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Review Article

Chemical Constituents and Pharmacological Activities of Steroid Saponins Isolated from *Rhizoma Paridis*

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Rhizoma Paridis, the rhizome of liliaceous plants *Paris polyphylla*, is one of the most commonly used herbal drugs in China. Phytochemical and pharmacological studies have shown that steroid saponins were the major effective ingredients of *Rhizoma Paridis* to exert antitumor, anti-inflammatory, hemostasis, and antifibrosis functions. In this review, we discussed the chemical structures of steroid saponins and their related biological activity and mechanisms in cellular and animal models, aiming to provide a reference for future comprehensive exploitation and development of saponins.

1. Introduction

Rhizoma Paridis, the dried rhizome of liliaceous plants *Paris polyphylla* Smith var. *yunnanensis* (Franch.) Hand.-Mazz or *Paris polyphylla* Smith var. *chinensis* (Franch.) Hara, is a commonly used herbal drug in China, which has a long clinical application history to treat multiple diseases including malignant boils, carbuncles, snake and insect bites, and injuries [1]. It is also one of the core ingredients of Yunnan Baiyao, a well-known haemostatics Chinese medicine. The *Rhizoma Paridis* family comprised 24 species discovered in the world, 22 of them was found in the Yunnan, Sichuan, Guizhou, and Guangxi provinces of China [2].

As an essential component of complementary and alternative therapies, medicinal plants have been accepted worldwide to improve health and prevent or cure diseases because of their rich sources and composition diversity. To understand their function and underlying mechanism, it is critical to analyze the major active substances within these plants. Recent phytochemical and pharmacological studies demonstrated that the extract of *Rhizoma Paridis* contains a large number of chemically active components, including steroid saponins, cholestanol, flavonoids, sterols, and triterpenoids [3–6]. The steroid saponins were shown to be the major effective ingredient exerting antitumor [7], antibacterial [8], antivirus [9], anti-inflammatory [10], hemostasis [11], immune regulation [7], antiliver fibrosis [12], and other biological functions. In particular, the antitumor pharmacological activity of *Rhizoma Paridis* extracts has emerged a major focus of research. Recent several years, polyphylla saponins have been widely reported to inhibit tumor growth in cancer of the breast [13], liver [14], lung [15], ovary [16], and colon [17], as well as other types of malignancy. All these findings bring lights to the discovery of new drugs for cancer. In this review, we summarized the chemical constituents and pharmacological functions of *Rhizoma Paridis* extracts and discussed the chemical structures of Paris saponins (PSs), their related biological activity, and potential mechanism.

2. Chemical Structure of Paris Saponins Derived from *Rhizoma Paridis*

Approximately hundreds of steroid saponins, a family of glycosides with a chemical structure that contains either a steroid or a triterpenoid attached via C-3 and an ether bond to a sugar side chain, have been extracted from *Rhizoma Paridis*, which are considered as the major bioactive ingredients of *Paris* species [18]. According to the configuration of C-25 and the cyclized state of F ring in the

spirostanane structure, steroid saponins are divided into four types (Figure 1): (1) spirostanol, (2) isosprirostanol, (3) furostanol, and (4) pseudospirostanol [3]. Among them, isosprirostanol-type saponins are the main active substance basis of this genus. Moreover, most of the aglycones are diosgenin and pennogenin which generally have hydroxyl substituents at 3β, 7β, and 17β sites and D-glucose, L-rhamnose, and L-arabinose on the sugar groups. The representative active ingredients of isosprirostanol saponins include polyphylin I, polyphylin II, polyphylin V, polyphylin VII, parisyunnanoside G-I, and pariposides A-D. Furthermore, phytochemical investigation shows that pennogenyl saponins mainly exist in *Rhizoma Paridis*, whereas diosgenyl saponins are rich in *Rhizoma Dioscoreae nipponicae* [19]. Furostanol-type saponins, with a β-glucopyranosyl moiety at C-26 of the aglycone, are a class of F-ring cracking compounds. It is generally considered that the furostanol-type saponins are usually the precursor compounds of sprirostanol-type saponins [19]. The aglycones of pseudospirostanol-type saponins are all nautigenin, which can be isolated from the stems and leaves of *P. diyunnanensis* and are also the special components of the upper part of *P. diyunnanensis*. Those nautigenin compounds commonly have hydroxyl substituents at positions 3, 7, 17, and 26. The representative active constituents of pseudospirostanol-type saponins include chonglou SL-9 ~ SL-15 and abutiloside L.

3. Pharmacological Activities of Paris Saponins

As described above, PSs extracted from *Rhizoma Paridis* were capable of exerting antitumor [7], antibacterial [8], antivirus [9], anti-inflammatory [10], hemostasis [11], immune regulation [7], antiliver fibrosis [12], and other biological functions. The possible mechanisms are discussed as follows.

3.1. Antitumor Activity. Accumulating studies have shown various antitumor effects of PS in various tumor models. The underlying mechanisms were associated with inhibiting proliferation, inducing apoptosis, antiangiogenesis, inducing differentiation, blocking metastasis, and reversing multidrug resistance of cancer.

A few studies have investigated the cytotoxicity influence of PS in liver cancer. Pennogenin 3-O-Rha-(1⟶2)-[Glc-(1⟶3)]-Glc (Compound 1), polyphyllin D, pb/formosanin C, and polyphyllin VII isolated from *Rhizoma Paridis* were found to exhibit dose-dependent antitumor effect in HepG2 cells which are involved in a number of signaling pathways including the activation of the Fas and JNK pathways, deregulation of the MAPK pathway, and inhibition of the PI3K/Akt/mTOR pathway. Furthermore, polyphyllin VII was able to cause autophagic cell death and interfere with the metabolism in HepG2 cells [20–22]. Pennogenin 3-O-Rha-(1⟶2)-[Glc-(1⟶3)]-Glc (Compound 1) and polyphyllin VII showed significant antitumor activity in HepG2, MCF-7, and PC-3 cells by activation the mitochondrial apoptotic cascades, inhibition of the CDK1 and PI3K/Akt pathways, and modulation of MAPK pathway [23]. Polyphyllin D was revealed to induce the expression of p21 and cyclin E1 leading to G2/M cell cycle arrest in HepG2 cells [21]. A proteomic study demonstrated that PS was capable of downregulation of dUTPase, hnRNP K, and GMP synthase, whereas upregulation of DNase-γ, nucleoside diphosphate kinase A, and centrin-2 [24]. This study provided a deep insight into the antitumor mechanism of polyphyllin D and pb/formosanin C [24]. PS also inhibits the oxidation of fatty acids pathway and the gluconeogenesis cascade, two core metabolic pathways affecting energy metabolism, to block the tumor growth in the H22 mouse hepatocarcinoma model. Interestingly, the effects in the tumor mice appear to be very different from those in normal mice. In a normal animal group, polyphyllin D, pb/formosanin C, polyphyllin V, polyphyllin VI, polyphyllin VII, Paris saponin H, and gracillin significantly reduced the concentration of lipid and glycerate, but increased glucose level. However, these three compounds in H22 mice with hepatocarcinoma had opposite effects, i.e., increase in lipid and glycerate and decrease in glucose level [25]. In addition, the mixed compounds of polyphyllin D and pb/formosanin C exhibited more robust and powerful antitumor effects than either of them alone in HepG2 and Bel-7402 cells. The combinations significantly strengthened cycle arrest at G1 phase and promoted mitochondria-dependent apoptosis in hepatocarcinoma cell [26].

Polyphyllin D, pb/formosanin C, polyphyllin VI, and polyphyllin VII have potent proapoptotic effect on human ovarian cancer. A recent study showed that pb/formosanin C induced the expression levels of several proapoptotic proteins, including Bax, cytosolic cytochrome c, activated-caspase-3, and activated-caspase-9 in the SKOV3 cellular model [27]. Moreover, formosanin C was shown to suppress NF-κB signaling, resulting in inhibition of the expression of VEGF and angiogenesis [27]. In addition, reduction of ERK1/2 phosphorylation and Bcl-2 expression was observed upon the treatment of SKOV3 cells with formosanin C compound [28]. Polyphyllin VII treatment of ovarian cancer cells (A2780 and SKOV3) was found to trigger the mitochondrial location of dynamin-related protein 1 (DRP1) and inhibit the PP2A/AKT pathway, leading to mitochondrial dysfunction [29]. It was also demonstrated that polyphyllin D promoted apoptosis and hampered migration cells by reducing caspase-9 and Wnt5a levels and elevating c-Jun expression *in vitro* and *in vivo* [16]. In addition to cytotoxic effects, pb/formosanin C markedly compromised angiogenesis by reduction of VEGF and inhibition of VEGFR2 phosphorylation as well as inactivation of proangiogenic kinases Src, FAK, and Akt in xenograft models established with either SKOV3 or HOC7 cell line [30].

A number of studies have also examined the PS in lung cancer models. In DEN-induced mouse lung cancer, polyphyllin D, pb/formosanin C, dioscin, polyphyllin V, polyphyllin VI, polyphyllin VII, Paris saponin H, and gracillin displayed significant inhibitory effects on tumor development and growth, and the possible mechanism was due to reduction of the expression levels of TNF-α, IL-6, COX-2, PGE2, CK8, and CK18 and inactivation of the EGFR/PI3K/Akt, EGFR/Ras/Erk, and NF-κB pathways [15]. In the LA795

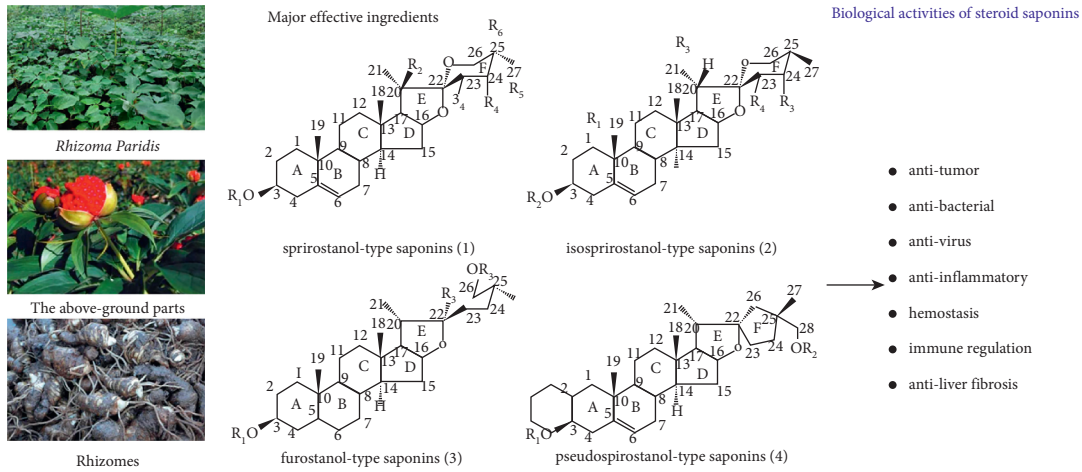

Figure 1: The major effective ingredients of *Rhizoma Paridis* and their biological activities.

cellular and xenograft model, polyphyllin D, pb/formosanin C, dioscin, Paris saponin H, and polyphyllin VII were also shown to have significant antitumor activity by inducing apoptosis and blocking the migration [31]. Moreover, pb/formosanin C was found to restrain the proliferation and induce the apoptosis, autophagy, and paraptosis by activation of the JNK pathway in NCI–H460 and NCI–H520 lung cancer cells [32]. In addition, pb/formosanin C was able to inhibit cell migration, invasion, and metastases by repression of MMP-2 and MMP-9 enzyme activity as well as MMP-1, -2, -3, -9, and -14 expression in LA795 cells and T739 mice with lung adenocarcinoma [33]. Combination of polyphyllin D with hyperthermia (43°C) potently induced apoptosis and G2/M cell cycle arrest via decrease of Bcl-2 expression and increase of Bax level [34]. Notably, polyphyllin D was shown to reverse gefitinib-resistance in non-small cell lung cancer by increasing Bax/Bcl-2 ratio and total caspase-3 level both *in vitro* and *in vivo* [35].

PSs were also evaluated for their antitumor properties in the cervical cancer model. A previous study showed that polyphyllin VII significantly induced apoptosis in HeLa cells, and the underlying mechanism involved in increasing the expression of caspase-3, caspase-9, and Bax and decreasing Bcl-2 level [36].

Except for the abovementioned effects, a recent study using UHPLC-qMS spectrum-effect analysis manifested that polyphyllin VII, dioscin, polyphyllin I, and progenin III were identified as the main antitumor chemical compositions in HT29 and MDA-MB-231 cell lines [37]. In addition, polyphyllin VI was shown to trigger S and G2/M cell cycle arrest and extrinsic apoptosis by activation of the p38/p53 and the caspase 3/8 pathways in tongue squamous carcinoma SCC-15 cells [38]. Furthermore, polyphyllin D, Paris saponin H, and polyphyllin VII also displayed notable antitumor and antimetastasis activity in B16 melanoma cells [39].

Interestingly, Paris saponin H was demonstrated to induce cell cycle arrest at G1 phase and accelerate cell apoptosis by blocking A1 adenosine receptor (ARA1) and ARA3 expression and suppressing the Akt and MAPK cascades in glioma U251 cells [40]. Polyphyllin D also hampered vasculogenic mimicry (VM) formation, an indication of cancer metastasis, through inhibition of the PI3K-Akt-Twist1-VE-cadherin pathway in several HCC cell lines including SMMC7721, PLC, HepG2, Hep3B, and Bel-7402 [41].

According to the abovementioned compounds, the antitumor activities of steroid saponins *in vitro* and *in vivo* are summarized in Tables 1 and 2.

Recently, it has been widely used to study the interaction between drugs and proteins by simulating the docking of small-molecule drug ligands and protein receptor targets [42]. The interaction between ligand and receptor is a process of mutual recognition between molecules through hydrogen bond, electrostatic interaction, and van der Waals force [43]. The binding mode and affinity could be predicted by calculation. In this case, molecular docking is often used as an essential reference for designing targeted drugs and screening effective compounds [44]. Using bioinformatics analysis and molecular docking in hepatitis B virus-related liver cancer, polyphyllin I had been shown to have good affinity with various protein targets, including STAT3, PTP1B, IL2, BCL2L1, FIS1, MFN1, MFN2, and OPA1 [45, 46]. Computational docking also manifested that polyphyllin I has a high affinity with the allosteric drug and metabolite site of AMPK, which induces autophagy and inhibits NSCLC cell growth after activation. This finding was further supported by microscale thermophoresis (MST) and drug affinity responsive targeting stability (DARTS) assays [47].

3.2. Anti-Inflammatory. Polyphyllin D has been show to inhibit LPS/IFN-γ-stimulated inflammatory cytokine secretion from peritoneal elucidated macrophages (PEMs) and attenuate IKKα/β and p65 phosphorylation *in vitro*. Furthermore, polyphyllin I alleviated the bone erosion and synovitis and prevented M1-like macrophage and T-cell infiltration from ankle joint in the collagen-induced arthritis (CIA) mouse model [48]. Polyphyllin D has also been demonstrated to suppress the inflammation by inhibition of the activation of NF-κB pathway in acne. Accordingly, inflammatory cytokines, including interleukin (IL)-6, IL-8, and

Table 1: Efficacy of *Rhizoma Paridis*-derived steroid saponins against cancer *in vitro*.

Compound	Cell line and IC50	Targeting pathways	Ref.
Polyphyllin D	HepG2 (4.01 uM, 24 h)	Fas and JNK pathways; p53-Bax/Bcl-2 and p53-p21-cyclin E/CDK2 pathways; NF-kB and MMP-9	[21]
	Bel-7402 (4.74 uM, 24 h)		[25,26]
	PC-9 (2.69 μg/ml, 48 h)	Bcl-2/Bax	[34]
	PC-9-ZD (2.51 μg/ml, 24 h; 2.07 μg/ml, 48 h; 1.53 μg/ml, 72 h)	Bax/Bcl-2-caspase-3	[35]
	Hela (2.62 μM, 24 h)	Bcl-2/Bax-caspase-3/9	[36]
Pb/formosanin C	HepG2 (13.62 ug/mL, 24 h; 3.29 ug/mL, 48 h)	NMR metabolic pathways	[22]
	Bel-7402 (4.36 uM, 24 h)	p53-Bax/Bcl-2 and p53-p21-cyclin E/CDK2 pathways; NF-kB and MMP-9	[25,26]
	SKOV3 (20.99 uM,24 h; 10.44 uM, 48 h; 8.83 uM, 72 h)	NF-κB-VEGF and NF-κB-Bcl-2/Bcl-xL	[27]
	CaSki (5.7 μM), SiHa (3.7 μM), HEC-1A (2.1 μM), and A549 (4.0 μM)	Bax-caspase-3/9 and ERK/Bcl-2	[28]
	HOC-7 (6.44 uM, 48 h)	VEGF	[30]
	NCI–H460 (2.0 μM, 48 h) and NCI–H520 (1.6 μM, 48 h)	JNK pathway	[32]
Compound 1	HepG2 (2.35 uM, 48 h) MCF-7 (2.59 uM, 48 h) PC-3 (4.76 uM, 48 h)	Mitochondrial apoptotic, CDK1, PI3K/Akt, and MAPK pathways	[23]
Polyphyllin VII	HepG2 (1.77 uM, 48 h), MCF-7 (2.71 uM, 48 h), PC-3 (4.67 uM, 48 h)	Mitochondrial apoptotic, CDK1, PI3K/Akt, and MAPK pathways	[23]
	A2780 (3.0 μM, 24 h) and SKOV3 (3.0 μM, 24 h)	PP2A/AKT/DRP1 signaling axis	[29]
Polyphyllin VI	SCC-15 (25.80 μM, 24 h; 21.22 μM, 48 h; 19.57 μM, 72 h)	p38/p53 and caspase 3/8 pathways	[38]
Paris saponin H	U251 (100 μg/ml, 48 h)	ARA1/ARA3 and Akt/MAPK	[40]

Table 2: Summary of the anticancer activities of steroid saponins *in vivo*.

Animal models	Drug dose	Effects	Ref.
HepG2 xenografts in nude mice	Intraperitoneal injection with 1 or 3 mg/kg compound 1 and polyphyllin VII for 3 weeks	Compound 1 and polyphyllin VII significantly and dose-dependently inhibited the growth of HepG2 xenografts through regulation of MAPK and PI3K/Akt pathways	[20]
SKOV3 xenografts in nude mice	Intraperitoneal injection with 1, 2, and 3 mg/kg polyphyllin VII for 3 weeks	Polyphyllin VII markedly restrained tumor growth meanwhile increased the ratio of BAX/BCL-2 and cleaved caspase-3 expression	[29]
SKOV3 or HOC-7 xenografts in nude mice	Intraperitoneal injection with 1, 2, and 3 mg/kg pb/formosanin C for 4 weeks	Formosanin C remarkably compromised angiogenesis by reduction of VEGF and inhibition of VEGFR2 phosphorylation as well as inactivation of proangiogenic kinases Src, FAK, and Akt	[30]
PC-9-ZD xenografts in nude mice	2, 4, and 8 mg/kg polyphyllin D by gavage administration for 2 weeks	Polyphyllin D treatment robustly decreased 18F-FDG-uptake compared with the control group	[35]
PLC xenografts in nude mice	Intragastrical administration with 10 mg/kg polyphyllin D for 25 days	Polyphyllin D hampered vasculogenic mimicry (VM) formation, an indication of cancer metastasis, through inhibition of the PI3K-Akt-Twist1-VE-cadherin pathway	[41]

tumor necrosis factor (TNF)-α were decreased after Paris I treatment [49]. In addition, polyphyllin G was shown to be able to decrease the synthesis of NO and PGE_2 and reduce the expressions of cytokines (TNF-α, IL-1β, and IL-6) and enzymes (inducible NO synthase, cyclooxygenase-2, and matrix metalloproteinase-9) at both protein and mRNA levels [10].

3.3. Antifibrosis. Liver fibrosis is a pathological change in the structure and function of the liver, resulting from excessive proliferation and abnormal deposition of extracellular matrix (ECM) components. Progression of liver fibrosis may lead to cirrhosis or hepatocellular carcinoma [50]. However, liver fibrosis is reversible and PS had been reported as one of the effective therapeutic agents. It has been demonstrated that polyphyllin G, polyphyllin VI, pb/formosanin C, and polyphyllin D were efficacious in improving CCl_4-induced hepatic fibrosis and cirrhosis in Sprague Dawley rat models. These 4 compounds not only relieved the degeneration and

necrosis of liver tissue but also reduced the degree of fibroplastic proliferation via the suppression of VEGF, ERK1/2, RASAL1, PDGF, and α-SMA [12,51,52]. Furthermore, polyphyllin G was also shown to induce the apoptosis of hypertrophic scar fibroblasts through the modulation of the ERK/JNK pathway [53]. Collectively, these results indicate that PS is a class of potential antifibrosis agents, which deserve future serious investigation.

3.4. Hemostasis. As described above, *Rhizoma Paridis* is a key ingredient of two Chinese hemostasis medicines, "Yunnan Baiyao" and "Gongxuening" [1]. Thus, it has been widely used as a hemostatic medicine in China. A recent study demonstrated that Paris saponin H significantly enhanced thrombin activity, thereby shortening the bleeding time in the mouse tail snipping model, suggesting that Paris saponins could interact with thrombin [54]. Polyphyllin VII was found to act directly on platelets and hemostasis and cause 62% platelet aggregation at 300 ug/ml concentration [11]. Another study showed that polyphyllin VII, polyphyllin II, dioscin, and polyphyllin I all could serve as favorable hemostatic agents [37]. These results indicate that PSs are promising candidates for development of hemostatic drugs.

3.5. Other Effects. Polyphyllin G has been shown to be a potential stimulator of interferon gene (STING) agonist, which initiates macrophages activation and accelerates cytotoxic T lymphocytes infiltration in tumor microenvironment. In the meantime, polyphyllin G treatment robustly increased the expression of PD-L1 on macrophages, suggesting that the combination polyphyllin G with anti-PD1/PD-L1 immunotherapy is beneficial for the cancer treatment [55]. In addition, predominant antibacterial activity against propionibacterium acnes was found in several PSs including chonglouoside SL-2, chonglouoside SL-3, chonglouoside SL-6, trillin, polyphyllin V, diosgenin 3-O-Rha-(1⟶4)-Glc, dioscin, pennogenin 3-O-Rha-(1⟶4)-Rha-(1⟶4)-Glc, polyphyllin VII, and methylprotodioscin [8].

4. Conclusions and Prospect

Active ingredients extracted from medicinal plants and metabolic products are the primary resources for developing medical drugs. The compounds isolated from *Rhizoma Paridis* have significant pharmacological activities, among which steroid saponins are the major active material components. Saponins have antitumor, antifibrosis, anti-inflammatory, hemostasis, and other properties. In particular, polyphyllin D, pb/formosanin C, polyphyllin VI, and polyphyllin VII displayed considerable antitumor activity in both *in vitro* and *in vivo* cancer models. The possible mechanisms include inducing cell apoptosis, hampering angiogenesis, inhibiting cell invasion and metastasis, regulating the tumor microenvironment, and reversing tumor drug resistance. Several signaling pathways were modulated by these compounds, including PI3K/Akt, Ras/Erk, mTOR, PP2A, and NF-κB cascades. Hepatic fibrosis and cirrhosis have been one of the most serious diseases to cure. Polyphyllin D, pb/formosanin C, polyphyllin VI, and polyphyllin VII exhibited dramatic antifibrosis activities against liver fibrosis and cirrhosis.

In summary, the saponins have great potential for anticancer and antifibrosis drug discovery. The chemical constituents and biological activities of isolated sterol saponins need to be further studied.

Abbreviations

PSs: Paris saponins
Fas: Factor-related apoptosis
JNK: c-Jun N-terminal kinase
MAPK: Mitogen-activated protein kinase
PI3K: Phosphoinositide 3-kinase
mTOR: Mammalian target of rapamycin
CDK1: Cyclin-dependent kinase 1
Bax: Bcl-2-associated X
Bcl-2: B-cell leukemia/lymphoma 2
VEGF: Vascular endothelial growth factor
NF-κB: Nuclear factor kappa-B
Caspase-3: Cysteine-aspartic acid specific protease 3
Caspase-9: Cysteine-aspartic acid specific protease 9
ERK1/2: Extracellular-regulated kinase 1/2
DRP1: Dynamin-related protein 1
PP2A: Protein phosphatase 2A
VEGFR2: Vascular endothelial growth factor receptor 2
Src: Sarcoma gene
FAK: Focal adhesion kinase
TNF-α: Tumor necrosis factor alpha
IL-6: Interleukin-6
COX-2: Cyclooxygenase-2
PGE2: Prostaglandin E2
CK8: Cytokeratin 8
CK18: Cytokeratin 18
MMP-2: Matrix metallopeptidase 2
MMP-9: Matrix metallopeptidase 9
ARA1: A1 adenosine receptor
ARA3: A3 adenosine receptor
VM: Vasculogenic mimicry
LPS: Lipopolysaccharides
IFN-γ: Interferon γ
PEMs: Peritoneal elucidated macrophages
IKKα/β: Inhibitor of nuclear factor kappa-B kinase α/β
CIA: Collagen-induced arthritis
NO: Nitric oxide
PGE2: Prostaglandin E2
ECM: Extracellular matrix
RASAL1: Ras GTPase-activating-like protein 1
PDGF: Platelet-derived growth factor
α-SMA: α-Smooth muscle actin
STING: Stimulator of interferon gene
PD-L1: Programmed death ligand 1
PD-1: Programmed cell death protein-1.

Data Availability

All data included in this study are available upon request by contact with the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Shulong Jiang and Wenxue Sun contributed to the conception of the review. Fen Liu wrote the manuscript with support from Shulong Jiang, Luning Li, and Wenxue Sun. Xinchen Tian and Dengtian Zhang collected the related literature. All authors have read and approved the final version of the manuscript.

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