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Review Article

Integrative Review on the Chemical Components, Pharmacology and Toxicology of *Psoralea Corylifolia* L. (Bu Gu Zhi)

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Abstract

Psoralea corylifolia L. (PCL) is widely used in clinical practice and is commonly used in the treatment of osteoporosis, tumors, and dermatosis. However, in recent years, adverse reactions of PCL and its related preparations have been frequently reported, and there are even case reports of acute liver injury caused by taking PCL alone, which seriously affects the safe and rational clinical application of PCL. In this paper, the main chemical components, pharmacology, and toxicology of PCL are analyzed and summarized, and the effect-toxicity relationship of PCL and its main active components are sorted out and compared. On this basis, the active components of PCL for treating osteoporosis and causing hepatotoxicity are further systematically compared and summarized, to clarify its effect-toxicity relationship, reduce the toxicity risk of PCL, increase the benefit/risk ratio and provide evidence for the safe clinical application of PCL.

Introduction

Psoralea L. is a large genus of herbs comprising about 130 species that are mainly distributed throughout tropical and subtropical regions.[1] *Psoralea* means "affected with the itch or with leprosy" which is derived from the Greek term *psoraleos*.[2] *Psoralea corylifolia* L. (PCL) is one of the species in this genus *Psoralea*. The entire plant of PCL, especially its seed or fruit, has significant medicinal properties for the treatment of many diseases. Bu Gu Zhi is the dried fruit of the legume PCL. It is a commonly used Chinese herbal medicine in clinical practice and is mostly used for the treatment of osteoporosis, tumors, dermatosis, *etc.*, and is particularly effective in the treatment of osteoporosis. However, in recent years, reports of adverse events and reactions of PCL-related preparations have gradually increased, and more clinical cases of liver and skin injuries caused by a single PCL have been reported, which seriously affects the safe clinical application of PCL. To sum up, this paper makes an integrative analysis of the pharmacology and toxicology of PCL, so as to provide theoretical support for the safe clinical application of PCL and its preparations.

Keywords: *Psoralea corylifolia* L.; Toxicity-effect integration; Pharmacology; Toxicology; Chemical components.

Abbreviations: BMD, bone mineral density; cAMP, Cyclic adenosine monophosphate; PCL, *Psoralea corylifolia* L.

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Main chemical components of PCL

The chemical components of PCL are mainly coumarins and flavonoids; coumarins contained include furanocoumarins (Fig. 1a) and coumestrol (Fig. 1b), and flavonoids contained include flavonols (Fig. 1c), dihydroflavones (Fig. 1d), isoflavonoids (Fig. 2) and chalcones (Fig. 3a). In addition, the chemical components of PCL also include monoterpene phenols (Fig. 3b) and benzofurans (Fig. 3c).[3–5] Other components in PCL mainly include trace elements such as potassium, manganese, calcium and selenium, lipids such as monoglyceride, diglyceride, triglyceride and free fatty acid, glycosides such as daucosterol, methylglycoside and PCL polysaccharide, as well as fatty acids in volatile oils and non-volatile terpenoid oils such as palmitic acid, oleic acid, linoleic acid and stearic acid.

Pharmacology of PCL

Anti-osteoporosis effect

PCL is currently one of the most important herbs for the clini-

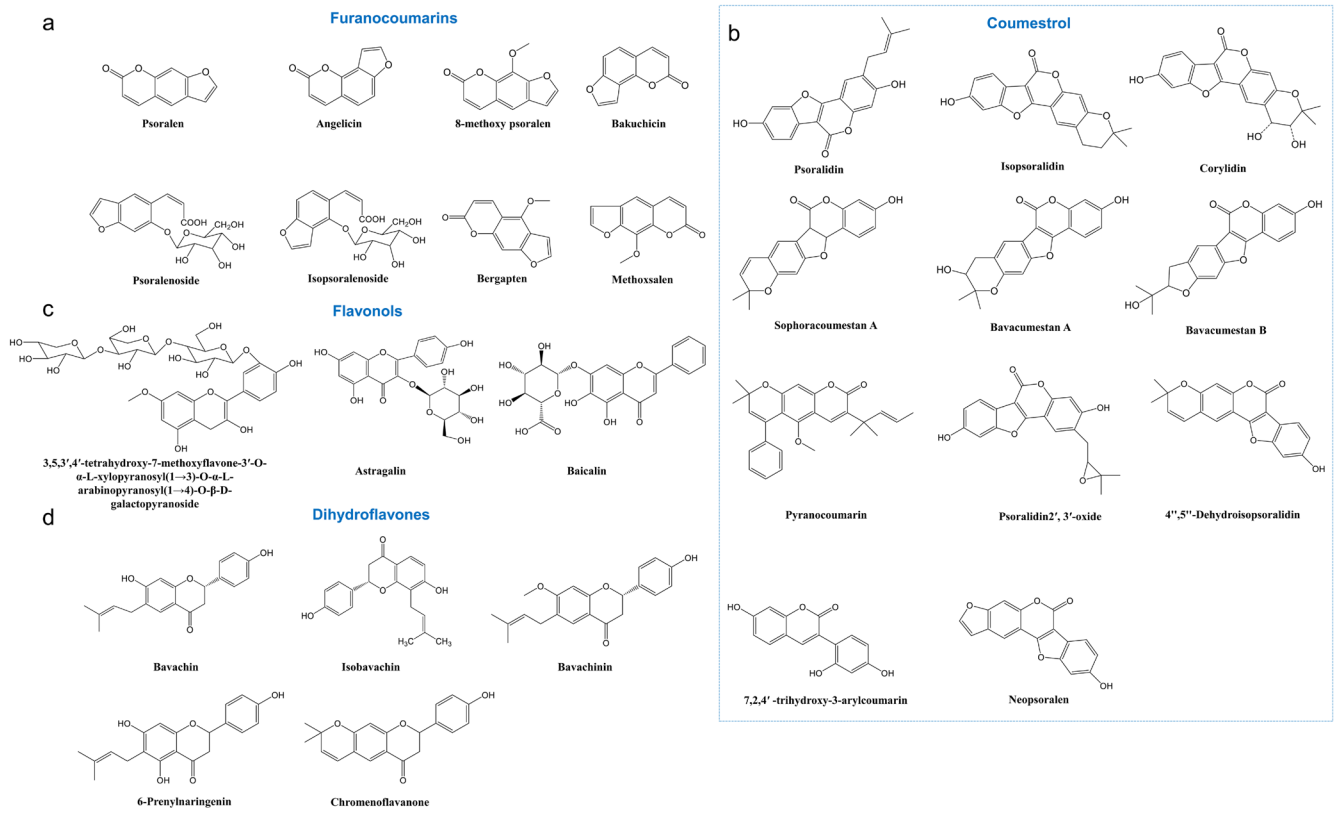

Fig. 1. Structures of important compounds isolated from PCL. Chemical structures of furanocoumarins (a), coumestrol (b), flavonols (c), dihydroflavones (d) isolated from PCL. PCL, *Psoralea corylifolia* L.

cal treatment of osteoporosis within traditional Chinese medicine. Multiple research groups have carried out related studies on the anti-osteoporosis effect of PCL, and it has been found that different concentrations of aqueous extract of PCL can promote an increase in the mRNA ratio of osteoblasts osteoclastogenesis inhibitory factor and Receptor Activator of Nuclear Factor-κ B ligand. In particular, 1.0 mg/mL and 10 mg/mL of aqueous PCL extract have a significant regulatory effect on rat osteoblast models.[6] Coryfolin promotes rat bone marrow-derived mesenchymal stem cells to differentiate into osteoblasts by regulating the Cyclic adenosine monophosphate (cAMP) /protein kinase A/cAMP response element-binding protein signaling pathway to upregulate the mRNA and expression of protein kinase A and cAMP response element-binding protein.[7] Psoralen can increase the gene expression level of specific markers (*e.g.*, osteoblasts, glucose transporter 3, Runx2, and type I collagen [Col-I]), enhance ALP activity, activate bone morphogenetic protein signaling and promote osteoblast differentiation.[8–11] In addition to its effects on osteoblasts, psoralen can reduce osteoclast differentiation by inhibiting the activation of the activator protein-1 and protein kinase B pathways.[12] Moreover, psoralen can also reduce the serum level of carboxy-terminal telopeptide of type I collagen in patients with osteoporosis, thereby significantly inhibiting bone resorption, reducing bone turnover rate, and further relieving osteoporosis symptoms.[13] Isopsoralen can promote osteogenic differentiation of bone marrow-derived mesenchymal stem cells.[14] Besides, psoralidin has a significant anti-postmenopausal osteoporosis effect, and significantly improves the bone mineral density (BMD) of the lumbar vertebrae and femur, femoral bending strength, and trabecular bone area rate in ovariectomized rats.[15] Bakuchiol can promote bone development and calcification in normal zebrafish and shows a concentration-dependent correlation with BMD increase in a zebrafish osteoporosis model.[16] Furthermore, it has also been found in related studies that Xianlinggubao Capsule, a Chinese patent medicine preparation containing PCL, can increase the BMD of lumbar vertebrae and femur and serum calcium and phosphorus levels in rats, so as to achieve anti-osteoporosis effects.[17] In summary, PCL and its active components have a good anti-osteoporosis effect (Table 1).[6–17]

Dermatosis treatment effect

PCL and its active components can be used for the treatment of dermatosis, such as vitiligo and Sezary's syndrome, and can also be combined with ultraviolet A to treat psoriasis (PUVA therapy).[18] 8-methoxypsoralen (methoxsalen), the active component of PCL, has a good clinical effect in the treatment of vitiligo and psoriasis.[19,20] Corylin can effectively antagonize the apoptosis of skin cells, and 10^{-5} mol/L corylin can significantly increase the proliferation rate of ultraviolet radiation b (UVB)-induced HaCaT cells, reduce the apoptosis rate, and significantly increase the activity of antioxidant enzymes.[21] Topical PCL tincture combined with NB-UVB is effective in the treatment of psoriasis vulgaris.[22] Isopsoralen has also been found to be a potential candidate drug for PUVA therapy.[23] Psoralen can reduce the survival rate of melanocytes to some extent but cannot significantly alter the activity of keratinocytes. In addition, ointments made using pharmaceutical powder containing PCL are effective for vitiligo when applied alone.[24] In summary, PCL and its active components have a certain

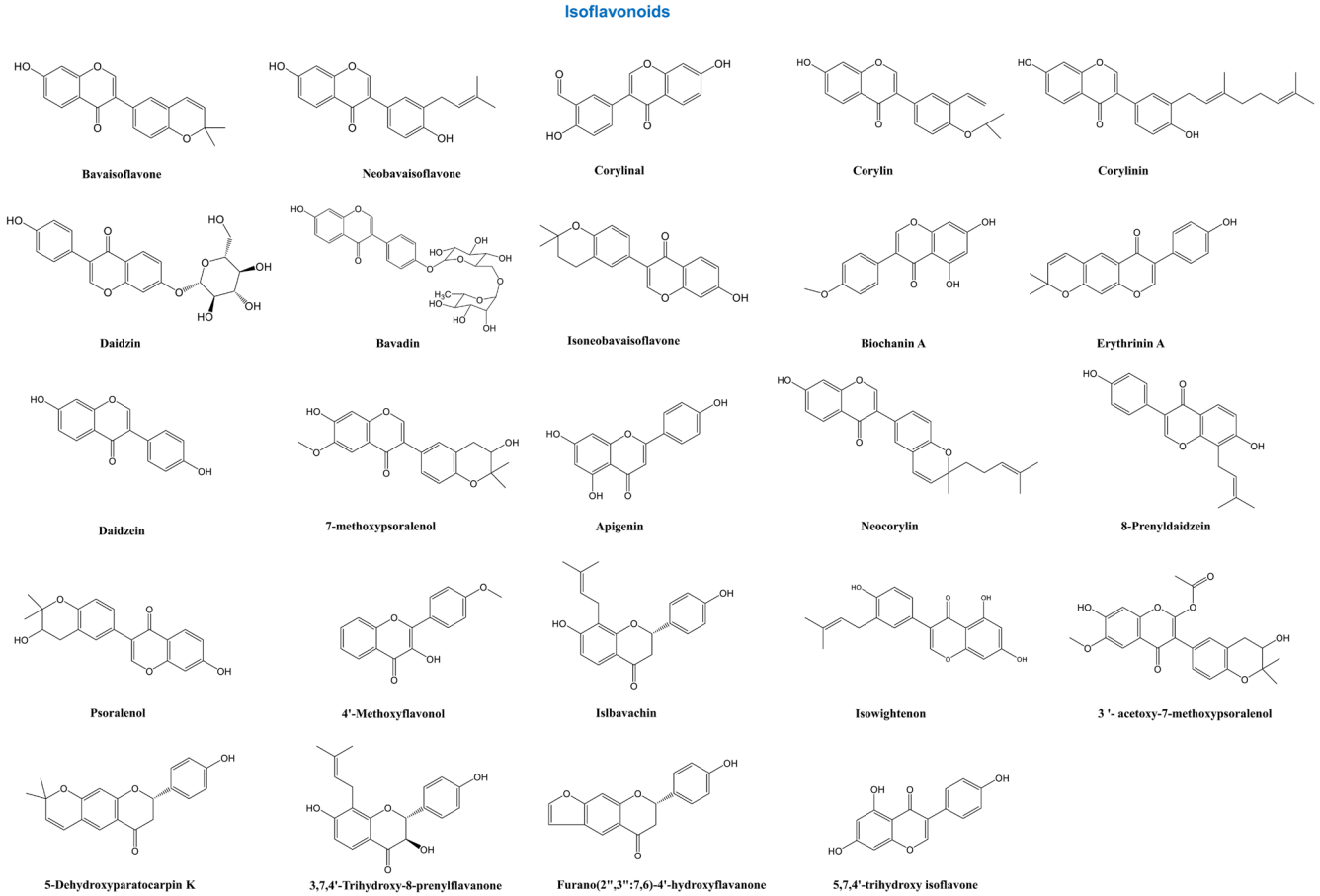

Fig. 2. Chemical structures of isoflavonoids isolated from *Psoralea corylifolia* L.

therapeutic effect for refractory dermatosis such as vitiligo and psoriasis (Table 2).[19–24]

Antidepressant effect

Depression is a chronic mental illness with a high disease burden, high disability rate, and high suicide rate. In recent years, multiple studies have shown that PCL also has a good effect in anti-depression, and it has been found in forced swimming and tail suspension mice models that coryfolin and psoralidin can significantly increase the content of 5-HT in the hippocampus and serum of mice and reduce the immobility time of mice in a behavioral limitation model (forced swimming and tail suspension).[25] Total furanocoumarins in PCL can achieve an antidepressant effect by regulating monoamine oxidase, the hypothalamic–pituitary–adrenal axis, and oxidative systems.[26] In addition, bakuchicin can reduce the fixation time of behavioral despair mice and the contents of plasma epinephrine and norepinephrine in chronically stressed mice, showing good antidepressant and anti-stress effects.[27]

Antitumor effects

In vitro and *in vivo* studies have shown that PCL and its active components also have good efficacy in antitumor treatment, such as the treatment of breast cancer, liver cancer, and skin cancer. Psoralen can inhibit the proliferation of HepG2 cells, or upregulate the expression of BCL2-associated X protein (Bax) and CCAAT-enhancer-binding protein homologous protein by activating Caspase-3/8, thereby inducing apoptosis of HepG2 cells.[28,29] It has also been stated in studies that psoralen can reverse multidrug resistance of the drug-resistant cell line MCF-7 in human breast cancer.[30] One research study indicates that isobavachalcone could attenuate the growth of pancreatic cancer via activating immune activity and inducing cell apoptosis.[31] Besides, isopsoralen can inhibit the growth of osteosarcoma xenografts in nude mice and induce apoptosis or necrosis in tumor cells without significant toxicity.[32] Bakuchicin can upregulate the expression of tumor necrosis factor-related apoptosis-inducing ligand receptors, death receptor 4 and death receptor 5, and thus significantly inhibit the proliferation of HepG2 cells.[33] Some reports indicate that bakuchiol has the potential for the treatment of many cancers, such as breast cancer, skin cancer, or gastric cancer. Bakuchiol could suppress the human gastric carcinoma cell lines through the phosphoinositide 3-kinase/protein kinase B and mitogen-activated protein kinase signaling pathways.[34] In addition, the antitumor effects of bakuchiol on SGC-7901 were also mediated by the inhibits cell proliferation and inducing apoptosis and cell cycle arrest.[35]

Cardiovascular relaxation effect

PCL and its active components also have certain protective effects on the cardiovascular system. Psoralen can reduce Tumor Necrosis Factor-α-induced tissue factor release from human umbilical vein endothelial cells and reduce the risk of thrombosis.[36] In physi-

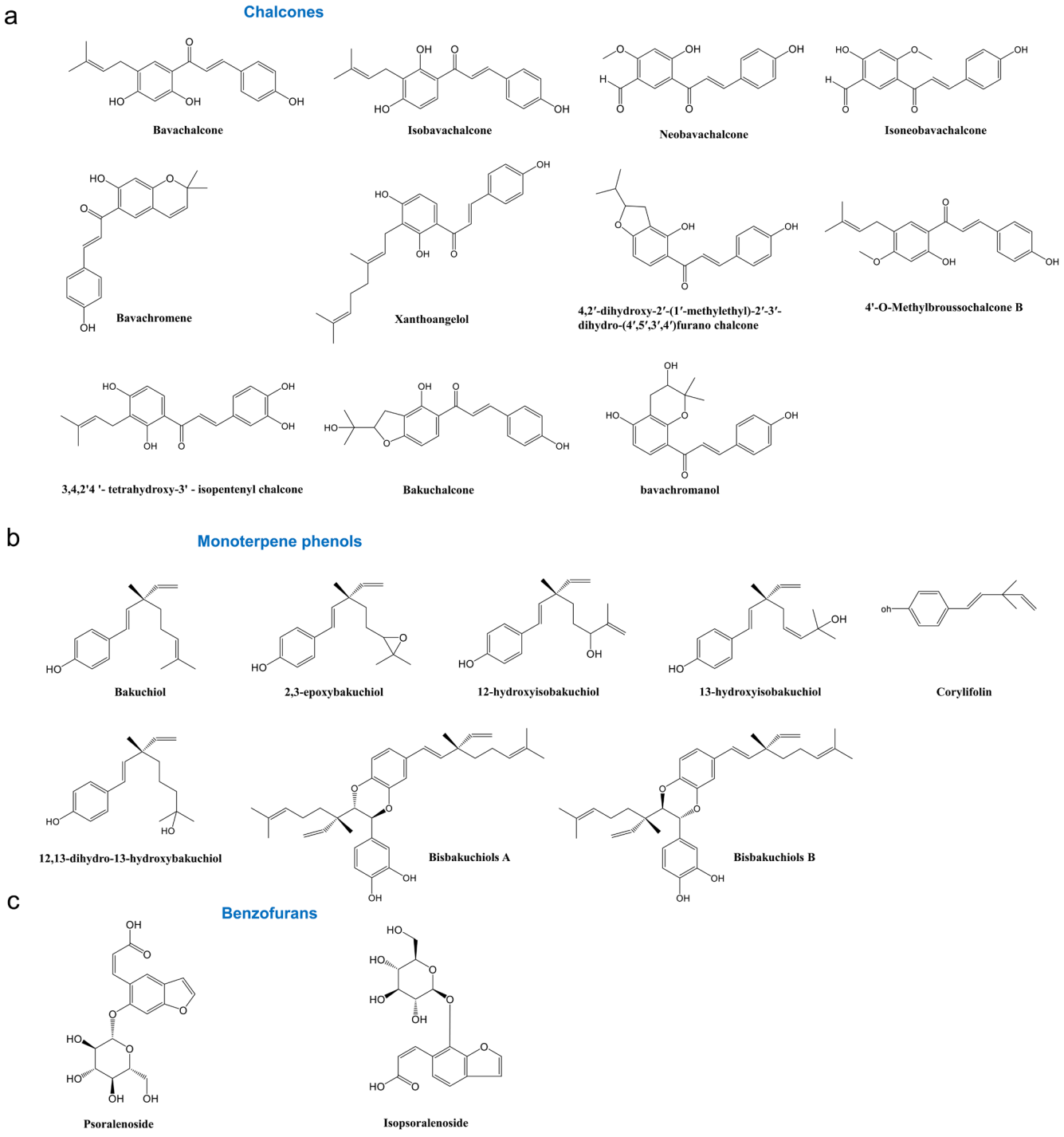

Fig. 3. Chemical structures of chalcones (a), monoterpene phenols (b) and benzofurans (c) isolated from *Psoralea corylifolia* L.

opathological conditions such as hypoxia, bakuchicin can induce vascular relaxation in rat aortic tissue.[37] Psoralen and bakuchicin can stretch blood vessels through the endothelium-dependent nitric oxide pathway and up-regulation of the expression of Endothelial Nitric Oxide Synthase protein in endothelial cells.[38] In addition, flavonoids extracted from PCL could alleviate atherosclerosis based on high-fat diet-induced Low-Density Lipoprotein Receptor$^{-/-}$ mice.[39]

Toxicology of PCL

Hepatotoxicity

With the widespread use of PCL preparations, reports on adverse reactions involving PCL-related liver injuries at home and abroad have significantly increased in recent years. The National Medical Products Administration has issued warnings and notifications on

Table 1. The anti-osteoporosis effect of the major compounds in *Psoralea corylifolia* L.

PCL	Model	Dosage	Time	Results	Reference
Aqueous extract of PCL	Rat osteoblast models	1.0, 10 mg/mL	24 h,48 h, 72 h	Promote the increase in mRNA ratio of osteoblasts OPG and RANKL, and in particular, 1.0 mg/mL and 10 mg/mL of aqueous extract of PCL	6
Xianlinggubao Capsule	An ovariectomized rat model	0.4g/kg	8 weeks	Down-regulation of BMP-2, BMP-4 and PKC protein expression and up-regulation of TGF-β1 protein expression	17
Coryfolin	Bone mesenchymal stem cells (BMSCs)	2 μg ,6 μg, 18 μg	6 days,9 days, 12 days	Regulate cAMP/PKA/CREB signaling pathway to up-regulate the mRNA and expression of PKA and CREB	7
Psoralen	Osteoblast cells	0, 1, 10, 100, and 1,000 μM	48 h	Up-regulated the expression of Bmp2 and Bmp4 genes, increased the protein level of phospho-Smad1/5/8, and activated BMP reporter (12xSBE-OC-Luc) activity in a dose-dependent manner, as well as enhanced the expression of Osx, the direct target gene of BMP signaling	8
Psoralen	An ovariectomized rat model	20 mg/kg	3 months	Significantly improve bone mass indicators including increase trabecular thickness and decrease trabecular space	9
Psoralen	hFOB1.19 cell	0, 5, 10, 15, 20 μM	0, 24, 36, 48, 72 h	Increase levels of GLUT3 and p65, and stimulate osteoblast proliferation through NF-κB-MAPK signaling	10
Psoralen	MC3T3-E1 cells	10 mM	5,10,20,30,60 min	Regulates osteoclast and osteoblast differentiation through the ERK1/2 signaling pathway	11
	Tibia fracture model	20 mg/kg,	28 days	Promote bone fracture healing via the activation of osteoclasts and osteoblasts	
Psoralen	Osteoclast precursor cells	0.01,0.05,0.1,0.5 μM	1–15 days	Ameliorate M-CSF plus RANKL-induced osteoclast differentiation and bone resorption via inhibition of AKT and AP-1 pathways activation *in vitro*	12
Psoralen	An ovariectomized mice model	20 mg/kg/d	6 weeks	The level of CTX-1 was significantly decreased. And the maximum load, maximum stress and flexure modulus were significantly increased	13
isopsoralen	Bone marrow stromal stem cells, BMSCs	1×10^{-4}, 1×10^{-5}, 1×10^{-6}, mol/L	0–16 days	Significantly enhance osteogenesis, calcium salt sediment yield, osteocalcin, and calcified tubercle amount. Also enhance the mRNA level of bFGF, IGF-1, Osterix and Runx-2	14
psoralidin	An ovariectomized rat model	4 mg/kg, 16 mg/kg,	13 weeks	Up-regulate the bone density of the lumbar vertebra and thighbone, the maximum bending strength of thighbone, and serum E 2 and CT	15
bakuchiol	Zebrafish osteoporosis model	0.05,0.17,0.50 mg/L	6 days	Prevent bone loss of zebrafish induced by prednisolone, and accelerate the growth of zebrafish bone	16

AP-1, Activator Protein 1; bFGF, basic fibroblast growth factor; BMP, bone morphogenetic protein; cAMP, Cyclic adenosine monophosphate; CREB, cAMP-response element binding protein; CT, calcitonin; CTX-1, C-terminaltelopeptide of typeⅠcollagen; ERK, extracellular regulated protein kinases; E 2, estradiol-17beta; GLUT3, glucose transporters 3; IGF-1, insulin-like growth factors-1; MAPK, mitogen-activated protein kinase; M-CSF, macrophage-stimulating factor; NF-κB(nuclear factor kappa-B; OPG, osteoprotegerin; Osx, osterix; PCL, *Psoralea corylifolia* L.; PKA, protein kinase A; PKC, protein kinase C; P65, RelA; RANKL, receptor activator of NF-κB ligand; TGF-β1, transforming growth factor-β.

the risk of liver injury caused by PCL-containing preparations (including Zhuangguguanjie Pill, Xianlinggubao Capsule, and Baishi Pill).[40–42] Cases of liver injury caused by Zhuangguguanjie Pill, Xianlinggubao Capsule, and Baishi Pill have also been reported successively in clinical practice. In addition to case reports on liver injury caused by PCL-containing Chinese patent medicines, there are case reports on acute liver injury caused by PCL-containing tea drinks alone.[43] Of particular note, one group designed a long-term, follow-up, cohort study to clarify the clinicopathological features of PCL-induced liver injury, which manifested more often as a hepatocellular injury pattern with mild-to-moderate hepatocellular damage, but most patients recovered after cessation of PCL within 6 months.[44] At the whole animal level, multiple independent research teams have confirmed that chronic administration of

Table 2. The dermatosis treatment effect of the major compounds in *Psoralea corylifolia* L.

PCL	Model	Dosage	Time	Results	Reference
8-methoxypsoralen (methoxsalen)	Imiquimod-induced psoriasis was examined in a BALB/c mouse model	200 ul, 0.25–0.5 J/cm2	3 times in 2 weeks	8-methoxypsoralen plus ultraviolet A (PUVA) down regulated baseline levels of miRNA27a and 29a, as well as interferon-γ, interleukin-17 and -9, cytokines, which reduces the inflammation of established psoriasis induced by imiquimod, but also makes the skin beneficial to reducing the reactivity to Toll like receptor activation	19
	74 patients with moderate-to-severe psoriasis (54 male, 20 female; with median age of 40 years, range from 19–77 years)	0.5–0.7 mg/kg (orally), 0.0001% 8-MOP (immersed), UVA (0.2–1.5 J/cm^2)	4 times a week, 6 weeks in total	Photosensitizer 8-methoxypsoralen (8-MOP) can be taken orally (PUVA system) or applied locally in the warm water bath (PUVA bath) to improve psoriasis	20
Corylin	The apoptosis of HaCaT cell induced by UVB	10^{-3},10^{-4},10^{-5}, 10^{-6},10^{-7},10^{-8}, 10^{-9},10^{-10},10^{-11} mol/L	5,10,15,20 min	The cell proliferation and apoptosis rates were significantly increased, SOD, GSH- Px and CAT activities significantly increased. The relative expression level of Caspase-3 mRNA was significantly decreased, and the relative expression levels of p-AKT and Caspase-3 protein were significantly decreased	21
PCL tincture	Psoriasis vulgaris	0.3–0.5 J/cm^2	3 times a week	Topical PCL tincture combined with NB-UVB is effective in the treatment of psoriasis vulgaris	22
Isopsoralen	Psoriasis-like lesions generated by imiquimod stimulation in a mouse model.	0.2 mg/6cm^2	Administered continuously for 4 days for 30 minutes each time	Isopsoralen-treated groups were significantly reduced compared with those of the imiquimod-treated group. A significant scaling and inflammation activated by imiquimod could be diminished by the furocoumarins. Isopsoralen suppressed IL-1β and IL-6 expression induced by imiquimod in parallel group	23
Psoralen	20 patients (age range from 25–65 years)	Apply ointment on the selected white lesions once a day	12 weeks	Ointment containing seed powder of PCL could be an effective monotherapy for small circular white lesions of vitiligo	24

CAT, catalase; NB-UVB, narrowband ultraviolet radiation b; GSH-Px, Glutathione peroxidase; p-AKT, Phosphorylated-Akt; PCL, *Psoralea corylifolia* L.; SOD, Superoxide dismutase.

PCL can cause liver injury in experimental animals.[45–47] However, under immune stress conditions, the risk of PCL-induced liver injury is further amplified.[48] In addition, several research groups have carried out studies on the mechanism of PCL-induced liver injury. Zhou Kun *et al.* reported that isopsoralen, a furanocoumarin component in PCL, can lead to increased bile acid in HepG2 cells and cytotoxicity by inhibiting multidrug resistance-associated protein 2 and multidrug resistance-associated protein 3,[49] they also found based on HepG2 cells that bakuchiol bakuchicin, another active component in PCL, may lead to the development of cytotoxicity by affecting mitochondrial function or hepatocyte bile acid transport.[50] Psoralen is also cytotoxic to HepG2 cells and is closely related to the expression of proteins affecting the bile salt export pump and Na^+-taurocholate co-transporting polypeptide.[51] Corylisoflavone A has been found to be cytotoxic to a variety of cells.[52] It has been found in some studies that liver injury induced by bavachin, psoralidin, bavachinin, neobavaisoflavone, and bakuchicin may be closely related to oxidative stress and mitochondrial injury-mediated apoptosis.[53] In addition, bavachin, the active component of PCL, can lead to immune idiosyncratic liver injury by activating NLRP3 inflammasome.[54] Besides, bavachinin can reduce protein synthesis and thus cause hepatocyte injury *in vitro*.[55] Isobavachalcone can increase the activity of alanine transaminase and aspartate transaminase in hepatocytes and then play a significant inhibitory role in hepatocytes *in vitro*.[56] These clinical and laboratory studies suggest that PCL and its active components do have a potential risk of hepatotoxicity (Table 3).[45–56]

Reproductive toxicity

In recent years, PCL has also been found to induce reproductive toxicity. PCL extract can inhibit androgen levels, reduce testicular and epididymal mass, and damage germ cells in the seminiferous

Table 3. The hepatotoxicity of *Psoralea corylifolia* L.

PCL	Model	Dosage	Time	Results	Reference
Aqueous extract of PCL	ICR mice	20,40,80 g/kg	4 weeks	Lead the liver injury in mice and influence the expression of bile acid transporter	45
The debris after decoction of Fructus Psoraleae	SD rat	3,6 g/kg	4 weeks	The toxicity of PCL aqueous extract residues is relatively smaller than the crude drug	46
Aqueous extract of PCL	Wistar rat	1.05,2.10 g/kg	12 weeks	The aqueous extract 2.10 g/kg group was hepatomegaly, and its liver coefficient increased significantly	47
PCL	LPS model	0.22 g/kg	1 day	Increase the responsiveness of the liver to LPS or other inflammatory mediators via modulation of multiple metabolic pathways	48
isopsoralen	HepG2	6.25,25,100,400 μmol/L	24 h	Caused the down-regulation of MRP2, MRP3, CYP7A1 mRNA at 25 μmol/L, and the up-regulation of OATP2, OSTα, CYP27A1, FXR, and PXR with 100 μmol/L, but there was no significant change of BSEP and NTCP	49
bakuchiol	HepG2	62.5,93.8,125.0,156.3, 187.5 μmol /L	2,6,24 h	Increase the level of AST and ALP. BSEP was inhibited at 2 h after bakuchiol treatment in HepG2 cells, while the mRNA levels of BSEP, NTCP, FXR and CYP7A1 were increased at 24 h	50
Psoralen	HepG2	62.5,125,250,500 μmol /L	2,6,24,48 h	Inhibite BSEP and enhance the expression of NTCP	51
corylisoflavone A	NB4, A549, SHSY5Y, PC3, MCF7	/	24 h	Display the cytotoxicity against NB4, SHSY5Y, PC3, A549, and MCF7 cells with IC50 values of 12.6, 5.3, 15.5, 4.8, and 11.2 μmol/L, respectively	52
bavachin, psoralidin, bavachinin, neobavaisoflavone, bakuchicin	L02 and HepG2	Bavachin (17,34, and 68μmol/L), psoralidin (11.5 23, and 46 μmol/L), bavachinin (15, 30, and 60 μmol/L), neobavaisoflavone (23.5, 47, and 94 μmol/L), bakuchicin (13, 26, and 52 μmol/L)	24 h	Bavachin, psoralidin, bavachinin, neobavaisoflavone, and bakuchicin induced cell apoptosis and AST, ALT, and ALP leakages. Furthermore, these five constituents increased intracellular lipid accumulation and ROS levels but decreased the MMP level	53
Bavachin	BMDMs	2.5,5,10 μmol/L	/	Boost the secretion of IL-1β and caspase-1 caused by ATP or nigericin, specifically increases the production of nigericin-induced mitochondrial reactive oxygen specie	54
	C57BL/6 mice	25 mg/kg	1 day	Increase the levels of ALT and AST in serum	54
Bavachinin	HepaRG	6.25 μmol/L	24 h	Induce the expression and differentiation of many proteins in HepaRG cells, including 372 differentially expressed proteins, 170 upregulated proteins and 202 downregulated proteins	55
Psoralen, bakuchiol, Isobavachalcone, Psoralidin, Isopsoralen, Coryfolin	L02	6.25,12.5,25,50, 100,150,200 mg/L	24,48,72 h	Psoralen, bakuchiol, Isobavachalcone, Psoralidin, Isopsoralen, Coryfolin could induce cytotoxicity on L02 cells	56

ALP, alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BSEP, bile salt export pump; CYP7A1, Recombinant Cytochrome P450 7A1; CYP21A1, Recombinant Cytochrome P450 27A1; FXR, farnesoid X receptor; MMP, Mitochondrial membrane potential; MRP2, Multidrug resistance-associated protein 2; MRP3, Multidrug resistance-associated protein 3; NTCP(sodium taurocholate cotransporting polypeptide; OATP2, organic anion transporting polypeptide2; PXR, Pregnane X Receptor; ROS, reactive oxygen species.

Table 4. The relationship between pharmacology and toxicology of *Psoralea corylifolia* L.

Extract or composition	Efficacy related reports						Toxicity related reports			
	anti-osteoporosis	anti-depression	anti-tumor	antioxidation	skin disease	cardiovascular system	hepatotoxicity	Nephrotoxicity	phototoxicity	reproduction toxicity
Xianlinggubao Capsule	△						○			
Aqueous extract of psoraleae fructus	○						△			△
Residue of psoraleae fructus after water extraction							△			
Alcohol extract of psoraleae fructus					◇					△
Total furanocoumarins		△								
Flavonoids				○						
Psoralen	△		○			△	△	○	○	
Angelicin	○		△				△			
Bavachin	○	△	○				○			
Isobavachalcone	○						○			
Corylin					○					
Bakuchiol	△	△	○	○		△	○△	○		
Psoralidin	△	△		○			○			

△: Animal experiment verification; ○: Cell experiment proved; ◇: Clinical proof.

tubules of developing rats, resulting in reproductive toxicity.[57] In addition, it has also been found in a study that, after administration of aqueous PLC extract to pregnant female rats at 8 $g \cdot kg^{-1}$ daily, the total number of fetuses, the number of live fetuses, and the live fetus rate were significantly decreased, and the number of absorbed fetuses, absorbed fetus rate, and post-implantation loss rate also increased. Although this study did not find significant malformed fetuses or embryotoxicity, it could also indicate that the aqueous extract of PCL has certain embryotoxicity.[58] Moreover, chronic administration of psoralen to mice can cause reduced uterine mass, decreased ovarian function, decreased ovulation and reduced estrogen levels, suggesting that psoralen can be toxic to the reproductive system.[59]

Other toxicities

PCL and its active components can not only induce hepatotoxicity and reproductive toxicity but also increase the risk of phototoxicity and nephrotoxicity. PCL has strong photosensitive activity and can cause phototoxic contact dermatitis.[60,61] Besides, bakuchicin, the active component of PCL, has the risk of inducing nephrotoxicity.[62] 5-methoxypsoralen can produce skin toxicity and have a potential risk of causing photosensitivity cytotoxicity, chromosomal mutation, and chromosome breakage.[63]

Integrative analysis of the pharmacology and toxicology of PCL

In conclusion, PCL and its active components have good clinical efficacy in anti-osteoporosis, the treatment of dermatosis, and antidepressant effects but also increase the risk of inducing liver injury and phototoxicity in the process of treatment of the above diseases. Therefore, in this paper, a comprehensive summary and analysis of the pharmacology and toxicology of PCL were conducted (Table 4). It was found, through comparison, that, although PCL is more widely used in the treatment of a variety of diseases, PCL and its active components have a significant anti-osteoporosis effect, while, in terms of toxicity, PCL and its active components have the highest risk of hepatotoxicity. Therefore, in this paper, the relationships between the active components of PCL and hepatotoxicity and anti-osteoporosis efficacy were systematically sorted out (Fig. 4). It was found that bavachin, isobavachalcone, psoralidin, psoralen, isopsoralen, and bakuchicin are reported in the hepatotoxicity-related literature at the cellular level *in vitro* or at the overall animal level, and corylin, isobavachalcone, bavachin, psoralidin, psoralen, isopsoralen, and bakuchicin are reported in the anti-osteoporosis effect-related literature at the cellular level *in vitro* or at the overall animal level, and, especially, some active components of PCL, including isobavachin, isobavachalcone, psoralidin, psoralen, isopsoralen, and bakuchicin are reported in the literature both for hepatotoxicity and anti-osteoporosis effects.

Outlook

PCL is a commonly used tonic drug in clinical practice, and multiple Chinese patent medicine preparations containing PCL, such as the Xianlinggubao Capsule and the Zhuangguguanjie Pill, have significant clinical efficacy. However, with the widespread use of PCL preparations, reports on the adverse reactions of PCL-related liver injuries at home and abroad have shown a significant increase in recent years, causing high concern at home and abroad. At present, reported studies on the effective and toxic components of PCL have only conducted evaluations separately from the per-

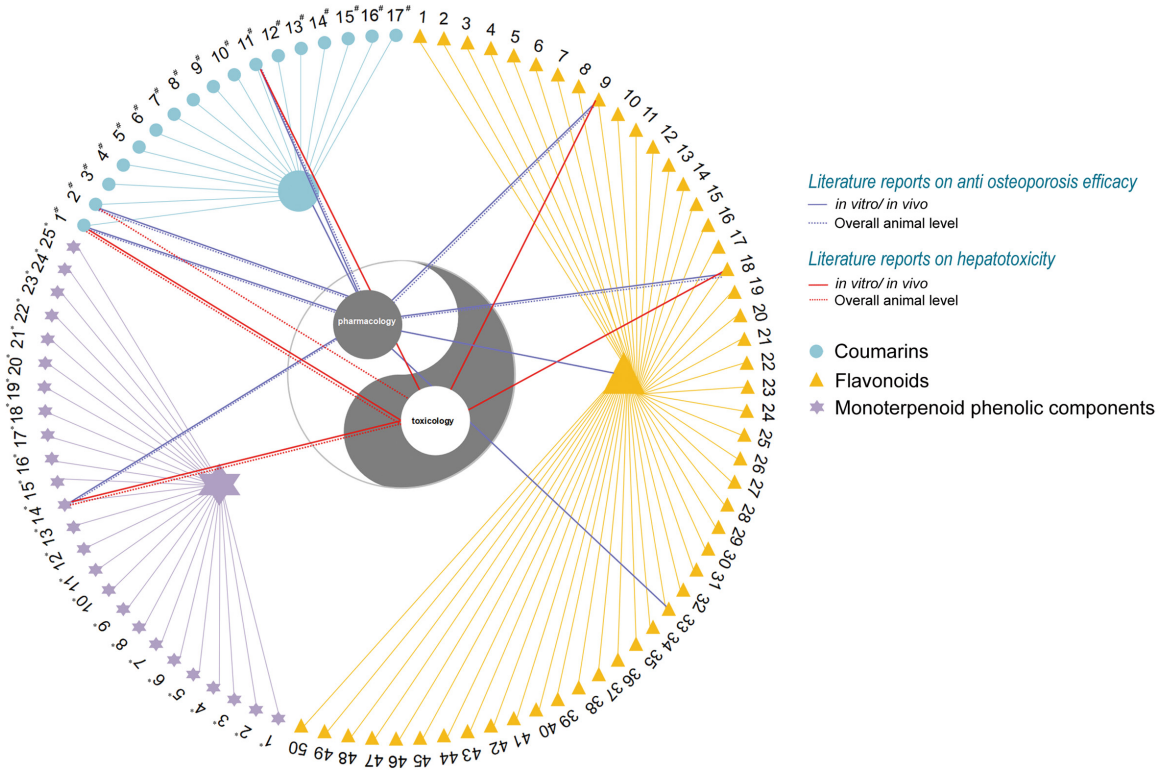

Fig. 4. Integrative analysis on the anti-osteoporosis and hepatotoxicity of *Psoralea corylifolia* L. *Flavonoids* (▲): 1: 4′-Methoxyflavonol; 2: Apigenin; 3: Chromenoflavanone; 4: 3,7,4′-Trihydroxy-8-prenylflavanone; 5: Baicalin; 6: 3,5,3′,4′-tetrahydroxy-7-methoxyflavone-3′-O-α-L-xylopyranosyl(1→3)-O-α-L-arabinopyranosyl(1→4)-O-β-D-galactopyranoside; 7: Furano(2″,3″:7,6)-4′-hydroxyflavanone; 8: 5-Dehydroxyparatocarpin K; 9: Bavachin(corylifolin); 10: Isbavachin; 11: Bavachinin; 12: 6-Prenylnaringenin; 13: Neobavachalcone; 14: Isoneobavachalcone; 15: Bavachromene; 16: Isobavachromene; 17: Bavachalcone; 18: Isobavachalcone (corylifolinin) 19: 4,2′-dihydroxy-2′-(1′-methylethyl)-2′-3′-dihydro-(4′,5′,3′,4′)furanochalcone; 20: 4′-O-MethylbroussochalconeB; 21: 3,4,2′4′-tetrahydroxy-3′-isopentenylchalcone; 22: 4,2′,4′-trihydroxy-3′-(3″methyl-2″-hydroxy-3″-butenyl) chalcone; 23: Bakuchalcone; 24: bavachromanol; 25: (2E)-1-[(2S,3S)-2,3dihydro-3,4-dihydroxy-2-(1-hydroxy-1-methylethyl)-5-benzofuran]-3-(4-hydroxybenzene)-2-propen-1-keton; 26: (R, Z)-2-oxo-3,4,5,6,7,10-hexahydro-2H-oxheterocyclodecane-5-yltridecane; 27: Xanthoangelol; 28: Daidzein; 29: 5,7,4′-trihydroxyisoflavone; 30: Corylinal; 31: Biochanin A; 32: Corylinin; 33: Corylin; 34: Erythrinin A; 35: neobavaisoflavone; 36: isoneobavaisoflavone; 37: Neocorylin; 38: 8-Prenyldaidzein 39: Corylin A; 40: Psoralenol; 41: 7-hydroxy-(2″-isopropanol-3′,4′-dihydrofuran)isoflavones; 42: 5,7,4′-trihydroxy-6-isopentenylisoflavones 43: Isowightenon; 44: 7-methoxypsoralenol; 45: 7-hydroxy-(1″-hydroxy-2″-isopropanol-3″,4′-dihydrofuran)isoflavones; 46: 4′,7-dihydroxy-3′-geranylisoflavones; 47: 3′-acetoxy-7-methoxypsoralenol; 48: neobavaisoflavone; 49: Daidzin; 50: Bavadin. *Coumarins* (●): 1#: Psoralen; 2#: Angelicin; 3#: Bakuchi-cin; 4#: Bergapten; 5#: Methoxsalen; 6#: Psoralenoside; 7#: Isopsoralenoside; 8#: Neo-psoralen; 9#: 4″,5″-Dehydroisopsoralidin; 10#: Sophoracoumestan A; 11#: Psoralidin; 12#: Psoralidin2′,3′-oxide; 13#: Bavacoumestan A; 14#: Bavacoumestan B; 15#: Corylidin; 16#: Pyranocoumarin; 17#: 7,2,4′-trihydroxy-3-arylcoumarin. *Monoterpenoid phenolic components* (✳): 1*: corylifolin; 2*: Δ^1-3-Bakuchiol; 3*: 12,13-dihydro-13-hydroxybakuchiol; 4*: Cyclopsoralen A; 5*: Cyclopsoralen B; 6*: 15-demethyl-12,13-dihydro-13ketobakuchiolΔ^1-3-Hydroxybakuchiol; 7*: Δ^3-3-Hydroxybakuchiol; 8*: 12,13-epoxypsoralen; 9*: 4-[(1S, 2S, 5R, 7S)-2,8,8-trimethyl-2-vinyl-6-oxoheterocyclic[3.2.1]oct-7-yl]phenol; 10*: 4-[(1R, 2S, 5S, 7R)-2,8,8-trimethyl-2-vinyl-6-oxoheterocyclic [3.2.1] oct-7-yl]phenol; 11*: 4-[(1R, 2R, 3S)-2-hydroxy-3-methyl-6-(propan-1-en-2-yl)-3-vinylcyclohexyl] phenol; 12*: Cyclopsoralen C; 13*: Bakuchiol; 14*: Δ10-12, 13-dihydro-12-(R)-methoxyIsopsoralenol; 15*: Δ10-12,13-dihydro-12-(S)-methoxyIsopsoralenol; 16*: 13-methoxy-isobakuchiol; 17*: 4-[(S)-hydroxy[(2S, 3S, 6S)-3-methyl-6-(propan-1-en-2-yl)-3-vinyltetrahydro-2H-pyran-2-yl]methyl]phenol; 18*: 4-[(1R, 2S, 5R, 7R)-5-isopropanol-2-methyl-2-vinyl-6, 8-dioxa[3.2.1]oct-7-yl]phenol; 19*: 4-[(1S, 2S, 5S, 7S)-5-isopropanol-2-methyl-2-vinyl-6, 8-dioxa[3.2.1]oct-7-yl]phenol; 20*: 12,13-Hydroxybakuchiol; 21*: 13-ethoxy-isopsoralen; 22*: (12S)-bispsoralen C; 23*: Bisbakuchiols A; 24*: Bisbakuchiols B.

spective of toxicity or pharmaceutical effects, but there is no integrated analysis on effective and toxic components, which greatly limits the safe and rational clinical application of PCL. Therefore, in this paper, the pharmacology and toxicology of PCL were compared, and, especially, based on the clinical application of PCL, an integrative analysis of the efficacy mechanism of PCL against osteoporosis and the toxicity mechanism of PCL for hepatotoxicity was made. The study on the effective and toxic components of PCL suggested that the transformation law and relationship between effective and toxic components of PCL are complex, and it is urgent to carry out the study on the effective and toxic substance basis of PCL. In addition, the sizing treatment of PCL is also a key factor for clinical attenuation and synergism. *Lei Gong's Treatise on Preparation* records a special pretreatment method for PCL herbs. Specifically, PCL is soaked in Chinese Baijiu for one night and then taken out and dried, followed by washing with running water for three days, continuous steaming and stewing for 8 hours, and dried before use. Based on the above pretreatment methods of PCL, it was found that the sizing treatment of Baijiu soaking and rinsing recorded in *Lei Gong's Treatise on Preparation* can significantly reduce the potential hepatotoxicity of PCL and is an attenuation method with good application prospects.[64] On this basis, the pharmaceutical effects of PCL after sizing treatment of Baijiu soaking and rinsing can be investigated in the rat osteoporosis model to interpret the scientificity of attenuation and the synergism of PCL and the component transformation law. In

summary, an in-depth study on the effective and toxic substance basis of PCL and clarification of its effective and toxic substances are expected to maximize treatment benefits, reduce toxicity risk, and increase benefit/risk ratio, providing evidence and support for the safe clinical application of PCL.

Conclusions

The main chemical components, pharmacology, and toxicology of PCL were summarized in this paper. PCL contains a wide variety of chemical constituents belonging to various groups, including flavonoids, coumarins, monoterpene phenols, and benzofurans, which are more dominant. PCL and its active components also have certain protective effects on anti-osteoporosis, dermatosis, antidepressant, antitumor, and cardiovascular relaxation. Moreover, PCL and its active components can not only induce hepatotoxicity and reproductive toxicity but also increase the risk of phototoxicity and nephrotoxicity. Therefore, the effect-toxicity relationship of PCL and its main active components are sorted out and compared.

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Conflict of interest

Two of the authors, YG and JBW, are editorial board members of *Future Integrative Medicine*. The authors have no other conflict of interests to report.

Author contributions

Study concept and design (JBW and YG), acquisition of the literature (CC), and drafting of the manuscript (YKZ). All authors read and approved the final manuscript.

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