REVIEW

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Biological activity and health promoting effects of psoralidin

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Psoralidin, a prenylated coumestrol isolated from the seed of a traditional Chinese medicine *Psoralea corylifolia* L., has been demonstrated to exhibit anti-inflammatory, anti-cancer, anti-oxidative, estrogenic, neuroprotective, anti-bacterial, and anti-parasite activities. Due to prenylation, psoralidin exhibits stronger estrogenic activity with no obvious adverse effects and shows a close association with management of osteoporosis and some cancers. However, the hydrophobicity and low bioavailability of psoralidin limit its clinical application, although recent investigation has gained valuable data. This review will discuss the biological activities of psoralidin in health.

1. Introduction

Psoralidin (Fig. 1), 3,9-dihydroxy-2-(3-methylbut-2-enyl)-[1] benzofuro[3,2-*c*]chromen-6-one, is one of the main furo-coumarins found in the seeds of the traditional Chinese medicine *Psoralea corylifolia* L. (PCL), which has been widely used as an aphrodisiac and a tonic and for treating many diseases, such as hypertension, inflammatory disease, cardiovascular disease, nephritis, and skin disease (Chopra et al. 2013). Recently, psoralidin has been totally synthesized (Pahari and Rohr 2009; Pahari et al. 2016) and was shown to exhibit various biological effects, including anti-inflammatory (Chiou et al. 2011; Rao et al. 2018), anti-cancer (Srinivasan et al. 2010; Jin et al. 2016a), anti-oxidative (Das et al. 2014; Ren et al. 2016), anti-depressant (Yi et al. 2008), anti-bacterial (Khatune et al. 2004), and estrogenic (Liu et al. 2014) activities. Psoralidin is a prenylated coumestrol. Modification with a prenyl group has been demonstrated to be able to increase the affinity of psoralidin to cell membrane and improve its absorption and bioactivities (Mukai et al. 2013).

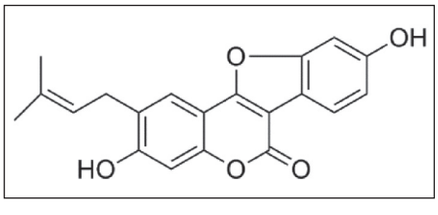

Fig. 1: Chemical structure of psoralidin

2. Metabolism of psoralidin

Cytochrome P450 3A4 (CYP3A4), the most abundant metabolic enzyme, plays a crucial role in the bio-activation and detoxification of drugs (Liu et al. 2007). Psoralidin has been reported to suppress the activity of CYP3A4 dose-dependently in differentiated HuH-7 and HepaRG cells or human recombinant CYP3A4 with IC_{50} values of 57.7 μM, > 200 μM, and 30.8 μM, respectively. No obvious cytotoxicity has been observed at the tested concentration of psoralidin (1-200 μM) (Liu and Flynn 2015) (Table). However, long-term use of psoralidin has been demonstrated to exhibit hepatotoxicity in mice and rats (Wang et al. 2012). In addition, psoralidin inhibits CYP1A2, CYP2C8, UDP-glucuronosyltransferase (UGT) 1A1, and UGT1A7 with C_{max}/K_i values of 5.67, 26.21, 1.15, and 27.12, respectively. CYP2C19 has been identified as the main metabolic enzyme for psoralidin in humans. The possible metabolites (Fig. 2) of psoralidin have been identified in the liver microsome incubation system among different species, such as rat, rabbit, dog, minipig, monkey, and human. After intravenous administration of psoralidin in rats, the pharmacokinetic parameters are as follows: $AUC_{(0-\infty)}$ = 1.95 ± 0.5 mg/L/h, $t_{1/2}$ = 4.45 ± 0.95 h, and C_{max} = 2.19 ± 0.48 mg/L (Shi et al. 2016) (Table).

Eleven compounds including psoralidin from PCL have been studied for pharmacokinetics and cerebral nuclei distribution in rats. After oral administration at a dose of 1.2 g/kg PCL extract to rats, psoralidin is absorbed quickly into the plasma and distributed to the cerebral nuclei with a higher concentration than that of prenylflavonoids. However, prenylflavonoids shows a higher total ratio of brain-concentration/plasma-concentration (Yang et al. 2018). Like prenylflavonoids, psoralidin also has a prenyl group, which increases its hydrophobicity and makes it more readily to enter the brain (Yang et al. 2018). Due to its low bioavailability, psoralidin has been continuously under investigation for a delivery system with a goal of improving solubility and absorption. A nano-encapsulation formulation of psoralidin developed by water-soluble chitosan and Eudragit S100 increased the bioavailability of psoralidin by 339.02%, compared to a control group. This enhancement of oral bioavailability might be associated with excellent intestinal adhesion and trans-epithelial permeability (Yin et al. 2016).

3. Anti-inflammatory activity

Reactive oxygen species (ROS) and granule proteases generated by human neutrophils have been implicated in the development of various inflammatory diseases. The isolated compounds from PCL have been screened for anti-inflammatory effects on human neutrophil pro-inflammatory responses by inhibiting the generation of fMLP/CB-induced ROS and the release of elastase. Psoralidin suppresses ROS generation with an IC_{50} value of 19.38±6.88 μM, inhibits the release of elastase with an IC_{50} value of 18.15±5.53 μM, and abrogates NO generation in lipopolysaccharide (LPS)-induced RAW264.7 macrophages with a IC_{50} value of less than 27.46±2.75

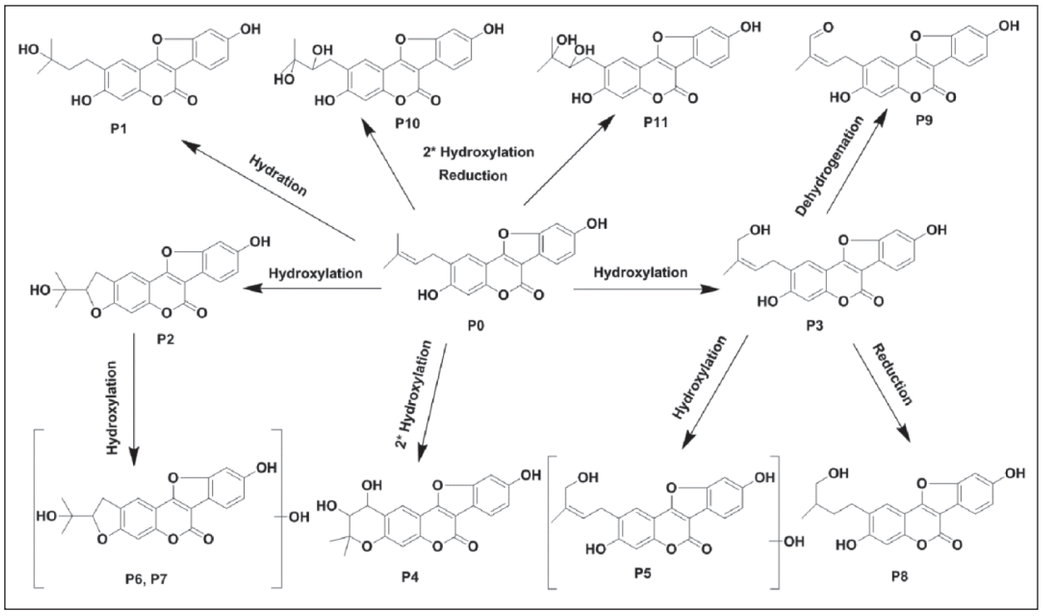

Fig. 2: Proposed chemical structures and major metabolic pathway of psoralidin

μM (Chen et al. 2017). Consistently, psoralidin has been demonstrated to significantly attenuate the accumulation of nitrite (NO_2^-), a marker of NO production, with IC_{50} value of 23 μM in LPS-induced RAW264.7 macrophages (Matsuda et al. 2009) (Table).

LPS-induced activation of RAW264.7 macrophages requires involvement of non-receptor tyrosine kinases, such as Bruton's tyrosine kinase (Btk), c-Src, Janus kinase (JAK)-2, and spleen tyrosine kinase (Syk). These kinases are upstream factors of PI3K/Akt signaling. It has been shown that LPS induces iNOS-NO expression in RAW264.7 macrophages by activating the PI3K-NF-κB signaling pathway. Among the inhibitors of non-receptor tyrosine kinases, Syk inhibitor piceatannol shows the highest activity in suppressing LPS-induced NO production. Psoralidin pretreatment significantly blunts LPS-induced NO expression through abrogation of phosphorylation of Syk and PI3K and inactivation of NF-κB signaling pathway (Chiou et al. 2011).

Chondrocytes apoptosis plays a crucial role in the development of osteoarthritis. Interleukin-1β (IL-1β) treatment often induces osteoarthritic chondrocyte. Psoralidin has been demonstrated to reverse the effects of IL-1β on chondrocytes, as indicated by down regulation of caspase-3, caspase-9, Bax, and MMPs expression and up regulation of Bcl-2 expression, and lead to chondrocytes protection from apoptosis. These might be associated with the amelioration of NF-κB signaling expression by psoralidin (Rao et al. 2018). NF-κB ligand (RANKL) interacts with its receptor RANK to form a complex, which recruits tumor necrosis factor receptor-associated factor 6 (TRAF6) and subsequently activates downstream signaling pathways, including NF-κB and the three MAPKs (Suda et al. 1999). In pre-osteoclast cultures, psoralidin significantly suppresses RANKL-induced osteoclast formation, as shown by attenuating the expression of osteoclastogenesis marker genes, including TRAP, cathepsin K, and OSCAR, and c-Fos and NFATc1. These might be associated with the abrogation of p38, ERK, JNK, and p65 phosphorylation and reduction of I-κB degradation. Consequently, psoralidin inhibits LPS-induced bone resorption by decreasing the ratio of RANKL: osteoprotegerin (OPG) and the expression of TNF-α and IL-6 (Kong et al. 2017) (Table).

4. Anti-cancer activity

Recently, cancer stem cells (CSCs) have been reported to govern the tumorigenicity and capacity for self-differentiation in cancers. Aldehyde dehydrogenase (ALDH) enzyme is a functional marker of breast CSCs and linked to the metastasis, prognosis, and clinical outcome in breast cancer patients (Yoshioka et al. 2011). Notch signaling has been associated with cell fates and implicated in cancer initiation, progression, and chemoresistance and radioresistance (Velasco-Velázquez et al. 2012). Psoralidin has been shown to attenuate the activity of notch signaling, leading to cell growth inhibition, apoptosis induction, and suppressive expression of EMT markers (β-catenin and vimentin) in $ALDH^+$ and $ALDH^-$ cells isolated from MDA-MB-23 cells. In addition, psoralidin improves breast cancer cells chemoresistance, as indicated by suppression of the number and the size of mammosphere formation and increased expression of E-cadherin (Suman et al. 2013) (Table).

In SW480 human colon cancer cells, psoralidin exhibited anti-proliferative effects and induced cell apoptosis by suppressing the expression of Bcl-2 and NF-κB signaling and enhancing the activity of Bax and caspase-3, as indicated by decreased activity of p65 (Jin et al. 2016a). Similarly, psoralidin significantly attenuates proliferation and increases apoptosis in human esophageal carcinoma Eca9706 cells in a dose-dependent manner through downregulation of NF-κB and PI3K/Akt signaling pathways, as demonstrated by the fact that the PI3K agonist can reverse the effects of psoralidin on Eca9706 cells (Jin et al. 2016b). Cadmium, a persistent metal toxicant, is continuously released into the environment. The relationship between cadmium exposure and cancer risk has been established (Jones et al. 2016). Chronic exposure of cadmium leads to transformation of normal cells to malignance. Psoralidin has been found to inhibit cell growth in cadmium-transformed prostate epithelial cells (CTPE), as proved by suppressive expression of placenta specific 8 (Plac8), which is a lysosomal protein required for autophagosome and autolysosome fusion. Importantly, psoralidin selectively causes non-toxicity to normal prostate epithelial cells (RWPE-1). In addition, psoralidin promotes cell apoptosis and decreases autophagy in CTPE (Pal et al. 2017) (Table).

In human stomach carcinoma SNU-1 and SNU-16 cell lines, psoralidin has been demonstrated to exhibit cytotoxicity to cancer cells with IC_{50} values of 53 μg/mL and 203μg/mL, respectively (Yang et al. 1996). In human liver cancer HepG2 cells, psoralidin significantly reduces cell viability and promotes cell apoptosis dose-dependently, as indicated by up regulation of Bax, Bid, p53, caspase-3, and caspase-9 and down regulation of Bcl-2 and Bcl-xL. Administration of caspase-3 inhibitor, p53 inhibitor, or cyclosporine A can critically attenuate the pro-apoptotic effects of psoralidin (Yu et al. 2016). Activation of epidermal growth factor receptor (EGFR) and its downstream factors Raf, MAPK, and ERK1/2 has been involved in regulation of mitogenic events and transition of androgen-dependent prostate cancer to androgen inde-

pendent prostate cancer (AIPC). Inhibition of EGFR and its downstream cascades by psoralidin has been showed to be associated with attenuation of proliferation, induction of apoptosis, and suppression of progression. In addition, the xenograft tumors of prostate cancer in nude mice are also suppressed by psoralidin significantly through oral administration (Kumar et al. 2010) (Table).

On the other hand, psoralidin did not induce cell apoptosis but triggers autophagy in human lung cancer A549 cells, as indicated by not significant changes in Hoechst 33342 and Annexin V-FITC staining but dramatically increased the expression ratio of LC3-II/LC3-I and intensity of MDC-fluorescence. ROS scavenge N-acetyl cysteine (NAC) pretreatment can reverse the cytotoxicity of psoralidin. This suggests that psoralidin exerts an anti-proliferative effect on A549 cells by generation of ROS and activation of autophagy (Hao et al. 2014) (Table).

5. Anti-oxidative activity

Consistently, psoralidin triggers protective autophagy through induction of ROS in MCF-7 breast cancer cells. Excessive ROS production leads to oxidative stress. As the main ROS source, NADPH oxidases (NOXs) play a crucial role in cancer therapy. Psoralidin can significantly increase the expression of NOX4, which causes cells proliferation inhibition. The underlying mechanism might be related to DNA damage, increased expression of γH_2AX, elevated phosphorylation of ATM, ATR, Chk1, and Chk2 in MCF-7 cells (Ren et al. 2016) (Table).

ROS participate in the development of prostate cancer through alternative expression of pro-survival machinery (Lim et al. 2005). Psoralidin-induced ROS are showing inhibitory activity in PC-3 and C4-2B cells growth and metastasis, which might be associated with decreased expression of β-catenin, snail, and slug and decreased activity of epithelial mesenchymal transition (EMT). These can be rescued by overexpression of anti-oxidants, such as superoxide dismutase 1 (SOD1), SOD2, and catalase. In addition, psoralidin can induce cell apoptosis, as shown by loss of mitochondrial membrane potential ($\Delta\Psi m$), release of cytochrome-*c*, and activation of poly (ADP-ribose) polymerase (PARP) and caspase-3 and caspase-9 (Das et al. 2014) (Table).

6. Estrogenic activity

Many phytoestrogens have been identified from the seeds of PCL, which has been used for managing osteoporosis and cardiovascular diseases. Coumestrol is known to be a phytoestrogen. Due to prenylation, psoralidin is expected to exhibit stronger estrogenic activity than coumestrol in all of the measurements (Zhai et al. 2017). Psoralidin is an agonist for estrogen receptors (ERs). The molecular docking of psoralidin to ERα and ERβ has been conducted with IC_{50} values of 1.03 μM and 24.6 μM, respectively. The direct binding of psoralidin to ERα and ERβ to form a complex, which can activate estrogen response element (ERE) gene transcription by binding at the promoters of target genes with EC_{50} values of 3.68 μM and 6.88 μM, respectively, in ER-negative CV1 cells transfected with either ERα or ERβ. At the dose of 10 μM, psoralidin can stimulate the maximum activity of reporter gene expression, compared to that in estradiol (E2)-treated cells (Liu X et al. 2014) (Table).

In ovariectomized (OVX) rats, psoralidin has been shown to increase the bone density of lumbar vertebra and thighbone and the maximum bending strength of thighbone, leading to protection against postmenopausal osteoporosis (Li et al. 2013). The anti-osteoporosis activity of psoralidin has been linked to increase the bone formation of osteoblasts and decrease bone resorption of osteoclasts, as indicated by lower tartrate-resistant acid phosphatase activity, smaller area, and fewer resorption pits. The underlying mechanism might be associated with increased expression of collagen-I, BMP-2, osteocalcin, osteopontin, IGF-1, β-catenin, Runx-2, Osterix, OPG, and the ratio of OPG/RANKL and decreased expression of RANKL, COX-2, and ROS (Zhai et al. 2017) (Table). In OVX rats, psoralidin significantly suppresses bone loss, as shown by upregulation of total bone mineral content, bone density, mineral apposition rate, bone biomechanical properties, microstructure and trabecular bone formation, osteogenic differentiation, and PI3K/Akt signaling pathway and downregulation of adipogenic differentiation of BMSCs, GSK-3β/β-catenin signaling, and Nrf2/HO-1 signaling (Zhai et al. 2018).

7. Neuroprotective activity

In forced swimming test (FST) in male ICR strain mice, psoralidin pretreatment significantly increased the time of immobility and decreased the time of swimming behavior without any alternations of climbing behavior. In addition, the levels of 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleactic acid (5-HIAA) have been found to be elevated in some brain regions. The serum concentrations of corticotropin-releasing factor (CRF), adrenal corticotropin-releasing hormone (ACTH), and corticosterone induced by swimming stress are also found to be ameliorated. The anti-depressant-like properties of psoralidin might be associated with regulation of monoamine neurotransmitter and the hypothalamic-pituitary-adrenal (HPA) axis systems (Yi et al. 2008).

8. Anti-bacterial and anti-parasite activity

Psoralidin shows anti-bacterial activity against a number of Gram(+) and Gram(-) bacteria at doses of both 200 μg/disc and 400 μg/disc, especially against Gram(-) *Shigella sonnei* and *S. flexneri* (Khatune et al. 2004). *Ichthyophthirius multifiliis* (also called ich), a fish parasite, often causes massive economic damage to the aquaculture industry. It has been demonstrated that all the theronts can be killed by psoralidin at a dose of 0.8 mg/L during 4 h exposure *in vitro*. In addition, all the reproduction of the protomonts and the encysted tomonts are terminated by exposing to psoralidin at 0.9 mg/L and 1.2 mg/L, respectively. *In vivo*, the infected fish have been showed to reduce the releasing number of theronts from tomonts after 5 h exposure of 2.5 mg/L psoralidin. The underlying mechanism of psoralidin against ich might be associated with induction of apoptosis (Song et al. 2015).

9. Clinical perspective

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a crucial immune effector in the surveillance and defense, triggers cell apoptosis in tumors. However, some cancer cells are resistant to TRAIL-induced apoptosis. Many naturally occurring compounds have been shown to sensitize TRAIL-resistant tumor cells and enhance the apoptotic activity. Psoralidin significantly enhanced the cytotoxic and apoptotic activities of TRAIL in HeLa cancer cells through elevated expression of TRAIL-R2/DR5 and depolarization of $\Delta\Psi m$ (Bronikowska et al. 2012).

Similarly, psoralidin at the dose of 50 μM could augment the apoptotic percentage to 64.4±0.5 % in TRAIL-resistant human hormone-sensitive prostate cancer cells (LNCaP) (Szliszka et al. 2011). Herb-drug interaction dramatically limits their clinical application. Irinotecan-induced diarrhea is associated with glucuronidation of SN-38 catalyzed by UGT 1A1. Psoralidin has been found to inhibit SN-38 glucuronidation dose-dependently with a K_i value of 5.8 μM in human intestinal microsomes incubation system. This indicates that psoralidin or psoralidin-containing herbs administration may increase the toxicity of irinotecan (Zhang et al. 2015).

TNFα has been demonstrated to function both as a pro-survival and pro-apoptotic factor. Clinically, toxicity of TNF inhibitors to normal cells has limited their extensive applications for cancer management, although inhibition of TNF signaling has obtained great importance in cancer treatment (Sethi et al. 2008). Psoralidin has been showed to inhibit the constitutive and TNF-induced expression of TNFα and its downstream factor Bcl-2 and NF-κB/p65 signaling in AIPC cells (PC-3 and DU-145 cells) with IC_{50} values of 60±3 μM and 45±3 μM, respectively (Srinivasan et al. 2010; Pahari et al. 2016) (Table). In addition, psoralidin activates the death receptor (DR4/DR5)-mediated signaling and promotes cell apoptosis (Srinivasan et al. 2010).

Table: Biological activities of psoralidin

List	Models	Doses	Biological activities of psoralidin	Ref.
1	LPS-induced RAW264.7	10, 20, and 30 μM	iNOS-NO↓, NF-κB signaling↓, Syk and PI3K-p85 phosphorylation ↓	(Chiou et al. 2011)
2	IL-1β-induced chondrocyte	5, 10 or 15 μM	Caspase-3↓, caspase-9↓, caspase-3↓, MMPs↓, NF-κB signaling↓, Bcl-2↑, apoptosis↓	(Rao et al. 2018)
3	PC-3, DU-145	60 and 45 μM	TNFα↓, Bcl-2↓, NF-κB/p65↓, FADD↑, DR4↑, DR5↑, Fas↑, FasL↑, caspase-3↑, caspase-9↑	(Srinivasan et al. 2010)
4	SW480	5, 10, and 20 μM	Bcl-2↓, NF-κB signaling↓, Bax↑, caspase-3↑	(Jin et al. 2016a)
5	MCF-7	2.5, 5, and 10 μM	Autophagy↑, ROS↑, NOX4↑, DNA damage↑, γH_2AX↑, ATM↑, ATR↑, Chk1↑, Chk2↑	(Ren et al. 2016)
6	PC-3, C4-2B	20 μM	growth↓, metastasis↓, β-catenin↓, snail↓, slug↓, EMT↓, ΔΨm↓, cytochrome-*c*↑, PARP↑, caspase-3↑, caspase-9↑	(Das et al. 2014)
7	FST in male ICR strain mice	20, 40, and 60 mg/kg	Immobility time↑, swimming behavior time↓, 5-HT↑, 5-HIAA ↑, CRF↓, ACTH↓, corticosterone↓	(Yi et al. 2008)
8	MCF-7	10 μM	Activates ERα and ERβ (IC_{50}=1.03 μM and 24.6 μM,), binds to ERE(EC_{50}=3.68 μM and 6.88 μM,)	(Liu et al. 2014)
9	HuH-7,HepaRG	1-200μM	CYP3A4↓, IC_{50}=57.7 μM and 200μM	(Liu and Flynn 2015)
10	Liver microsome	100μM	Inhibits CYP1A2, CYP2C8, UGT1A1, and UGT1A7 with C_{max}/K_i values of 5.67, 26.21, 1.15, and 27.12, respectively. CYP2C19 is the main metabolic enzyme	(Shi et al. 2016)
11	LPS-induced RAW264.7	1, 3, 10, 30, and 100 μM	NO_2^- accumulation↓, IC_{50} = 23 μM	(Matsuda et al. 2009)
12	Osteoclasts	1, 10, 30, and 50 μM	TRAP↓, Cathepsin K↓, OSCAR↓, c-Fos↓, NFATc1↓, p-p38↓, p-ERK↓, p-JNK↓, p-p65↓, RANKL: OPG ratio↓, TNF-α↓, IL-6↓	(Kong et al. 2017)
13	$ALDH^+$, $ALDH^-$ cells	20 μM	Notch signaling↓, cell growth↓, apoptosis↑, EMT↓, mammosphere formation↓, E-cadherin↑	(Suman et al. 2013)
14	Eca9706	5, 10, and 20 μM	NF-κB signaling↓, PI3K/Akt signaling↓, proliferation↓, apoptosis↑	(Jin et al. 2016b)
15	CTPE	4 μM	Cell growth↓, Plac8↓, LC3B↓, autophagy↓, apoptosis↑, NF-κB↓, Bcl-2↓	(Pal et al. 2017)
16	SNU-1, SNU-16	Unknown	IC_{50} values for SNU-1is 53 μg/mL and for SNU-16 is 203μg/mL	(Yang et al. 1996)
17	HepG2	4-60 μM	Bax↑, Bid↑, p53↑, caspase-3↑, caspase-9↑, Bcl-2↓, Bcl-xL↓	(Yu et al. 2016)
18	PC-3, DU-145	60 and 45 μM	Survivin↓, Bcl-2↓, pEGFR↓, Raf-1↓, MEK-4↓, MEKK-1↓, pMEK1/2↓, Bax↑, cleaved caspase-3↑, JNK/c-Jun↑	(Kumar et al. 2010)
19	A549	5, 10, and 20 μM	ROS↑, ratio of LC3-II/LC3-I↑, autophagy↑, no changes in apoptosis.	(Hao et al. 2014)
20	Osteoblasts, osteoclasts	1 μM	Bone formation↑, bone resorption↓, collagen-I↑, BMP-2↑, osteocalcin↑, osteopontin↑, IGF-1↑, β-catenin↑, Runx-2↑, Osterix↑, OPG↑, the ratio of OPG/RANKL↑, RANKL↓, COX-2↓, ROS↓	(Zhai et al. 2017)
21	OVX rats	10 mg/kg body weight/day	Total bone mineral content↑, bone density↑, mineral apposition rate↑, bone biomechanical properties↑, microstructure and trabecular bone formation↑, osteogenic differentiation↑, PI3K/Akt signaling↑, adipogenic differentiation↓, GSK-3β/β-catenin signaling↓, Nrf2/HO-1 signaling↓	(Zhai et al. 2018)
22	HeLa	50 μM	Apoptosis↑, TRAIL-R2/DR5↑, ΔΨm depolarization	(Bronikowska et al. 2012)
23	LNCaP	50 μM	Augment the apoptotic percentage to 64.4 ± 0.5%	(Szliszka et al. 2011)
24	Intestinal microsomes	1-100μM	SN-38 glucuronidation↓, K_i = 5.8 μM	(Zhang et al. 2015)
25	IR-induced HFL-1, MRC-5	50 and 100 μM	COX-2↓, PGE2↓, 5-LOX↓, LTB4↓, NF-κB signaling↓	(Yang et al. 2011)
26	RBL-2H3	30, 60, and 100 μM	No effects on β-hexosaminidase, the antigen-induced degranulation↓, IC_{50} = 100 μM	(Matsuda et al. 2007)

The goal of radiotherapy is to kill cancer cells but not normal cells. However, it inevitably triggers irradiation in normal cells when the radiotherapy is conducted. Inflammation has been involved in limitation for radiotherapy (Molla and Panes 2007). Ionizing radiation (IR) might induce inflammation by accumulating reactive oxygen species (ROS), followed by activation of factors in signaling pathways, including cyclooxygenases-2 (COX-2) and 5-lipoxygenase (5-LOX). In HFL-1 and MRC-5 cells, psoralidin inhibited IR-induced inflammation and LTB4 production by regulating the activity of the NF-κB signaling pathway, but not of the PI3K/Akt signaling pathway. Furthermore, this anti-inflammatory effect of psoralidin was verified in IR-induced mice, as shown by suppression of pro-inflammatory cytokines expression (Yang et al. 2011) (Table).

The main PCL components, including psoralidin, corylifolinin, neobavaisoflavone, coryfolin, corylin, and bavachinin, have been

screened for inhibiting the activity of human carboxylesterase 1 (CES1). Psoralidin has been demonstrated to significantly inhibit CES1 activity in a concentration-dependent manner, leading to possible disruption of CES1-catalyzed metabolism of endogenous substances and xenobiotics (Sun et al. 2016). Protein tyrosine phosphatase 1B (PTP1B) is a negative mediator of insulin signaling and has become a therapeutic target for managing diabetes. Psoralidin significantly suppressed the activity of PTP1B dose-dependently with an IC_{50} value of 9.4±0.5 μM (Kim et al. 2005). β-Hexosaminidase has been considered as an antigen-IgE-induced degranulation marker of mast cells. The ethyl acetate fraction of methanol extract of PCL has been demonstrated to inhibit the release and activation of β-hexosaminidase in RBL-2H3 cells. However, psoralidin does not show any inhibitory effects on β-hexosaminidase but against the antigen-induced degranulation with IC_{50} value of 100 μM, stronger than those of anti-allergic agents, tranilast (IC_{50} = 282 μM) and ketotifen fumarate (IC_{50} = 158 μM) (Matsuda et al. 2007) (Table).

10. Concluding remarks

In this review, we focused on the biological activities of psoralidin, including anti-inflammatory, anti-cancer, anti-oxidative, estrogenic, neuroprotective, anti-bacterial, and anti-parasite activity. Interestingly, prenylated modification greatly increases the biological activity of psoralidin without any obvious adverse effects, compared to that of coumestrol. This makes psoralidin to be a good potential lead compound with valuable clinical perspective. Due to its estrogenic activity, psoralidin shows a significant potential for the management of some estrogen-related diseases, such as osteoporosis and cancers. However, the hydrophobicity and low bioavailability of psoralidin limit its clinical application.
More efforts are still needed for its underlying mechanism and clinical prospective.

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