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"Preparation and characterization of psoralea corylifolia linn. exosome-like nanovesicles"

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1. Introduction

Psoralea corylifolia L. is a plant species belonging to the genus psoralea in the family Fabaceae. It contains a variety of bioactive compounds, including coumarins (psoralen, isopsoralen, psoralidin, etc.), flavonoids (psoralen A, psoralen B, isopsoralen flavone, etc.), monoterpenoid phenols (psoralenol, 2,3-epoxy psoralenol, etc.), as well as other volatile oils, fixed oils, saponins, polysaccharides, benzofuran derivatives, and trace elements[1, 2]. Psoralenol, one of the active components in psoralea corylifolia, is able to activate collagen synthesis-related signaling pathways in skin cells, such as the transforming growth factor-β (TGF-β) pathway and the insulin-like growth factor-1 (IGF-1) pathway, thereby promoting collagen synthesis and cell proliferation[3]. Additionally, it is also capable to inhibit the activity of collagen-degrading enzymes, such as matrix metalloproteinases (MMPs), reducing collagen loss[4, 5]. Moreover, through acting on sebaceous gland cells, psoralenol inhibited their proliferation, regulating their metabolism, and modulating hormone levels, thereby reducing excessive sebum secretion[6, 7]. Meanwhile, psoralenol has demonstrated inhibitory effects on various skin surface microorganisms, including Propionibacterium acnes, Staphylococcus aureus, Staphylococcus epidermidis, Candida albicans, and fungi[8, 9]. However, psoralen and isopsoralen, which are present in psoralea corylifolia, exhibit phototoxicity. When in contact with the skin and exposed to ultraviolet light (especially UVA), they may cause phototoxic reactions such as skin erythema, itching, vesicles, and even hyperpigmentation[10]. In addition, neopsoralen, a flavonoid component, has no direct reports of photosensitivity, but it may enhance skin irritation or allergy risks when acting synergistically with psoralen and other coumarin components. Especially, psoralidin, which coexists with psoralen and isopsoralen in psoralea corylifolia, has been shown to potentially induce hepatotoxicity through mechanisms such as affecting mitochondrial function. Given the strong efficacy and potential toxicity of psoralea corylifolia, its extracts can be considered a double-edged sword.

In contrast to the potentially toxic components that may be present in psoralea corylifolia extracts, psoralea corylifolia exosome-like nanovesicles (PCLELNVs) are prepared through strict screening and processing, resulting in relatively pure components and lower toxicity[11]. Compared with plant extracts, plant-derived exosome-like nanovesicles exhibit good biocompatibility, allowing better interaction with human cells and tissues and reducing damage to normal cells. They also have a relatively stable structure, which enables them to

maintain their bioactivity and functionality over a longer period, facilitating storage and transportation. The bioactive substances carried by plant-derived exosome-like nanovesicles are relatively singular and well-defined, making them easier to control in quality and standardize in production. In contrast, plant extracts contain a complex mixture of chemical components, and there may be significant variations in the components and content between different batches, which poses challenges for quality control and efficacy assessment[12].

In this study, PCLELNVs were prepared using ultracentrifugation and size exclusion chromatography. The content of allergens, psoralenol content, cytotoxicity, and anti-inflammatory effects were evaluated. The results showed that PCLELNVs have potential applications in the fields of pharmaceuticals and daily-use chemicals.

2. Materials and Methods

2.1 Preparation and characteristics of PCLELNVs

As shown in Figure 1, the seed parts of psoralea corylifolia (Yunnan Xishuangbanna, China) were first washed with distilled water to remove dust and soil. Subsequently, a blender was used to extract the components with PBS buffer (Wuhan Servicebio Technology, China) as the solvent. The mixture was then centrifuged sequentially at 700g for 10 minutes, 2,000g for 20 minutes, and 10,000×g for 30 minutes respectively to remove large plant debris. This was followed by ultracentrifugation at 3,000×g for 20 minutes to remove additional impurities. A centrifugal filter (Millipore, USA) was used to concentrate the extract, which was then subjected to size-exclusion chromatography (Beijing Enzecan Technology, China) for the separation of exosome-like nanovesicles (PCLELNVs). The isolated PCLELNVs were resuspended in PBS, sterilized by filtration through a 0.22μm filter (Merck Millipore, USA), and stored at -80°C for later use.

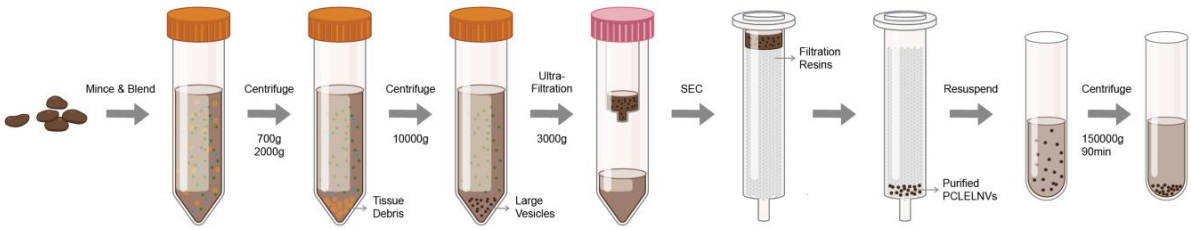


Figure 1. Schematic diagram of the extraction process for PCLELNVs

The particle size and concentration of PCLELNVs were measured using Resistive Pulse Sensing (RPS, Zhuhai Truth Optics Technology, China), and their morphology was observed using Transmission Electron Microscopy (TEM, Hitachi, Japan).

2.2 Quantification of psoralen and allergenic compounds

Psoralidin, neobavaisoflavone, isopsoralen, and psoralen are four compounds in psoralea corylifolia seeds that have potential skin irritation and toxicity. Therefore, it is necessary to test their content. In the HPLC test, the chromatographic column (Agilent Technologies, USA) used was a C18 column (100 mm × 4.6 mm × 5 μm) or an equivalent column. The gradient elution program for the mobile phase (A: acetonitrile, B: 0.1% acetic acid aqueous solution) was as follows: 0-11 min: 40% A, 60% B; 12 min: 40% → 70% A, 60% → 30% B; 13-15 min: 70% → 90% A, 30% → 10% B; 16 min: 90% → 40% A, 10% → 60% B.

The flow rate was 1.0 mL/min, the detection wavelength was 246 nm, the column temperature was 30°C, and the injection volume was 10 μL[13].

For the psoralen (with a purity of ≥98% (HPLC), Beijing Solarbio Science & Technology, China) content test, the chromatographic column used was AQ-C18, 2.7 μm, 100 × 4.6 mm. The flow rate was 0.6 mL/min, and the gradient elution for the mobile phase (A: water, B: methanol) was as follows: 0-4 min: 50% A, 50% B; 4-5 min: 50% → 10% A, 50% → 90% B; 5-16 min: 10% A, 90% B; 16-17 min: 10% → 50% A, 90% → 50% B; 17-20 min: 50% A, 50% B. The column temperature was 35°C, the injection volume was 5 μL, and the detection wavelength was 260 nm[14].

2.3 In-vitro antioxidant assay

The ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) scavenging assay is based on the interaction between antioxidants and pre-generated ABTS radical cations ($ABTS^{\bullet+}$). $ABTS^{\bullet+}$ has characteristic absorption peaks at 414, 417, 645, 734, and 815 nm. Since the PCLELNVs samples are yellow and interfere with absorption below 550 nm, the absorption peak at 730-734 nm is less affected by the samples and is therefore more commonly used[15]. Following the reference method, the absorbance of the mixed solution at 734 nm was measured immediately after the reaction. The ABTS scavenging rate of the samples was calculated by comparing the absorbance changes of $ABTS^{\bullet+}$ (98%, Beijing Solarbio, China)before and after the reaction[16].

2.4 Cytotoxicity assay

Hacat cells (Chinese Academy of Sciences, China) are an immortalized human keratinocyte cell line originally isolated from normal human skin. They are commonly used in research on skin diseases, drug screening, skin toxicity testing, and skin barrier function[17]. HeLa cells (Chinese Academy of Sciences, China) are derived from the cervical cancer tissue of a patient named Henrietta Lacks. This cell line has typical cancer cell characteristics, such as unlimited proliferation, genomic instability, and tolerance to environmental stress. HeLa cells are commonly used in research on cell biology, molecular biology, genetics, and cancer biology[18]. HK-2 cells (Chinese Academy of Sciences, China) are a proximal tubular epithelial cell line isolated from normal human renal cortex. This cell line has high proliferative capacity and good cell function, making it suitable for research on renal physiology and pathology. HK-2 cells are commonly used in research on kidney diseases, drug screening, renal toxicity testing, and renal regenerative medicine[19].

The CCK-8 (Cell Counting Kit-8) reagent is based on the reduction reaction of WST-8. Dehydrogenases in the mitochondria of living cells can reduce WST-8 to a water-soluble orange-yellow formazan dye, the amount of which is positively correlated with the number of living cells. The greater the cytotoxicity, the less formazan is generated, and the lighter the color. Following the reference method, the blank control group did not add samples. After incubation at 37°C for 2h, the absorbance was measured at 450nm with a multifunctional microplate reader (M200 Pro, Molecular Devices, USA) to calculate cell viability [20].

2.5 Inflammatory cytokine inhibition assay

Interleukin-6 (IL-6) is a multifunctional pro-inflammatory cytokine secreted by monocytes, macrophages, keratinocytes, and others, participating in acute inflammatory responses and immune regulation. Its functions include promoting B cell differentiation, inducing acute phase protein synthesis, and participating in cell proliferation and differentiation. In acne and psoriasis, IL-6 activates the NF-κB pathway to induce keratinocyte proliferation, exacerbating inflammation. Moreover, IL-6 promotes angiogenesis and collagen deposition, accelerating wound healing. However, long-term high expression can lead to skin edema and erythema [21]. Interleukin-8 (IL-8) is a potent chemokine mainly secreted by monocytes, endothelial cells, and keratinocytes. It plays a central role by attracting neutrophils, eosinophils, and others to the site of inflammation. In acne, psoriasis, and contact dermatitis, IL-8 activates chemokine receptors (such as CXCR1/2) to promote neutrophil infiltration, worsening the inflammatory

response. IL-8 can reduce antimicrobial peptide levels, weakening the skin's anti-infection ability. It also induces the expression of matrix metalloproteinases (MMPs), accelerating collagen degradation[22]. Interleukin-1α (IL-1α) is a member of the IL-1 family, secreted by activated keratinocytes, macrophages, and others. It is a core initiator of inflammatory responses, activating T cells and inducing the release of other pro-inflammatory cytokines (such as IL-6, TNF-α). IL-1α activates the NF-κB pathway to promote the secretion of TNF-α, IL-6, and others, exacerbating inflammatory skin diseases like acne and psoriasis. In acne, IL-1α stimulates excessive keratinocyte proliferation, leading to hyperkeratosis of the follicular infundibulum and comedone formation. Chronic IL-1α elevation can inhibit epidermal stem cell activity, reducing skin barrier repair capacity, accelerating photoaging, and wrinkle formation[23].

Studies have shown that psoralen can significantly inhibit the expression of inflammatory cytokines, including IL-6, IL-8, and IL-1α. These cytokines play important roles in various inflammatory diseases, such as psoriasis, rheumatoid arthritis, and inflammatory bowel disease[24]. Following the ELISA kit (Wuhan Cusabio, China) instructions, Hacat cells were stimulated with 100 ng/mL LPS (lipopolysaccharide) as a model group to enhance the expression of inflammatory cytokines. Under different sample concentrations, the model was treated with drugs to test the content of each inflammatory cytokine (in pg/mL).

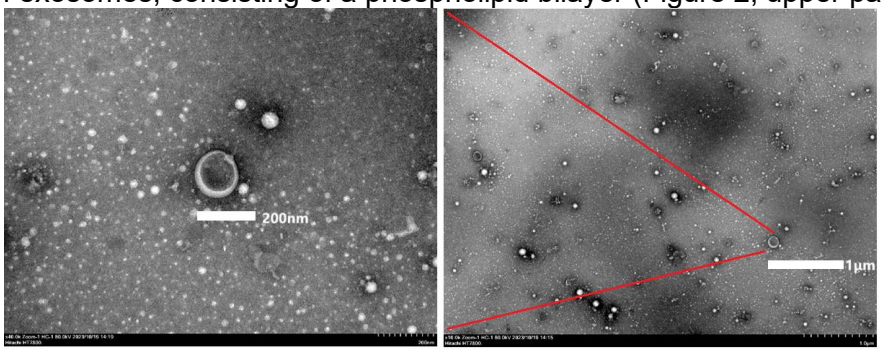
2.6 Statistical analysis

Data analysis was performed using SPSS 28.0. Results are presented as the mean ± standard deviation (SD). Comparisons between groups were analyzed using paired sample t-tests, with all statistical analyses being two-tailed. A significant difference was considered when $P<0.05$, an extremely significant difference when $P<0.01$, and a highly significant difference when $P<0.001$. These are indicated by “”, “”, and “” in the figures, respectively. When $P\geq0.05$, no significant difference was observed, indicated by the symbol “n.s.” in the figures.

3. Results

3.1 Morphology and particle size of PCLELNVs

After diluting PCLELNVs 100 times with PBS buffer solution for testing, the average particle size obtained from the size distribution was approximately 76 nm, with a D90 particle size value of 102 nm. The purity was calculated to be 3.47×10^{11} particles/mL (Figure 2, lower panel). These plant-derived extracellular vesicles have a vesicular structure composed of a lipid bilayer membrane, appearing as saucer-like or cup-shaped structures. This structure is similar to that of exosomes, consisting of a phospholipid bilayer (Figure 2, upper panel).



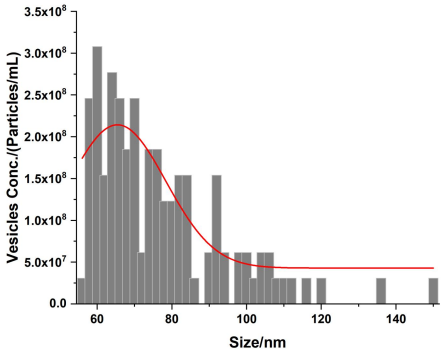


Figure 2. TEM morphology image (upper panel) and RPS test image (lower panel).

3.2 Content of allergen and psoralenol

In the HPLC chromatogram of the Psoralea corylifolia standard solution, the retention times for psoralen, isopsoralen, neopsoralen, and psoralidin were 5.978 min, 6.351 min, 9.194 min, and 9.788 min, respectively. The detected concentrations of these four substances were all <0.00006% (w/w), indicating that the sample PCLELNVs contain virtually no allergens. In the HPLC test, the retention time for psoralenol was 12.741 min (Figure 3), and the calculated content of psoralenol monomer in PCLELNVs was 65 mg/L.

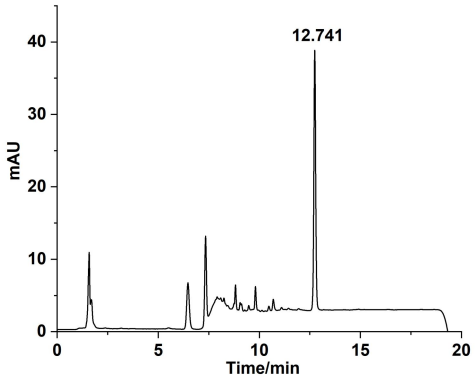


Figure 3. HPLC chromatogram of psoralenol in PCLELNVs

3.3 ABTS•⁺ Scavenging Activity

The IC_{50} value calculated from the ABTS•⁺ scavenging activity curve (Figure 4) was 3.17% (w/w). This demonstrates that PCLELNVs can scavenge ABTS•⁺ at low conc. and exhibit good antioxidant effects.

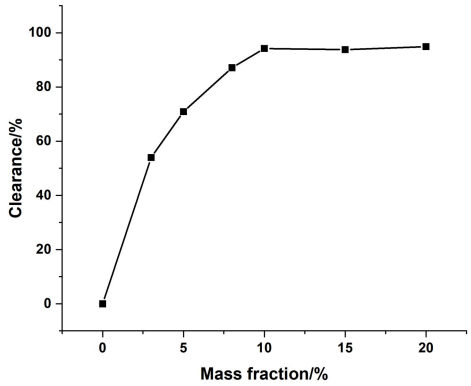


Figure 4. ABTS•⁺ ccavenging activity curve

3.4 Cytotoxicity

As shown in Figure 5, within a certain concentration range (≤230 μL/mL), PCLELNVs exhibited almost no cytotoxicity towards HK-2 (human renal tubular epithelial cells) and Hacat (human immortalized epidermal cells) (cell viability > 95%), while they showed inhibitory activity against HeLa (cervical cancer cells) in a concentration-dependent manner. This indicates that PCLELNVs have selective inhibitory activity against different cell types.

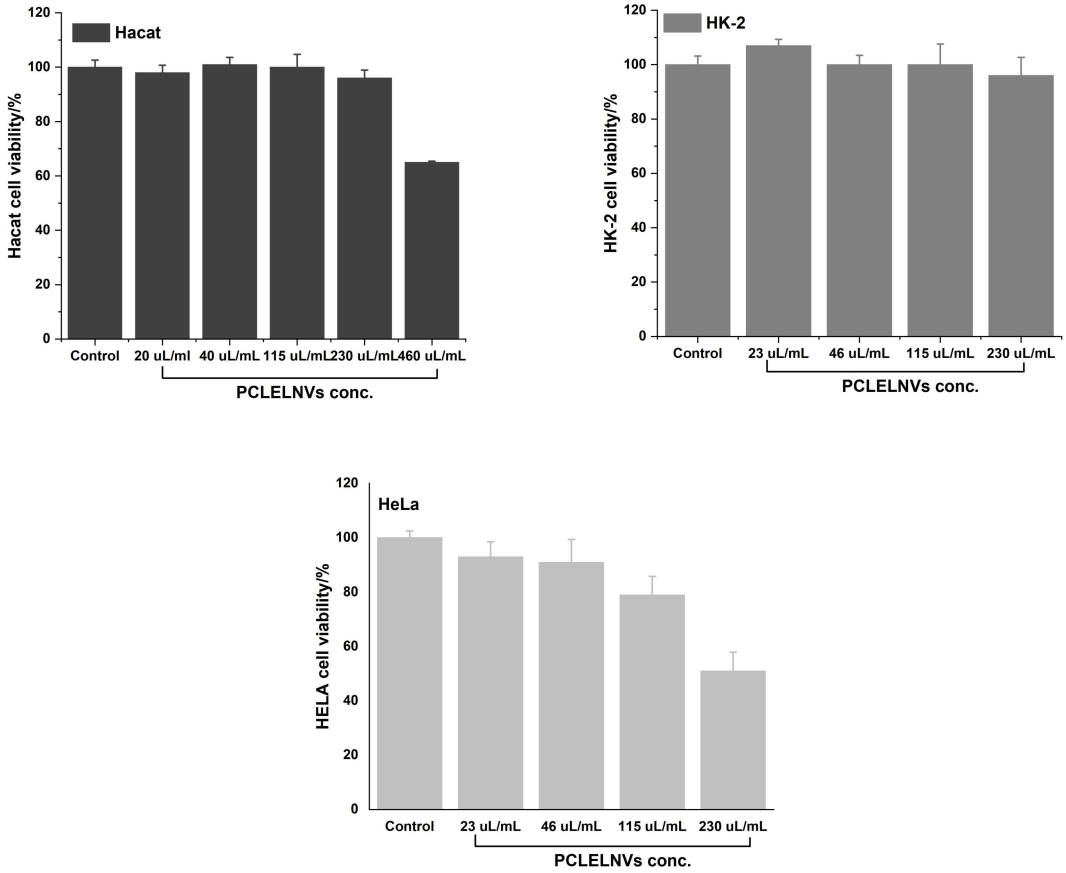


Figure 5. Schematic diagram of cytotoxicity for various cells

3.5 Anti-inflammatory effects

Based on the cytotoxicity test results of Hacat cells, the levels of three inflammatory cytokines (IL-6, IL-8, and IL-1α) were measured using ELISA kits at different concentrations of PCLELNVs. As shown in Figure 6, compared to the blank group, the levels of inflammatory cytokines were significantly increased in the model group ($P<0.05$), confirming the validity of the model. The inhibitory effects of PCLELNVs on these cytokines were concentration dependent. At a concentration of 40 μL/mL, PCLELNVs showed no significant inhibitory effect on IL-1α ($P>0.05$), but exhibited extremely significant inhibitory effects on IL-6 and IL-8 ($P<0.001$). When the concentration was ≥115 μL/mL, PCLELNVs showed significant inhibitory effects on IL-1α ($P<0.05$) and extremely significant inhibitory effects on IL-6 and IL-8 ($P<0.001$). This indicates that PCLELNVs have anti-inflammatory effects at certain vesicle concentrations.

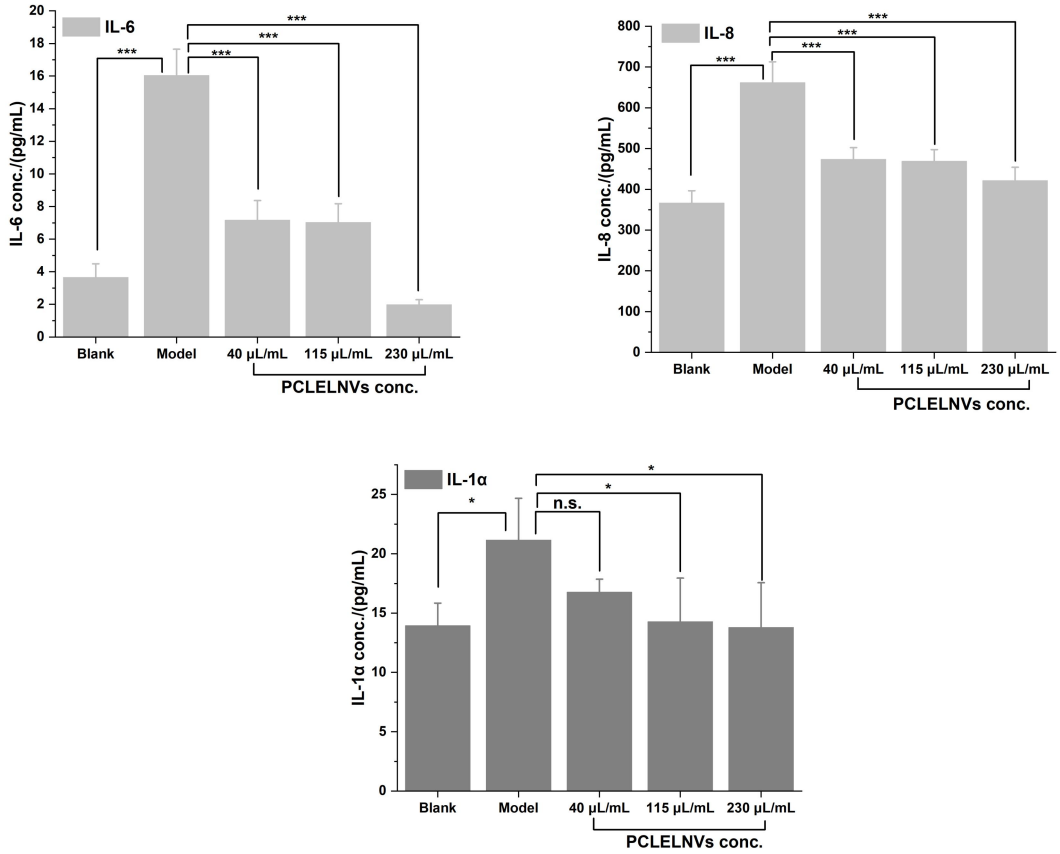


Figure 6. Schematic Diagram of Inhibitory Effects of PCLELNVs on Three Inflammatory Cytokines at Different Concentrations

4. Discussion

Exosomes-like nanovesicles (PCLELNVs) were extracted and separated from Psoralea corylifolia seeds sourced from Xishuangbanna, Yunnan, using ultracentrifugation and size exclusion chromatography. The resulting vesicles have a bilayer phospholipid structure resembling liposomes, with an average particle size of approximately 76 nm, classifying them as nanoscale vesicles, and a concentration of 3.47×10^{11} particles/mL. High-performance liquid chromatography (HPLC) analysis revealed a psoralenol content of 65 mg/L. In vitro antioxidant assays demonstrated that PCLELNVs can scavenge ABTS radicals at low concentrations. This effect may be attributed to the bioactive compounds in Psoralea corylifolia (such as psoralenol) that can neutralize free radicals by donating electrons or hydrogen atoms, thereby inhibiting the propagation of free radical chain reactions[25].

In toxicity tests, PCLELNVs exhibited no cytotoxicity towards HK-2 (human renal tubular epithelial cells) and Hacat (human immortalized epidermal cells), but showed inhibitory activity against HeLa (cervical cancer cells). HK-2 and Hacat cells are immortalized cell lines derived from normal tissues. PCLELNVs may specifically recognize cancer cells through surface proteins or nucleic acid molecules, while normal cells lack the corresponding targets. Normal cells may also more efficiently metabolize the active components within the vesicles through pathways such as the CYP enzyme system, thereby reducing toxic accumulation[26]. As cancer cells, HeLa cells may be targeted by PCLELNVs through mitochondrial pathways (e.g., activation of Bax and inhibition of Bcl-2) or death receptor pathways (e.g., the Fas/FasL system) to induce apoptosis. The bioactive components in PCLELNVs (such as psoralenol) may inhibit proliferation-related proteins in HeLa cells (e.g., Cyclin D1/E/A), leading to G1/S phase arrest[27].

In the anti-inflammatory cytokine inhibition experiments, PCLELNVs showed concentration-dependent inhibitory effects on inflammatory cytokines produced by LPS-stimulated Hacat cells. This effect may be mediated through the activation of the TGF-β1/Smad4 signaling pathway to suppress inflammatory responses. TGF-β1 has anti-inflammatory properties and can inhibit the production of various inflammatory cytokines, including IL-6, IL-8, and IL-1α. Additionally, it can modulate the functions of immune cells to reduce the production of inflammatory cytokines. For example, it can inhibit the activation of immune cells such as macrophages and monocytes, thereby reducing the secretion of inflammatory cytokines by these cells[28].

5. Conclusion

Psoralea corylifolia Exosome-like Nanovesicles (PCLELNVs) were prepared with an average particle size of 76 nm and a vesicle concentration of 3.47×10^{11} particles/mL. These vesicles exhibited a distinct lipid bilayer membrane structure, resembling a cup-shaped morphology. In physicochemical tests, high-performance liquid chromatography (HPLC) was used to determine the content of psoralen, which was found to be 65 mg/L. The $ABTS^{\bullet+}$ scavenging activity test showed an IC_{50} value of 3.17% (w/w), indicating the antioxidant properties of PCLELNVs. CCK-8 cytotoxicity and inflammatory factor inhibition tests demonstrated that within a certain concentration range, PCLELNVs exhibited inhibitory effects on cervical cancer cells, while being non-toxic to human epidermal cells and renal tubular epithelial cells in a concentration-dependent manner. When the concentration of PCLELNVs was ≥115 μL/mL, they showed significant inhibitory effects on IL-1α ($P<0.05$) and extremely significant inhibitory effects on IL-6 and IL-8 ($P<0.001$). Therefore, PCLELNVs have potential applications in selectively inhibiting harmful cells, as well as in antioxidant and anti-inflammatory functions, and can be further explored in the fields of pharmaceuticals and daily chemical products.

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