signaling pathways, PD exerts biological effects through epigenetic and metabolic regulatory mechanisms, as well as multi-target synergistic actions. In terms of epigenetics and metabolic regulation, PD ameliorated Polycystic ovary syndrome (PCOS)-related pathological damage by attenuating granulosa cell ferroptosis through targeted activation of the CD44/SLC7A11 axis ^[97]. Additionally, PD disrupted membrane cholesterol distribution on host cells, thereby inhibiting SARS-CoV-2 entry via blocking membrane fusion via suppression of both lysosomal and TMPRSS2-driven pathways, effectively preventing viral infection ^[98].

For therapeutic strategies for chemotherapy-resistant tumors, the core value of combination regimens lies in restoring tumor cell drug sensitivity through multi-target/multi-mechanism synergy and sequential drug administration strategies. Even though oxaliplatin-based treatments are commonly used as the initial treatment for metastatic colorectal cancer, resistance hinders their effectiveness, leading to treatment failure. PD has the potential to overcome chemoresistance by activating the LATS2/YAP1 pathway of the Hippo signaling pathway in order to combat oxaliplatin resistance in colorectal cancer ^[99]. PD acted synergistically with the BCL-2 inhibitor venetoclax to increase its cytotoxic effects on DLBCL cells and improve their sensitivity to the drug, resulting in the cooperative killing of DLBCL cells ^[17]. PD boosted the chemosensitivity of multiple myeloma (MM) cells to bortezomib (BTZ) by blocking the NF- κ B and JAK2/STAT3 signaling pathways ^[100]. The combination of PD and doxorubicin (DOX) exhibited

significantly enhanced anti-proliferative effects against human breast cancer cells (MCF-7 and MDA-MB-231 cells) compared to monotherapies, and PD enhanced the anti-proliferative effects of DOX while reducing its cardiotoxicity and clinical dosage of DOX without compromising its anticancer effects [14].

In short, the pharmacological mechanism of PD supports convoluted networks of multiple signals, epigenetics as well as metabolism pointing to its pleiotropic bioactivity. The PI3K/Akt/mTOR signaling pathway is important for the efficacy of the action. PD works to inactivate the overactive pathway to cause apoptosis, reverse drug resistance and protect from neural as well as metabolic injury. PD also tightly regulates the NF- κ B pathway, dampening excessive inflammatory responses in conditions ranging from ALI to cancer by suppressing pro-inflammatory cytokine production and inflammasome activation. Additionally, the Nrf2/HO-1 axis activation enables PD to counter oxidative stress, safeguarding cells from damage in diabetes, muscular injury, and pulmonary inflammation. Beyond canonical pathways, PD has unique effects through epigenetic and metabolic mechanisms, such as attenuating ferroptosis via CD44/SLC7A11 in PCOS, disrupting viral entry through cholesterol modulation, and reversing chemoresistance by engaging the Hippo pathway, while synergizing with chemotherapeutics to enhance efficacy and reduce toxicity. Collectively, all these mechanisms together indicate how PD can modulate various biological processes through modulation of the specific pathways according to context thereby being a potential agent across inflammatory.

4. Preparation and Metabolism of PD

The clinical utilization of PD is unmanageable because of prep efficiency, metabolism, and bioavailability issues. Examining how it is made and taken from the body, what happens to it and how it works will help make it a useful drug. This segment synthesizes the information currently available concerning the preparation methods, metabolic pathways and bioenhancement strategies of PD with a view to improving its clinical effectiveness.

4.1. Biotransformation and preparation methods

4.1.1. Enzymatic transformation

Deglycosylated saponins exhibit enhanced bioavailability compared to their glycosylated counterparts and demonstrate superior biological effects. The thermostable β -glucosidase from *Caldicellulosiruptor bescii* was employed to achieve the complete bioconversion of platycoside E and platycodin D3 present in Platycodi radix extract into bioactive PD [101], as evidenced by the transformation of platycoside E to PD through the removal of two glycosyl molecules under the action of deglycosylated enzymes [102] (**Fig. 5**). Balloon flower leaf extract (BFLE), recovered from the underutilized foliar by-products of *Platycodon grandiflorus* root production, possesses significant value due to its high content of platycoside E. The recombinant β -glucosidase from *Caldicellulosiruptor owensensis* can specifically hydrolyze the C-3 glucose residue of platycosides, enabling complete conversion of platycoside E from BFLE to PD under

optimized reaction conditions and thereby enhancing the deglycosylated platycoside production process ^[103]. Enzymatic transformation is an effective approach to enhance the bioavailability of PD, but further reduction of enzyme costs is required.

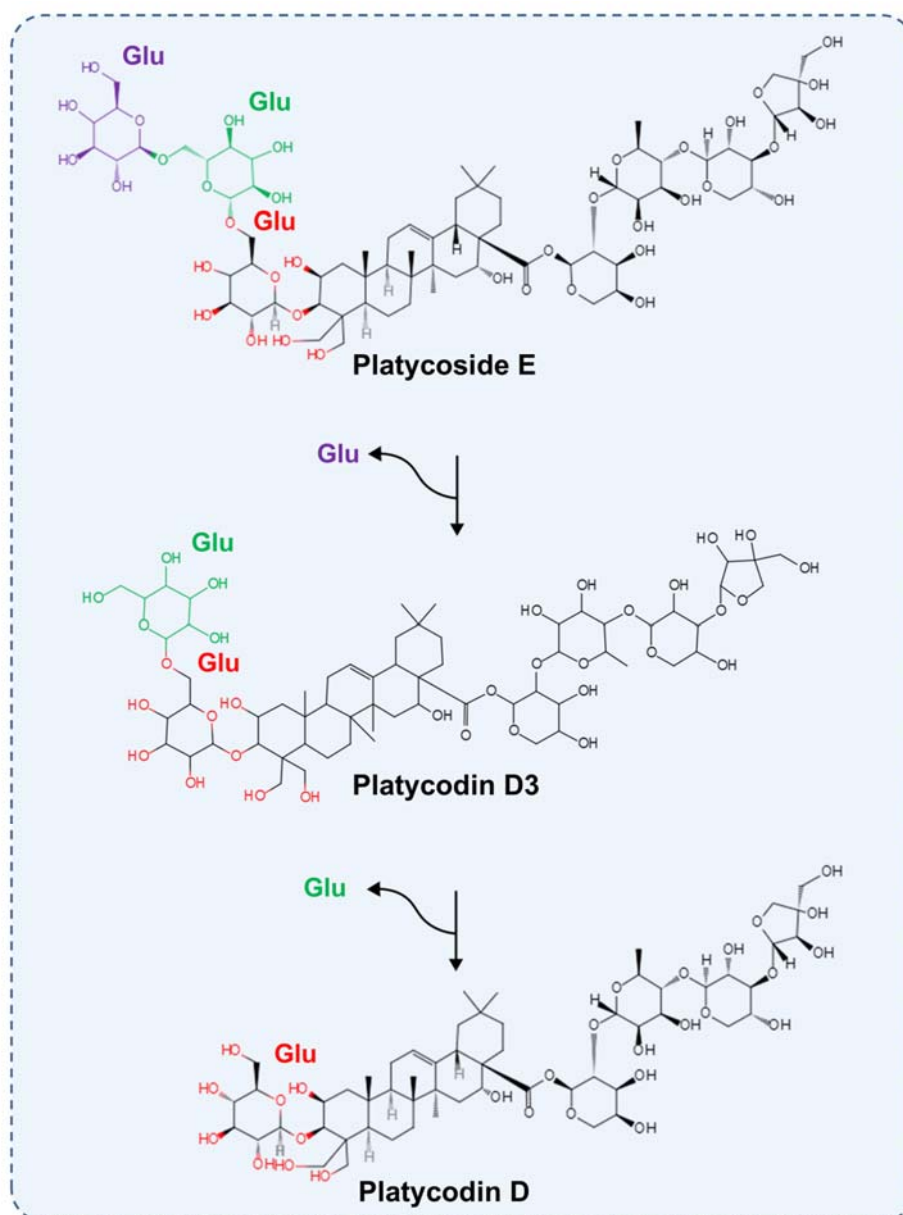


Figure 5. Biotransformation of platycoside E into platycodin D via platycodin D3. Platycoside E, containing multiple glucose (Glu) moieties (color-coded: black, teal, purple), undergoes sequential glucose (Glu) removal. First, it converts to Platycodin D3 (losing a purple-marked Glu), then further transforms to Platycodin D (losing a teal-marked Glu). The structural formulas depict the progressive elimination of glucose units, showing the chemical transition from the parent compound to the final product, Platycodin D. Arrows indicate the direction of biotransformation, highlighting the enzymatic or chemical cleavage of glucose residues in this metabolic pathway.

4.1.2. Optimization of extraction process by using response surface methodology

The optimization of its extraction conditions from PG roots has not been well solved, despite its biological importance. While conventional extraction methods like maceration, reflux, and Soxhlet extraction demonstrate applicability for isolating diverse bioactive compounds, they exhibit inherent limitations including low efficiency, poor selectivity, significant environmental burden, and complications in downstream purification processes ^[104]. Ultrasound-assisted extraction coupled with response surface

methodology represents a rapid and effective technology for PD preparation. Using polyethylene glycol (PEG) as an optimizing and additive conditions via single-factor experiments combined with Box-Behnken design, the established parameters comprised: 10% PEG solvent (consisting of PEG200-PEG400 in a 1:1 ratio), a liquid-to-solid ratio of 24 mL/g, an ultrasonic power of 288 W, an extraction time of 44 minutes, a temperature of 30 °C, a cavitation duration of 1.5 seconds, and a dwell time of 1.5 seconds. This resulted in a PD content of 5.22 ± 0.13 mg/g, which was notably higher compared to the yield obtained using ethanolic extraction solvents ^[105]. Optimization via Box-Behnken design-response surface methodology (BBD-RSM) established the optimal extraction conditions for PD as: ethanol concentration of 0%, temperature of 50 °C, as well extraction time of 11 h, yielding a PD content of 5.63 mg/g from PG roots and demonstrating enhanced PD yield ^[106]. Optimization of extraction process by using response surface methodology demonstrates high extraction efficiency and mature technology, making it suitable for industrial-scale production.

4.1.3. Mechanochemical-assisted extraction

Using water as a solvent in mechanochemical-assisted extraction makes it an environmentally friendly and cost-effective natural compound extraction method. The successful application of mechanochemical-assisted extraction with solid alkali in aqueous extraction of PD from PG roots achieved an optimal yield of 7.16 ± 0.14 mg/g by using NaOH-assisted grinding (5% w/w, 5 min), followed by room-temperature hydroextraction (20 min, 1:30 g/mL solid-liquid ratio) and acidification (pH 3.5). This method significantly increased PD yield, reduced extraction time and temperature compared to superfine grinding (3.26 ± 0.12 mg/g) and Soxhlet extraction (4.18 ± 0.11 mg/g) ^[107]. Mechanochemical-assisted extraction prioritizes cost-effectiveness and environmental sustainability, making it particularly suitable for small- to medium-scale production processes that are sensitive to solvent and energy consumption.

Comparative analysis of three distinct methods, including enzymatic transformation, response surface methodology-optimized ultrasound-assisted extraction, and mechanochemical-assisted extraction in terms of extraction efficiency, cost-effectiveness, environmental sustainability, and industrial feasibility was presented in **Table 3**.

Table 3. Comparative analysis of three biotransformation and preparation methods of Platycodin D in terms of extraction efficiency, cost-effectiveness, environmental sustainability, and industrial feasibility.

Method	Extraction efficiency	Cost-effectiveness	Environmental sustainability	Industrial feasibility
Enzymatic transformation	Medium (requires optimization of enzyme activity)	Low (high enzyme cost)	High (mild conditions)	Medium (requires enzyme engineering support)
Response surface methodology-optimized ultrasound-assisted extraction	High (model optimization)	Medium (equipment investment)	Medium (relatively high energy consumption)	High (easy to scale up)
Mechanochemical-assisted extraction	Medium (depends on mechanical strength)	High (low energy consumption)	High (no solvent pollution)	High (simple equipment)

4.2. Metabolism and pharmacokinetics

Although deglycosylation and dehydroxylation constitute the principal metabolic pathways of PD, studies reveal that both PD and its metabolites have anti-inflammatory effects in LPS-stimulated RAW 264.7 cells, whereas only PD mitigated lipid accumulation in free fatty acid (FFA)-stimulated HepG2 cells [108]. An integrated strategy combining network pharmacology, spectrum-effect relationship analysis, metabolomics, and molecular docking confirmed PD as an active ingredient manifesting efficacy in suppressing cough and reducing sputum, with its bioactive forms *in vivo* identified as 3-O- β -D-glucopyranosyl isoplatycodigenin, 3-O- β -D-glucopyranosyl platycodigenin, 7-hydroxyl-3-O- β -D-glucopyranosyl platycodigenin, platycodigenin, and isoplatycodigenin, which exert their antitussive and expectorant effects by binding to target proteins and modulating corresponding metabolomic pathways [109]. UHPLC-Q-TOF/MS screening of intestinal bacterial metabolites of PD identified seven metabolites, established hydrolysis, demethylation, dehydroxylation, and acetylation as the primary *in vitro* metabolic pathways, and revealed potent PD-metabolizing capabilities in four human fecal bacterial strains: *Enterococcus* sp. 41, *Bacillus* sp. 46, *Escherichia* sp. 49A, and *Escherichia* sp. 64 [110]. The PD compound had a much lower oral bioavailability compared to the PG extract, with PD being poorly absorbed in the intestine, and the differences in their pharmacokinetics primarily resided in their distinct hydrolysis profiles rather than absorption [111]. Licorice altered the pharmacokinetics of PD *in vivo* by prolonging its elimination half-life and time to peak concentration, thereby increasing systemic exposure to PD, the principal bioactive component of PG, with co-administration yielding synergistic therapeutic effects [112].

Optimizing the bioavailability and targeted delivery of PD in complex gastrointestinal systems remains a critical challenge. Researchers enzymatically developed PD nanocarriers (PD NPs), engineered their surface with lipoic acid esterification to create mitochondrialfunctionalized nanocarriers (PA NPs), which effectively mitigated cellular oxidative damage by selectively localizing to mitochondria. These nanocarriers were able to survive the gastric environment for controlled release in the intestines and helped regulate gut microbiota imbalance in diabetic mice induced by STZ. Experimental data suggested that these effects were likely due to the modulation of the GSK3- β /IRS1/AMPK signaling pathway, leading to improvements in pancreatic islet structure and function [113].

In summary, the preparation and metabolism of PD is characterized by versatile biotransformation and extraction strategies such as enzymatic deglycosylation, RSM optimized ultrasound-assisted extraction and mechanochemistry-assisted extraction. These strategies enhance yield and efficiency significantly as compared to conventional methods. PD has undergone dehydroxylation and deglycosylation *in vivo*. The gut microbiota is crucial in generating bioactive metabolites. The low oral bioavailability of PD is being overcome with novel nanocarrier systems. Examples include mitochondrial-targeted PA NPs to enhance targeting and stability. These advancements and knowledge about the pharmacokinetic interactions of PD is

useful to solve the existing limitations and promote more this compound as functional food and medicinal product.

5. Safety Evaluations

Safety analysis, toxicology testing and preclinical safety studies will further help in establishing the safety of PD and its regulatory approvals for food and pharma applications.

5.1. Toxicological studies

5.1.1. Hemolytic activity

PD has been reported to exhibit hemolytic activity on erythrocytes. At low doses, PD shows good safety, but higher concentrations administered intravenously can cause moderate hemolysis. This can result in the rupture of red blood cells, interaction with cholesterol on the cell membranes, causing membrane dissolution and reduced stability [30, 111, 114]. For instance, 10 μM PD treatment exhibited negligible hemolytic activity against rabbit erythrocytes [31]. Consequently, intravenous administration requires careful monitoring of monomeric compound purity and dosage. The hemolytic activity of PD is related to its molecular structure, and this question is anticipated to be addressed to enhance its safety profile for therapeutic applications.

5.1.2. Dose-dependent cytotoxicity

Multiple studies conducted *in vitro* and *in vivo* have shown that PD exhibits broad-spectrum cytotoxicity against multiple human cancer cell lines in a dose-dependent manner through diverse mechanisms, such as inhibiting cell growth and survival, triggering apoptosis and autophagy, arresting the cell cycle, reducing angiogenesis and metastasis, and altering transcription factors [25, 30, 72]. PD exhibited cytotoxicity against PC3, DU145, and LNCaP prostate cancer cell lines, with half-maximal inhibitory concentration (IC_{50}) values ranging from 11.17 to 26.13 μM [21]. PD treatment for 48 hours significantly reduced the viability of NSCLC cell lines in a dose-dependent manner, with an IC_{50} for PC-9 cells ($29 \pm 7 \mu\text{M}$) being higher than that for A549 cells ($11 \pm 0.95 \mu\text{M}$) [30]. PD exhibited potent cytotoxicity against H520 cells with an IC_{50} value of 15.86 $\mu\text{g/mL}$ [14]. PD showed high cytotoxic activity against human tumor cell lines SGC-7901, PC-12, Bel7402 (hepatoma), HeLa, and A549, with IC_{50} values of 18.6 ± 3.9 , 13.5 ± 1.2 , 19.8 ± 4.8 , 26.4 ± 2.2 , and $26.0 \pm 4.6 \mu\text{M}$, respectively [19]. Compared to the other cell lines, PD demonstrated the highest cytotoxic potency against PC-12 cells. The IC_{50} values demonstrate substantial cytotoxic efficacy of PD against the cancer cells.

5.2. Preclinical safety profile

Toxicity testing demonstrated no PD-related clinical signs, mortality, body weight/organ weight alterations, or histopathological changes in 14 major organs in female and male mice after being given a single oral dose of 2000 mg/kg; both the LD_{50} (50% lethal dose) and estimated LD for PD were determined to exceed 2000 mg/kg [115]. It indicates that it has high safety in human application. Additionally, subchronic oral administration of PD at 10 and 20 mg/kg/day for four consecutive weeks demonstrated no significant

liver or kidney toxicity in mice ^[32]. Collectively, current evidence supports a favorable safety profile for PD at therapeutic doses; however, concentration-dependent effects and interindividual variability necessitate careful dosage management.

6. Challenges and future perspectives

6.1. Current Research Limitations

6.1.1. Low Bioavailability

PD confronts dual pharmacotechnical constraints: low natural abundance and suboptimal bioavailability, necessitating innovative solutions. PD demonstrated low absolute bioavailability ($F=1.89\%$), administration route-dependent elimination half-lives (intravenous: 2.14 ± 0.18 h; oral: 5.42 ± 1.9 h), and a mean absorption time of 6.3 h ^[116]. The oral absolute bioavailability of PD in the monomer was significantly lower than that in the PG extract due to the hydrolysis of the glycosidic chain, and it could not be well absorbed in the intestine due to the intestinal first-pass effect ^[111]. Currently, there is a paucity of clinically viable formulations for PD, necessitating intensified research on advanced delivery systems to elucidate its functional bioavailability and develop effective nano-enabled carriers, thereby establishing foundations for large-scale human trials.

6.1.2. Inadequate mechanistic resolution

Research on the pharmacological mechanisms of PD in humans requires further validation due to fundamentally divergent pathophysiologies across diseases, with current evidence largely derived from animal and cellular models. Rigorous target identification and verification, spanning molecular, cellular, and animal levels, are essential to establish translatability to patients and deepen insights into tumor pharmacology. Advances in artificial intelligence (AI) and single-cell analytics are driving a paradigm shift in anti-cancer target discovery: from single-molecule focus toward dynamic network-level analyses. This transition provides novel frameworks for mechanistic pharmacological investigation and validation. Future research will pivot from “single-target” to “integrative network” perspectives and from population-based therapies toward precision oncology. Interdisciplinary merger will hasten the exploration of novel targets/dynamic biomarkers and their therapeutics. The integration will also drive technological innovation, translate quickly into clinical settings, and enable new solutions to drug resistance and tumor heterogeneity.

6.2. Translational Potential

6.2.1. Combination therapy

The experimental evidence suggest that PD has a significant anti-tumor activity and acts synergistically with various other chemotherapeutics while exhibiting low-cut toxicity towards normal cells. Combination therapy is a common way to enhance therapeutic effectiveness and reduce side effects. Chemotherapy resistance remains a major impediment in hepatocellular carcinoma (HCC) treatment. PD reversed histone deacetylase inhibitor (HDACi) resistance in HCC cells by suppressing ERK1/2-mediated cofilin-1 phosphorylation, and its combination with the class I HDAC inhibitor apicidin significantly enhanced

apoptosis in HDACi-resistant (HDACi-R) cells ^[117]. Castration-resistant prostate cancer refers to the resistance of prostate cells to traditional androgen deprivation therapy, resulting in the continued growth of the tumor. In phosphatase and tensin homolog (PTEN)-deficient prostate cancer, PD modulated TRAIL-induced cell death via the Akt/FOXO3a signal pathway and enhanced the antitumor efficacy of sorafenib by augmenting FOXO3a activity and expression; notably, the combination of PD and sorafenib increased FOXO3a expression than either agent alone, resulting in synergistic antitumor effects against both androgen-independent and PTEN-deficient prostate cancer ^[118]. PD exhibited potent anti-glioma efficacy by modulating Wnt/ β -catenin pathway, thereby sensitizing glioma cells to the frontline chemotherapeutic temozolomide (TMZ) and potentiating TMZ-mediated tumor suppression ^[119]. The combination of PD with AKT kinase inhibitor MK2206 overcame feedback activation of the AKT pathway, dysregulating AKT/4E-BP1 signaling to inhibit proliferation and induce apoptosis across multiple NSCLC genotypes, thereby enhancing therapeutic efficacy ^[120]. In both *in vitro* and *in vivo* experiments, PD suppressed the PD-L1 expression and enhanced the efficacy of pembrolizumab against papillary thyroid carcinoma (PTC) ^[89].

6.2.2. Novel therapeutic indications

PD mitigated ferroptosis in GCs through targeting CD44 to activate the system Xc-, thereby reducing PCOS-associated pathological injuries ^[97]. PD administration significantly ameliorated memory deficits, enhanced neuronal viability, and attenuated apoptosis in mice subjected to combined aluminum chloride and D-galactose induction by activating the AMPK pathway, indicating its potential as a therapeutic candidate for oxygen radical-induced neurodegenerative disorders ^[121]. Neuroinflammation, a common pathogenic factor, plays a critical role in neurodegenerative disorders. Thus, targeting microglia-driven neuroinflammation may benefit patients with inflammation-associated neurological diseases, including parkinson's disease and alzheimer's disease (AD) ^[122]. AD, one of the most prevalent neurodegenerative disorders, poses a substantial disease burden due to its high prevalence, with the abnormal accumulation of the beta-amyloid peptide (A β) in the brain representing a core pathological hallmark. PD exerted neuroprotective effects by protecting BV-2 microglial cells from A β -induced inflammation and oxidative stress through modulation of the TLR4/NF- κ B and Nrf2/HO-1 signaling pathways ^[123]. PD suppressed LPS-induced neuroinflammation by inhibiting inflammatory responses in primary rat microglia via LXR α -ABCA1 signaling activation, which disrupted lipid raft integrity and blocked TLR4 translocation into rafts, thereby offering therapeutic potential for neurodegenerative disorders ^[5]. Parkinson's disease as a common neurodegenerative disease associated with inflammation, PD enhanced cell viability, suppressed the elevated levels of inflammatory mediators and cytokine secretion, and consequently inhibited neuroinflammation via the TLR4/MyD88/NF- κ B pathway in 1-methyl-4-phenylpyridinium (MPP⁺)-induced BV-2 microglial cells ^[124].

6.2.3. Clinical research needs

PD holds significant promise for clinical application across multiple medical domains, particularly in oncology, inflammation-related disorders, diabetes management, organ damage, and neurodegenerative diseases. While preclinical evidence is promising, further in-depth animal studies and clinical trials are warranted to rigorously elucidate the toxicity, safety profile and therapeutic potential of PD, given the current reliance on cellular and animal models. Prior to the widespread clinical adoption of PD, a comprehensive assessment of its safety profile in human trials is imperative. However, as current evidence is largely confined to cellular and animal models, further *in vivo* experimentation and clinical studies remain imperative to establish its toxicity profile, safety, and therapeutic potential, while the precise mechanism of action warrants additional investigation and elucidation.

6.3. Dose optimization and toxicity assessment

To evaluate the potential health impacts of PD, the toxicity and drug metabolism profiles were determined by using the ProTox 3.0 and ADMETlab 3.0 platforms. ProTox 3.0 analysis predicted an LD₅₀ value of 4000 mg/kg for PD. Toxicity profiling indicated interactions with several targets, including cytochrome enzymes and nuclear receptors, and falling under classes such as organ toxicity and toxicity endpoints (**Fig. 6A**). The key organ toxicity predictions included immunotoxicity, cardiotoxicity, and nutritional toxicity (**Fig. 6B**), this highlight the potential risks to cardiac function, immune response, and nutrient metabolism. ADMETlab 3.0-generated radar plots (**Fig. 6C**) revealed the ADMET properties of PD (e.g., molecular weight [MW], logP) relative to established thresholds. Comprehensive toxicity attribute listings identified the potential manifestations across various endpoints, including hematotoxicity and ototoxicity (**Fig. 6D**). These findings suggest PD carries significant toxicological liabilities. Consequently, further experiments are required in the future: first, Long-term toxicity studies under clinically relevant dosing regimens are needed to evaluate cumulative organ effects and potential irreversible damage; second, The mechanisms underlying immunotoxicity require elucidation, specifically how PD affects immune cell function and signaling pathways; third, the basis of nutritional toxicity should be explored to understand how PD interferes with nutrient absorption, metabolism, or utilization. Integrating these assessments with population variability factors (e.g., age, pre-existing conditions) will enable more clinically relevant toxicity risk profiling and support the safe application of PD.

In summary, PD faces substantial challenges because of low oral bioavailability and a lack of mechanistic validation in human settings, which would require innovative delivery systems and integrative network analysis for bridging the preclinical and clinical divide. Its translational potential is strengthened by synergistic combination therapies (e.g., with HDAC inhibitors, sorafenib) that enhance efficacy against drug-resistant tumors and neurodegenerative disorders, as well as novel indications (e.g., PCOS and neuroinflammatory diseases) expand its therapeutic scope. However, to realize this potential, strong clinical trials will be required to confirm safety (due to predicted cardiotoxicity and immunotoxicity) and dose finding, along with mechanistic studies to confirm the multi-target actions of PD in humans. Ultimately,

interdisciplinary efforts integrating AI-driven target discovery [125], nanotechnology [126], and clinical pharmacology will be pivotal to unlocking PD's full therapeutic value.

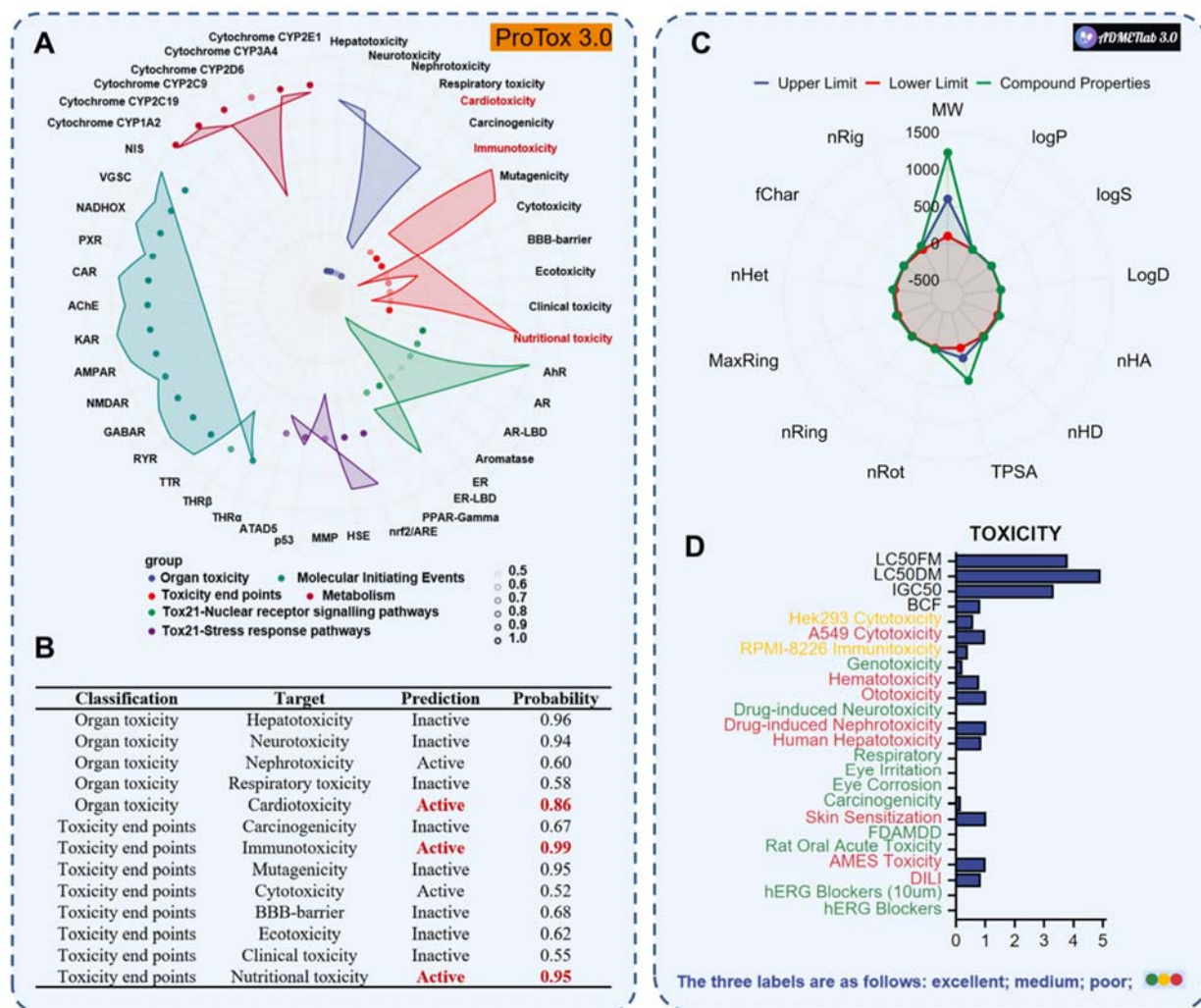


Figure 6. The toxicity prediction and assessment of PD was performed using the ProTox 3.0 platform and ADMETlab 3.0 platform. **(A)** Toxicity distribution map of PD from ProTox 3.0, visualizing interactions with targets (e.g., cytochrome enzymes, nuclear receptors) across categories: organ toxicity, toxicity end points, metabolism, molecular initiating events, Tox21-nuclear receptor signaling/stress response pathways. **(B)** Summary of PD's organ toxicity (hepatotoxicity, nephrotoxicity, etc.) and toxicity end points (carcinogenicity, immunotoxicity, etc.) from ProTox 3.0, with prediction (active/inactive) and probability values. **(C)** ADMET radar plot from ADMETlab 3.0, showing absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties (e.g., MW, logP, TPSA) against upper/lower limits. **(D)** Toxicity property and decision for PD from ADMETlab 3.0, listing endpoints (LC50FM, LC50DM, etc.) and classification (excellent/medium/poor). The data obtained from the following websites: <https://tox.charite.de/protox3/>. and <https://admetlab3.scbdd.com/>.

7. Conclusion

PD as a prominent triterpenoid saponin derived from PG, has emerged as a versatile bioactive molecule with multiple bioactivities, including anticancer, anti-inflammatory, metabolic regulation, and organ protection, mediated through intricate interactions with the key pathways such as PI3K/Akt, NF-κB, and Nrf2/HO-1. A strong foundation has been established through years of PD research, with studies increasing in pace since 2010, showcasing its potential for treating a variety of diseases including inflammatory disorders, tumors, metabolic syndromes, and neurodegenerative conditions. Nevertheless, there are still significant obstacles that need to be overcome, such as the low oral bioavailability and complex metabolic

profile of the treatment which hinder its effectiveness. Additionally, the mechanistic insights gained from preclinical models need to be confirmed in human systems, and there is a shortage of comprehensive safety evaluations, especially in terms of long-term toxicity and optimizing clinical-grade doses. Looking ahead, advancing professional development from bench to bedside will require interdisciplinary collaboration efforts. This includes developing innovative nanoformulations to improve bioavailability, utilizing single-cell analytics and AI to understand network-level mechanisms, and prioritizing rigorous clinical trials to prove the effectiveness and safety treatment, especially when used in combination therapies. Addressing these challenges will not only unlock PD's full therapeutic potential but also shed light on the translational value of natural saponins in modern medicine.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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