Journal of Applied Pharmaceutical Science Vol. 15(06), pp 001-009, June, 2025
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2025.231323
ISSN 2231-3354

Paeoniflorin and paeonol from *Paeonia* species are promising compounds with anticancer and other pharmacological properties

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ARTICLE HISTORY
Received on: 02/12/2024
Accepted on: 24/03/2025
Available Online: 05/05/2025

Key words:
Chinese peony, moutan peony, *Paeonia lactiflora*, *Paeonia suffruticosa*.

ABSTRACT

In this short review, information on the anticancer properties of paeoniflorin (PF) and paeonol (PN) from *Paeonia* species is collated with reference to the types of cancer, cell lines, effects, and molecular processes. The chemistry, botany, and uses of *Paeonia lactiflora* and *P. suffruticosa*, where respective PF and PN are often isolated, are briefly described. PF is a monoterpene glucoside while PN is a phenolic compound. The chemical structure of PF consists of a glucose moiety, a benzoyl moiety, and a cage-like pinane skeleton. PN has a ketone carbonyl side chain at C1, an OH group at C2, and a methoxy component at C4. PF has effects on eight types of cancer cells of which glioma cells are most affected. Liver cancer cells are most affected by PN. In this overview, the anticancer properties of PF and PN against five types of cancer cells are described. Information entails cancer cell types, cancer cell lines, effects, and molecular mechanisms. Some further studies on the anticancer properties of PF and PN are suggested.

INTRODUCTION

The genus *Paeonia* of the family Paeoniaceae consists of 33 species and 26 sub-species worldwide [1,2]. *Paeonia* is currently divided into three sections. *Moutan* includes 11 species and two sub-species of shrubs that are native to China and countries of East Asia. *Oanepia* includes two species of herbs distributed in America. *Paeonia* includes 22 species and 13 subspecies of herbs occurring from Europe to East Asia [1,2]. Traditional uses of *Paeonia* species have been recorded in plant parts such as the root, root bark, seed, leaf, flower, and whole plant [3]. In traditional Chinese medicine, the roots of *Paeonia* species such as *P. lactiflora*, *P. suffruticosa*, *P. emodi*, and *P. obovata* have anti-inflammatory, analgesic, and sedative properties [3−5]. They have also been used for inflammation, aches, cardiovascular disorders, neurological diseases, hypertension, asthma, hypertension, asthma, urinary diseases, female genital diseases, skin ailments, and trauma.

In *Paeonia* species, a total of 153 monoterpene glycosides have been reported. They are well-known for having cage-like pinane skeletons [3,6]. These cage-like compounds are hollow cage molecules having 3-D structures and a wide range of bioactivities [7]. Other classes of metabolites of *Paeonia* species reported include flavonoids, tannins, stilbenes, triterpenoids, steroids, and phenols [3,8].

Belonging to the family Paeoniaceae, *Paeonia lactiflora* Pall. (syn. *P. albiflora*) or Bai Shao is a stout and erect perennial herb [2,12]. Leaves are alternate and oblique-ovate to lanceolate in shape. Flowers of *P. lactiflora* are one to three per shoot, fragrant, and terminal or axillary. Petals of wild plants are single and white, red or pink in color, and those of cultivated plants are double and of varying colors (Fig. 1a). Flowers bear many stamens having yellow anthers and filaments. Fruits are oblong-ellipsoid follicles, dehisce when ripe, showing the seeds [2,12]. Roots of *P. lactiflora* are cylindrical and pale brown in color (Fig. 1b) without flavor and with a slight bitter taste. *Paeonia suffruticosa* (Andr.) or Mu Dan is a 1−4 m tall shrub. Leaves are ovate, lobed with an acuminate apex. Flowers of *P. suffruticosa* are large and are in colors of white, pink, red, or purple (Fig. 1c). Roots are cylindrical and yellowish–brown (Fig. 1d).

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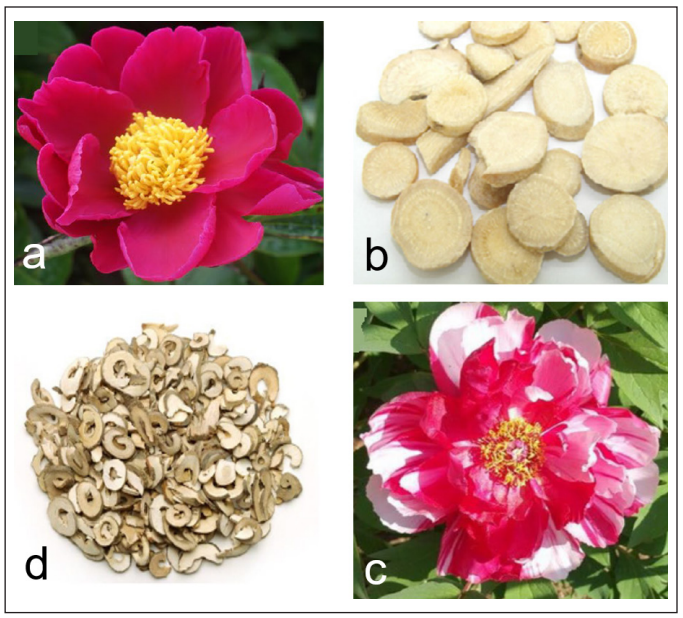

Figure 1. Red flower (a) [9] and *root slices* (b) [10] of *P. lactiflora*, and pink flower (c) [9] and root slices (d) [11] of *P. suffruticosa*.

Species such as *P. lactiflora* and *P. suffruticosa* are rich in chemical constituents responsible for a wide range of bioactivities. The major groups of secondary metabolites are polyphenols such as flavonoids, phenolic acids, terpenoids, polyphenols, stilbenes, tannins, and monoterpene glycosides [13,14]. Paeoniflorin (PF) from the root of *P. lactiflora* and paeonol (PN) from the root bark of *P. suffruticosa* are among the major compounds. From the aqueous ethanol root extract of *P. suffruticosa*, the content of PF and PN has been reported to be 1.18% and 2.12%, respectively [15].

PF AND PN

Chemistry

PF or peonidin is a monoterpene glucoside or an iridoid glycoside having a molecular formula and molecular weight of $C_{23}H_{28}O_{11}$ and 480 g/mol, respectively [16]. It is a β-glucoside of paeoniflorigenin. Important components of PF are a glucose moiety ($C_6H_{12}O_6$), a benzoyl moiety (COC_6H_5), and a pinane skeleton that is cage-like (Fig. 2a). The glucose moiety and the benzoyl moiety are connected to the pinane skeleton at C1 and C8, respectively. The cage-like pinane skeleton has a methyl unit and a hydroxyl unit at C2 and C4, respectively. Without the glucose and benzoyl moieties, PF loses its bioactivity [17]. These compounds are hollow cage molecules having a three-dimensional structure [7]. PF is a dominant monoterpene glucoside with cage-like structures isolated from *P. lactiflora*. Other compounds include albiflorin, benzoyl PF, benzoyl oxypaeoniflorin, PF sulfonate, dibenzoyl PF, and oxypaeoniflorin [7]. PF was first isolated from the root of *P. lactiflora* by Shibata and Nakahara in 1963 [18] and its chemical structure was rectified by Kaneda *et al.* only in 1972 [19].

PN or 2'-hydroxy-4'-methoxyacetophenone is a phenolic compound having a molecular formula of $C_9H_{10}O_3$ and a molecular weight of 166 g/mol [20]. The 4-methoxy component of PN is a functional group associated with anticancer activity while the ketone carbonyl side chain is a bioactive functional group at C1 (Fig. 2b) [21]. There is an OH group at C2. PN was first isolated from the root bark of *Paeonia moutan* by Harada and Yamashita in 1969 [22].

Anticancer properties

The anticancer properties of PF based on the types of cancer, cell lines, effects, molecular processes, and references are shown in Table 1. The five most reported types of cancer have been selected for review. Glioma (9) is the most reported cancer type followed by gastric (6), liver (6), breast (5), and colorectal (5). In the literature, there are three reviews on the anticancer properties of PF. They include the anticancer effects and underlying molecular mechanisms of PF [23], the diverse anticancer activities of PF [24], and the multi-faceted activities of PF in the treatment of tumors [25]. Other cancer types affected by PF are bladder, cervical, endometrial, leukemia, lung, myeloma, nasopharyngeal, osteosarcoma, ovarian, and renal [24,25].

The anticancer properties of PN with information on cancer types, cell lines, effects, molecular processes, and references are shown in Table 2. Liver (8) and lung (7) are the most reported cancer type followed by colorectal (5), gastric (5), and ovarian (4). The mechanisms and clinical prospects of PN for cancer therapy [21], and the effects and mechanisms of PN on anti-tumor and cancer therapy [57] are two recent reviews on the anticancer properties of PN. Other cancer types affected by PN are bladder, breast, cervical, esophageal, melanoma, osteosarcoma, ovarian, pancreatic, and renal [21,57].

Other pharmacological properties

Besides anticancer properties, PF possesses anti-inflammatory, analgesic, immuno-modulatory, neuroprotective, anti-depression, anti-platelet aggregation, reducing dyslipidemia, and vascular dilatory effects [88]. The prevention and treatment of neurodegenerative diseases are among its neuroprotective effects [89]. Beneficial effects of PF toward the nervous system include subarachnoid hemorrhage, on pathogenesis related to cognition, learning, and memory impairment, on Parkinson's disease, on post-traumatic stress, on neuro-inflammatory pain, on epilepsy, on depression, and on glioblastoma [90].

In the review of the neuroprotective functions and anti-depressive properties of PF [91], the following aspects included: (a) upregulation of the levels of neurotransmitters, (b) inhibition of the hypothalamic-pituitary-adrenal axis, (c) promotion of neuroprotection, (d) modulation of hippocampus neurogenesis, (e) up-regulation of brain-derived neurotrophic factor level, (f) inhibition of inflammatory reaction, and (g) down-regulation of nitric oxide level.

Besides anticancer properties, PN is endowed with anti-inflammatory effects against osteoarthritis and rheumatoid arthritis, periodontitis, skin inflammation, osteoporosis, organ injury, and colitis [92]. It also possesses neuroprotective activities against diabetic encephalopathy, cerebral ischemic

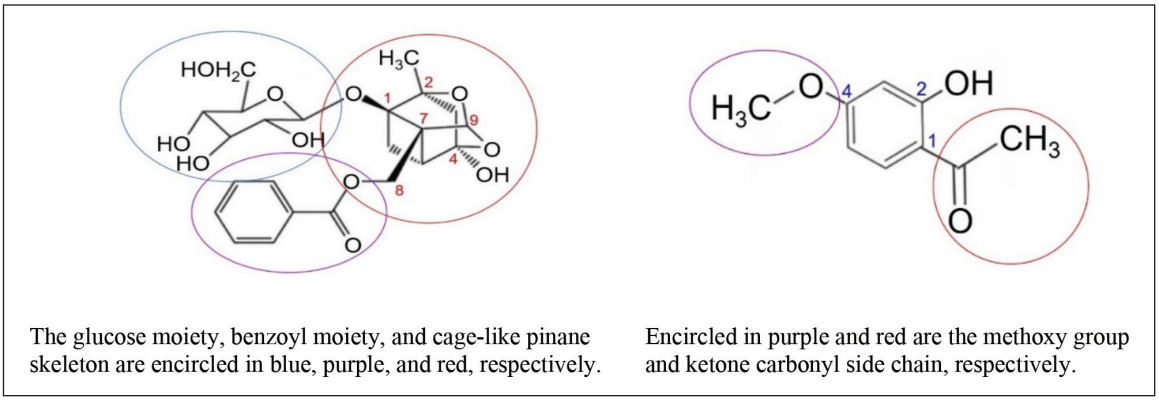

Figure 2. Chemical structures of PF (left) and PN (right).

Table 1. Anticancer properties of PF.

No.	Cancer type, cell line, effect, and molecular mechanism	Reference
	Glioma	
1	U87: PF inhibited proliferation and induced apoptosis of cancer cells via miRNA-16 up-regulation and MMP-9 down-regulation.	[26]
2	U87 & U251: Anticancer effects of PF involved degradation of STAT3 *via* the ubiquitin–proteasome pathway.	[27]
3	U87 & U251: PF inhibited proliferation, migration, and invasion of cancer cells; induced G2/M arrest and apoptosis; and exerted anti-tumor effects by inhibiting Skp2 expression.	[28]
4	U87, U251, & T98G: PF inhibited the migration and invasion of cancer cells via the suppression of the TGFβ pathway and inhibition of EMT.	[29]
5	U87 & U251: PF decreased tumor growth of cancer cells *via* targeting TLR4 and modulating the TLR4/Triad3A pathway, resulting in TLR4 protein degradation and cell progression inhibition.	[30]
6	T98G & U251: PF inhibited HGF-mediated migration, invasion, and suppressed rearrangement of actin cytoskeleton in cancer cells *via* the inhibition of c-Met/RhoA/ROCK signaling pathway.	[31]
7	U87 & U251: PF exerted anti-proliferative effects on cancer cells by inhibiting TSPO and neurosteroids. Inhibition was also demonstrated using a xenograft mouse model.	[32]
8	U87 & U251: PF inhibited EMT and angiogenesis of cancer cells *via* induction of autophagy activation and degradation of c-Met.	[33]
9	U87 & U251: PF inhibited tumor growth of cancer cells by inducing ferroptosis by up-regulating NEDD4L and by repressing Nrl2, GPX4, and STAT3.	[34]
	Gastric	
1	SGC7901: PF enhanced 5-fluorouracil-induced apoptosis of cancer cells by suppressing NF-kB and modulating IκBα.	[35]
2	SGC7901: Cancer cell inhibition by PF involved NF-κB activation, and down-regulation of MDR1, Bcl-X and Bcl-2.	[36]
3	MGC-803: PF inhibited cancer cell proliferation via the up-regulation of miRNA-124, and suppression of PI3K/Akt and STAT3 signaling.	[37]
4	GCAF: PF inhibited of cancer cells by suppressing the production and secretion of IL-6, by up-regulating microRNA-149 expression, and preventing cells from activating IL-6-STAT3-MMP signaling.	[38]
5	MGC803 & SGC7901: PF suppressed cancer cell growth, enhanced apoptosis, and reduced cell invasion via down-regulation of TAZ.	[39]
6	SNU638 & AGS: PF induced ER stress-mediated apoptotic cancer cell death *via* generating Nox4-derived ROS under radiation.	[40]
	Liver	
1	HepG2 & SMMC-7721: PF induced apoptosis of cancer cells by down-regulating EP_2 expression, increasing Bax-to-Bcl-2 ratio, and activating caspase-3.	[41]
2	HepG2 & Bel-7402: PF inhibited the growth, and significantly reduced invasion, metastasis, and adhesion of cancer cells.	[42]
3	HepG2: PF inhibited the viability and invasion of cancer cells *via* suppressing Skp2, a protein that contributes to carcinogenesis.	[43]
4	HepG2 & SMMC-7721: PF inhibited cancer cell growth by blocking the Wnt/β-catenin pathway and down-regulating 5-HT1D expression.	[44]
5	HepG2 & H22: PF inhibited cancer cell growth *in vitro* and *in vivo* by suppressing PD-L1 expression *via* the SOCS3/STAT3 signaling pathway.	[45]
6	H22 & Huh-7: PF increased anticancer efficacy of sorafenib in mice *via* suppression of the NF-κB/PD-L1 pathway. In vitro studies confirmed reduction of PD-L1 expression by inhibiting NF-κB expression.	[46]
	Breast	

Continued

No.	Cancer type, cell line, effect, and molecular mechanism	Reference
1	MCF-7 & MDA-MB-231: PF inhibited cancer cell proliferation and invasion by suppressing the Notch-1 signaling pathway.	[47]
2	MCF-7 & MDA-MB-231: PF suppressed cancer cell migration and invasion by preventing hypoxia-induced EMT in cells and by inhibiting HIF-1α expression via modulation of the PI3K/Akt signaling pathway.	[48]
3	MCF-7: PF inhibited the proliferation and invasion of cancer cells by reducing Notch-1 and HES-1 mRNA expression levels.	[49]
4	MCF-7 & T47D: In the presence of PF, cancer cells were more sensitive to tamoxifen involving the down-regulation of miRNA-15b and the FOXO1/CCND1/β-catenin pathway.	[50]
5	MCF-7 & T47D: PF enhanced the susceptibility of cancer cells to tamoxifen by suppressing STAT3 and promoting SIRT4 expression.	[51]
	Colorectal	
1	HT-29: PF inhibited the growth, and induced cell cycle arrest and apoptosis of cancer cells by modulating cell cycle regulators.	[52]
2	HCT116: PF inhibited cancer cell growth and induced cell cycle arrest through inhibition of FOXM1 expression.	[53]
3	HCT116 & SW480: PF inhibited cancer cell migration and invasion, reversed the EMT process by inhibiting the expression of HDAC2 and Vimentin, followed by increasing E-cadherin expression.	[54]
4	CAC: PF displayed therapeutic effect on CAC mice by inhibiting TLR4/NF-κB mediated inflammatory response and EGFL7 expression.	[55]
5	HCT116 & SW480: PF exerted antitumor effects on cancer cells by mediating cell stemness and by deactivating Wnt/β-catenin signaling *via* inhibition of the miR-3194-5p/CTNNBIP1 pathway.	[56]

Akt = protein kinase B; Bax = bcl-2-like protein 4; Bcl-2 = B-cell lymphoma 2; Bcl-X = B-cell lymphoma extra-large; CAC = colitis-associated cancer; CCND1 = cyclin D1; CTNNBIP1 = catenin beta-interacting protein 1; E-cadherin = epithelia-cadherin; EGFL7 = EGF-like protein 7; EMT = epithelial mesenchymal transition; EP_2 = prostaglandin E2 receptor 2; ER = endoplasmic reticulum; FOXM1 = forkhead box protein M1; FOXO1 = forkhead box protein O1; GCAF = gastric cancer associated fibroblast; GPX4 = glutathione peroxidase 4; HDAC2 = histone deacetylase 2; HES-1 = hairy and enhancer of split-1; HT1D = 5-hydroxytryptamine (serotonin) receptor 1D; IL6 = interleukin 6; IκBα = inhibitor of nuclear factor kappa B; MDR1 = multi-drug resistance 1; MMP = matrix metalloproteinase; NEDD4L = neural precursor cell expressed developmentally down-regulated protein 4; NF-κB = nuclear factor kappa B; Notch 1 = neurogenic locus notch homolog protein 1; Nox4 = NADPH oxidase 4; PD-L1 = programmed death ligand 1; PI3K = phosphatidylinositol 3-kinase; RNA = ribonucleic acid; ROCK = downstream RhoA/Rho associated kinase; ROS = reactive oxygen species; SIRT4 = sirtuin 4; Skp2 = S-phase kinase-associated protein; STAT3 = signal transducer and activator of transcription 3; TAZ = transcriptional coactivator with PDZ-binding motif; TGFβ = transforming growth factor β; TLR4 = toll-like receptor 4; TSPO = translocator protein 18 KDa.

Table 2. Anticancer properties of PN.

No.	Cancer type, cell line, effect, and molecular mechanism	Reference
	Liver	
1	HepG2 & SMMC-7721: PN exerted synergistic effects on growth inhibition and apoptosis of cancer cells when combined with cisplatin. The combined effects may involve cell cycle arrest and up-regulation of Bcl-2 expression.	[58]
2	HepG2: PN displayed significant growth inhibitory effect on cancer cells via apoptosis and cell cycle arrest. Cytotoxicity of cells was enhanced when used with chemotherapeutic agents such as cisplatin, doxorubicin, and 5-fluorouracil.	[59]
3	HepA: PN displayed anti-tumor effects on hepatoma mice via induction of apoptosis, decrease in Bcl-2/Bax ratio, and stimulation of TNF-α and IL-2 production.	[60]
4	BEL-7404 & SMMC-7721: PN inhibited cancer cell growth by up-regulation of PTEN, and down-regulation of Akt.	[61]
5	HCC: PN effectively decreased oxidative stress and improved immunity in DEN-induced HCC rats.	[62]
6	Huh7: PN significantly enhanced apoptosis of cancer cells by down-regulation of NF-κB and p-API-5, and inhibition of the NF-κB signaling pathway as possible mechanisms.	[63]
7	Hep3B & Huh7: PN inhibited proliferation, migration and invasion, and induced apoptosis of cancer cells by reversing the suppressing the miR-21-5p/KLF6 expression. PN also suppressed tumor growth in xenograft mice.	[64]
8	HepG2 & SMMC-7721: PN exerted anti-tumor effects on cancer cells by inhibiting survivin via the COX-2/PGE2 pathway.	[65]
	Lung	
1	A549 & LLC: PN inhibited proliferation and enhanced radiation-induced apoptosis of cancer cells by inhibiting the PI3K/Akt pathway, and by down-regulating COX-2 and survivin expression.	[66]
2	SBC-5: PN exhibited anti-proliferation, and inhibited cell migration and invasion of cancer cells. Cells treated with PN also showed decreased ability of bone adhesion and metastasis.	[67]
3	A549: A Schiff base derivative of PN possessing a 1,2,3-triazole moiety exhibited good *in vitro* cancer cell cytotoxicity with IC_{50} value of 45.0 μM.	[68]
4	A549: PN inhibited migration and invasion of cancer cells by stimulating IL-6 or TNF-α, and by reducing inflammatory cytokines. Anti-tumor effect was also demonstrated in xenograft nude mice.	[69]
5	H1975 & BGC823: PN enhanced TRAIL-induced cancer cell apoptosis by up-regulating DR-4 and -5 *via* the ROS-JNK/ERK-CHOP signaling pathway.	[70]
6	A549, HCC827, H522, & H1299: PN inhibited cancer cell viability, metastasis, and EMT *via* the miR-126-5p/ZEB2 axis.	[71]

Continued

No.	Cancer type, cell line, effect, and molecular mechanism	Reference
7	A549: PN inhibited cancer cell proliferation by regulating cell glycolytic reprogramming *via* m6A modification of ACADM.	[72]
8	A549 & H2405: PN exerted anticancer activity in cancer cells by inhibiting the Akt pathway, and up-regulating the expression of tumor suppressors TNNC1 and SCARA5.	[73]
	Colorectal	
1	HT-29: PN inhibited the proliferation of cancer cells by inducing apoptosis, down-regulating the expression of COX-2, and up-regulating the level of p27.	[74]
2	LoVo: The antitumor effect of PN involved apoptosis of cancer cells *via* an increased intracellular Ca^{2+} concentration and up-regulation of RUNX3 expression.	[75]
3	HCT116, SW620, & LoVo: PN exerted an anticancer cell effect *via* inhibition of PGE2 synthesis and COX-2 expression. PN also significantly inhibited tumor growth in xenograft mice.	[76]
4	LoVo: PN suppressed invasion, migration, and EMT of cancer cells through inhibition of COX-2 expression and PGE2 synthesis.	[77]
5	HCT116: PN exerted anti-tumor activity on cells by inducing anti-proliferative effect, G0/G1 phase arrest and cell apoptosis *via* inhibiting the Wnt/β-catenin signaling pathway.	[78]
	Gastric	
1	SGC-790 & MFC: PN inhibited proliferation and induced apoptosis of cancer cells by reducing the expression of Bcl-2 and increasing the expression of Bax.	[79]
2	SGC-7901: PN inhibited growth of cancer cells by inducing apoptosis and suppressing the expression of HULC.	[80]
3	SGC-7901: PN inhibited proliferation and induced cell apoptosis of cancer cells by down-regulating ERBB2 and inhibiting the NF-κB signaling pathway.	[81]
4	BGC-823 & MGC-803: PN inhibited the malignancy of apatinib-resistant cancer cells *via* the LINC00665/miR-665/MAPK1 pathway.	[82]
5	BGC-823: PN inhibited the growth, migration, and invasion of cancer cells by down-regulating MMP-2 and -9.	[83]
	Ovarian	
1	SKOV3: PN displayed cytotoxicity and induced apoptosis of cancer cells *via* activation of caspase-3 and down-regulation of survivin.	[84]
2	A2780: PN induced apoptosis of cancer cells by activating caspase-3/-9 *via* the AKT/GSK-3β signaling pathway.	[85]
3	SKOV3 & OVCAR3: PN enhanced the sensitivity of cancer cells to radiotherapy-induced apoptosis by down-regulation of the PI3K/Akt/PTEN pathway and inhibition of VEGF.	[86]
4	A2780 & SKOV3: PN promoted anti-proliferative activity and apoptosis of cancer cells, and induced cytoprotective autophagy by blocking the Akt/mTOR pathway.	[87]

ACADM = acyl-CoA dehydrogenase; Akt = protein kinase B; Bax = bcl-like protein 4; Bcl-2 = B-cell lymphoma 2; Ca^{2+} = calcium; CHOP = C/EBP homologous protein; COX-2 = cyclooxygenase 2; DEN = diethylnitrosamine; DR = death receptor; EMT = epithelial-to-mesenchymal transition; ERBB2 = epidermal growth factor receptor 2; ERK = extracellular signal-regulated kinase; GSK-3β = glycogen synthase kinase 3 beta; HCC = hepatocellular carcinoma; HULC = highly up-regulated in liver *cancer;* IL = interleukin; JNK = c-Jun NH2-terminal kinase; KLF6 = kruppel-like factor 6; LINC00665 = long intergenic non-protein coding RNA 665; LLC: Lewis lung carcinoma; m6A = N6-methyladenosine; MAPK = mitogen-activated protein kinase 1; MFC = mouse fore-stomach carcinoma; miR = microRNA; MMP = matrix metalloproteinase; mTOR = mammalian target of rapamycin; NF-κB = nuclear factor kappa B; p-API-5 = protein apoptosis inhibitor-5; PGE2 = prostaglandin E2; PI3K = phosphatidylinositol 3-kinase; PTEN = phosphatase and tensin homolog; ROS = reactive oxygen species; RUNX3 = runt-related transcription factor 3; SCARA5 = scavenger receptor class A member 5; TNF = tumor necrosis factor; TNNC1 = troponin C type 1; TRAIL = TNF-related apoptosis-inducing ligand; VEGF = vascular endothelial growth factor; ZEB2 = zinc finger E-box binding homeobox 2.

injury, aging, depression, and neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. It protects the cardiovascular system via suppression of angiogenesis and metastasis, treatment of myocardial infarction, and protection of vascular endothelial dysfunction [92]. Against atherosclerotic and cardiovascular disorders, PN confers protection against inflammation, lipid metabolism, autophagy, mitochondria damage, platelet aggregation, and endoplasmic reticulum stress.

PF and PN possess the following pharmacological properties such as anti-allergic effect in mice [93], attenuation of myelosuppression in mice [94], attenuation of neuropathic pain in mice [95], and protection of myocardial ischemia/reperfusion injury in rats [96]. In traditional Chinese medicine, PF and PN possess various pharmacological properties. They are used to treat diabetic nephropathy [97], dysmenorrhea [98], and endometriosis [99].

CONCLUSION

In many Chinese herbal medicines, PF and PN are the main active ingredients possessing a wide spectrum of bioactivities. They include significant and potent *in vitro* and *in vivo* anticancer effects. Notably, PF is effective against glioma, and against various types of cancer cells such as those of gastric, liver, breast, and colorectal. PN has anticancer properties against liver, colorectal, gastric, lung, and ovarian cancer cells. In clinical practice, the synergic use of PF and PN as combination drug therapy has been widely reported. PF and PN have reinforced the effectiveness of chemotherapeutic agents such as cisplatin, erlotinib, doxorubicin, and 5-fluorouracil. Similarly, their complementary use with other anticancer plant species has also been tested. In combination with PF and PN, their anticancer effects are more effective than chemotherapeutic agents when used alone. Toxicity is an important issue with regard to PF and PN. It is worthwhile to

synthesize derivatives that are more effective, selective, and yield less toxic side effects in cancer therapy. Studies on the pharmacokinetic profiles of PF and PN, involving absorption, distribution, metabolism, and excretion, would generate useful information. Currently, research on the effects of PF and PN on tumor prevention and therapy is mainly based on *in vitro* experiments and lacks clinical evidence to support research findings. Another suggested field of research is to synthesize and evaluate derivatives that are more potent in anticancer activities. Finally, properly designed and randomized controlled clinical trials are necessary to assess the safety and efficacy of PF and PN in tumor patients before they can be developed into commercial cancer drugs.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

FINANCIAL SUPPORT

There is no funding to report.

CONFLICTS OF INTEREST

The author reports no financial or any other conflicts of interest in this paper.

ETHICAL APPROVALS

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

DATA AVAILABILITY

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

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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How to cite this article:
Chan EWC. Paeoniflorin and paeonol from *Paeonia* species are promising compounds with anticancer and other pharmacological properties. J Appl Pharm Sci. 2025;15(06):001–009. DOI: 10.7324/JAPS.2025.231323