Antitumor, Anti-inflammatory, and Antibacterial Effects of *Poria cocos* Polysaccharide and Its Molecular Mechanisms

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Abstract This review summarizes recent research progress on *Poria cocos* polysaccharide (PCP) in the areas of anticancer, anti-inflammatory, and antibacterial effects. It focuses on elucidating its mechanisms of action and highlighting the current limitations in research. This aims to provide a reference for the further development and utilization of PCP.

Key words *Poria cocos*, *Poria cocos* polysaccharide, Immunomodulation, Pharmacological activity

1 Introduction

Poria cocos, the dried sclerotium of the fungus *P. cocos* belonging to the Polyporaceae family, boasts a long history of application in traditional medicine across East Asian countries such as China, Japan, and South Korea. *P. cocos* (Schw.) Wolf is a representative traditional Chinese medicinal herb categorized under "promoting diuresis and eliminating dampness". It was classified as a "superior-grade" medicinal in the *Shennong Bencao Jing* (*Shennong Classic of Materia Medica*), which documented its efficacy in treating symptoms such as rebellious qi in the chest and hypochondrium, anxiety, fear, palpitations, epigastric pain, alternating chills and fever, restlessness, cough, dry mouth and tongue, and promoting urination. With the advancement of modern separation techniques, researchers have isolated diverse components from *P. cocos*, including polysaccharides, triterpenoids, sterols, and fatty acids. Among these, *P. cocos* polysaccharide (PCP) has emerged as a research hotspot due to its broad spectrum of biological activities. As the principal active constituent of *P. cocos*, PCP constitutes approximately 3% -7% of the dry weight and exhibits multiple pharmacological effects, including anticancer, anti-inflammatory, antibacterial, and immunomodulatory activities.

PCP is a heteropolysaccharide primarily composed of a β-(1→3)-D-glucan backbone with β-(1→6)-D-glucose side chains. Its molecular weight ranges from 10 to 1 000 kDa, and its structure varies depending on the extraction method (e.g., hot water, alkaline, enzymatic extraction) and geographical origin[1]. In recent years, significant progress has been made in research on the pharmacological effects of PCP, with particularly in-depth studies focusing on its mechanisms of action in the fields of anticancer, anti-inflammatory, and antibacterial activities. Based on the latest domestic and international research, this article systematically reviews the pharmacological effects and mechanisms of PCP, aiming to provide a theoretical foundation for its clinical application and the development of new drugs.

2 Antitumor effects

2.1 Inhibition of cancer cell proliferation Cancer stands as one of the leading causes of death worldwide, posing a severe threat to human life, health, and quality of life[2]. As a natural antitumor agent, PCP exerts its anticancer effects primarily through three key pathways: first, inhibiting tumor cell proliferation and halting their uncontrolled division and growth; second, inducing tumor cell apoptosis, thereby promoting the programmed death of abnormal cells; and third, suppressing tumor cell migration and invasion, reducing their ability to spread to surrounding tissues. It is a highly promising natural candidate for anticancer therapy.

Dysregulation of the cell cycle is a hallmark characteristic of cancer cells. PCP inhibits cancer cell proliferation by arresting the cell cycle progression, a mechanism primarily involving the modulation of cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors (CKIs)[3]. The G_1 phase serves as a critical "checkpoint" in the cell cycle. The Cyclin D1 protein binds to CDK4/6 proteins to form a complex that promotes the transition of cells from the G_1 phase into the S phase. PCP can downregulate the expression levels of Cyclin D1 and CDK4 proteins while upregulating the expression of CKIs (such as p21 and p53), resulting in G1/S phase arrest. Zhang *et al.* treated human breast cancer MCF-7 cells with different concentrations of PCP for 72 h and found that in the group treated with 80 μg/mL PCP, Cyclin D1 protein expression decreased by 55%, Cyclin E protein expression decreased by 52%, and the expression of the anti-apoptotic protein Bcl-2 decreased by 60%. Flow cytometry results indicated that the proportion of cells arrested in the G_1 phase reached 90%, demonstrating a significant inhibition of cell cycle progression ($P < 0.01$)[3]. These results indicate that PCP effectively arrests the cell cycle progression and inhibits the abnormal proliferation of hu-

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man breast cancer MCF-7 cells by modulating the Cyclin-CDK complexes and CKIs expression. The

G_2 phase is a critical stage for cells to enter the mitotic (M) phase. Cyclin B1 protein binds to CDK1 protein to form the "Maturation-Promoting Factor" (MPF), which drives cells into the M phase. PCP can inhibit the activation of the PI3K/Akt signaling pathway, thereby reducing the expression of Cyclin B1 protein and leading to G_2/M phase arrest. Tang Enhong *et al.* treated human cervical cancer HeLa cells with different concentrations of PCP (30, 40, 50 mg/mL) and observed significantly reduced cell invasion and migration capabilities. Furthermore, PCP treatment increased the apoptotic rate, decreased the proportion of S-phase cells, and induced arrest at the G_2/M phase. The expression levels of Cleaved-Caspase 3, Cleaved-Caspase 8, Cleaved-Caspase 9, and Bax proteins were significantly increased, while the expression levels of Bcl-2, MMP-9, VEGFA, and p-ERK1/2 proteins were significantly decreased[4]. These results demonstrate that PCP arrests HeLa cells at the G_2/M phase and effectively inhibits their proliferation and migration capabilities.

2.2 Induction of cancer cell programmed cell death Programmed cell death (PCD) is a crucial mechanism for multicellular organisms to maintain homeostasis. It involves the "active removal" of senescent, damaged, or abnormal cells to make space for new cells or to prevent the spread of pathological cells, such as cancer cells. It is fundamentally distinct from cell necrosis. The main types include apoptosis, pyroptosis, and ferroptosis. PCP can induce cancer cell apoptosis through multiple pathways, including the activation of the mitochondrial pathway and the death receptor pathway, and it can also induce ferroptosis[5-7].

Mitochondria serve as the "control center" for apoptosis. The ratio of Bax (pro-apoptotic protein) to Bcl-2 (anti-apoptotic protein) determines mitochondrial membrane permeability. PCP can upregulate Bax expression and downregulate Bcl-2 expression, thereby increasing mitochondrial membrane permeability. This leads to the release of cytochrome c (Cyt c), which activates Caspase-9 (an initiator caspase) and subsequently Caspase-3 (an effector caspase), ultimately inducing apoptosis. Zhang *et al.* treated MCF-7 cells with PCP (400 μg/mL) for 72 h and found that the expression of the anti-apoptotic protein Bcl-2 was significantly reduced (by approximately 60% compared to the control group), while the expression of the pro-apoptotic protein Bax showed no significant change. The downregulation of Bcl-2 resulted in a significant increase in the Bax/Bcl-2 ratio, directly disrupting mitochondrial membrane stability[3]. These results indicate that PCP can disrupt the mitochondrial membrane potential balance in human breast cancer MCF-7 cells by modulating Bcl-2 family protein expression, promote cytochrome c release, activate the caspase cascade, and ultimately induce tumor cell apoptosis.

Death receptors, such as the TNF-α receptor and Fas receptor, initiate signaling cascades upon binding to their specific ligands. This leads first to the activation of Caspase-8, which then triggers the activation of the downstream effector Caspase-3, ultimately inducing programmed cell apoptosis. Chen *et al.* found that PCP, as a bioactive substance, significantly downregulated the expression levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β while simultaneously upregulating the secretion of the anti-inflammatory cytokine IL-10[6]. These results demonstrate that PCP can effectively exert antitumor effects by modulating cytokine levels, highlighting the multi-target and holistic regulatory advantages of natural polysaccharides in antitumor therapy.

Ferroptosis is a recently discovered novel form of cell death characterized by lipid peroxidation and reactive oxygen species (ROS) accumulation. Li B *et al.* found 30 common ferroptosis-targeting genes and 13 core genes shared between PCP and ovarian cancer. Further enrichment analysis suggested that these core genes may function synergistically through various ferroptosis-related biological processes and signaling pathways (including anti-inflammatory effects, immunomodulation, and microenvironment regulation)[7]. These results indicate that PCP may trigger ferroptosis by interfering with the expression of key molecules in iron metabolism, inducing iron ion accumulation and an imbalance in lipid peroxidation reactions within tumor cells.

2.3 Inhibition of cancer cell migration and invasion Migration and invasion are critical steps in cancer metastasis, and the epithelial-mesenchymal transition (EMT) is a key molecular mechanism underlying this process (where epithelial cells lose their polarity and acquire mesenchymal cell characteristics). PCP can inhibit cancer cell migration and invasion by suppressing the EMT process and downregulating *SATB1* gene expression.

Hallmarks of EMT include the downregulation of E-cadherin (an epithelial marker) and the upregulation of N-cadherin and Vimentin (mesenchymal markers). Chen *et al.* treated colorectal cancer cells with PCP and found a significant increase in the expression level of the epithelial marker protein E-cadherin. This effectively blocked the key biological process of epithelial-mesenchymal transition (EMT) in tumor metastasis, thereby significantly reducing the migration and invasion capabilities of cancer cells[6]. The *SATB1* gene plays a critical role in the invasion and metastasis of breast cancer. PCP can inhibit the expression of the *SATB1* gene, effectively controlling breast cancer metastasis. Hu Kang *et al.* found that PCP and its sulfated derivatives effectively inhibited *SATB1* gene expression and demonstrated potent inhibitory effects on the invasion capability of human breast cancer MDA-MB-231 cells[8]. These results indicate that PCP can inhibit the migration and invasion capabilities of cancer cells by modulating the key protein *SATB1*.

3 Anti-inflammatory effects

Inflammation is a defensive response of the body to injury or infection, but chronic inflammation can lead to various diseases (such as colitis, arthritis, cardiovascular diseases). The anti-inflammatory effects of PCP are primarily associated with the inhibition of

inflammatory signaling pathways, reduction of inflammatory cytokine release, and antioxidant activity, among others[9].

3.1 Inhibition of inflammatory signaling pathways Nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) are key signaling pathways in inflammatory responses. PCP can reduce the release of inflammatory cytokines (such as IL-1β, IL-6, TNF-α) by inhibiting these pathways. The NF-κB protein typically exists in the cytoplasm as a "p65/p50" heterodimer bound to its inhibitory protein, IκBα. Upon inflammatory stimulation, IκBα is phosphorylated and degraded, allowing NF-κB to translocate into the nucleus and initiate the transcription of inflammatory cytokine genes. PCP can inhibit the phosphorylation of IκBα, thereby preventing the nuclear translocation of NF-κB. Sun *et al.* found that a PCP fraction (PCP-W1), composed of specific sugar units including galactose and glucose and exhibiting a randomly coiled branched conformation, possesses potent immunomodulatory activity. This fraction binds to the hydrophobic site of the Toll-like receptor 4 (TLR4)/myeloid differentiation protein 2 (MD2) complex via its galactose chains, modulating the TLR4/MD2/NF-κB pathway. This leads to reduced release of pro-inflammatory factors NO, IL-6, IL-1β, and TNF-α, thereby exerting anti-inflammatory effects. Further molecular dynamics simulation experiments confirmed the strong stability of the TLR4-MD2-PCP-W1 complex, providing experimental support for structure-activity relationship studies of PCP's anti-inflammatory action[10]. These results demonstrate that PCP exerts anti-inflammatory effects by specifically binding to the TLR4/MD2 complex, effectively blocking the activation of the NF-κB signaling pathway.

3.2 Inhibition of MAPK phosphorylation and reduction of inflammatory cytokine release MAPK encompasses three subfamilies: p38, JNK, and ERK. Their phosphorylation can activate the transcription of inflammatory cytokines. PCP can inhibit MAPK phosphorylation, thereby reducing the release of inflammatory cytokines. Zhou *et al.* found that PCP significantly reduced neuronal damage in a rat model of Alzheimer's disease induced by D-galactose combined with aluminum chloride by modulating the MAPK/NF-κB signaling pathway[11]. Song *et al.* found that PCP inhibited RANKL-induced osteoclastogenesis by suppressing the activity of NFATc1 protein (nuclear factor of activated T cells 1, a key calcium-dependent transcription factor) and the phosphorylation of ERK and STAT3 proteins, thereby exerting anti-rheumatoid arthritis effects[12]. These results indicate that PCP can synergistically modulate inflammatory responses through multiple targets and pathways. It not only inhibits the activation of the NF-κB signaling pathway but also suppresses the phosphorylation of proteins associated with the MAPK pathway, thereby effectively reducing the release of multiple pro-inflammatory cytokines.

3.3 Antioxidant activity Sepsis often triggers acute kidney injury (AKI), a condition whose core pathological features are oxidative damage and inflammatory response. PCP can alleviate this injury through the synergistic effects of its antioxidant and anti-inflammatory activities. In an LPS-induced mouse inflammatory model, PCP inhibited the activation of NADPH oxidase, thereby reducing reactive oxygen species (ROS) generation. It also reversed the LPS-induced decline in glutathione (GSH) and adenosine triphosphate (ATP) levels and reduced caspase-3/7 activity, thus exerting antioxidant effects. On the other hand, PCP significantly reduced the levels of inflammatory cytokines such as IL-1β, IL-6, MCP-1, and TNF-α in serum and renal tissues. By inhibiting LPS-mediated phosphorylation of IκBα, it blocked NF-κB activation, thereby exerting anti-inflammatory effects. Further research revealed that LPS-activated NF-κB signaling participates in NADPH oxidase activation, indicating that PCP can achieve synergistic antioxidant and anti-inflammatory effects by modulating the NF-κB-NOX4 pathway, thereby mitigating renal injury[13]. These results demonstrate that PCP not only intervenes synergistically through multiple pathways at the core links of inflammation and oxidative stress but also plays an integrative regulatory role within cellular signaling networks.

4 Antibacterial effects

Bacterial infections are common clinical diseases. With the increasing prevalence of antibiotic resistance, the search for natural antibacterial agents has become a research hotspot. PCP exhibits good inhibitory effects against various bacteria (such as *Staphylococcus aureus*, *Escherichia coli*, *Helicobacter pylori*), and its mechanisms are primarily related to disrupting cell membrane integrity, inhibiting biofilm formation, and affecting bacterial metabolism. Carboxymethyl *P. cocos* polysaccharide (CMPCP), modified by carboxymethylation, possesses a strong ability to inhibit bacterial biofilm formation, and this effect is enhanced with increasing degrees of substitution. Bie Meng *et al.* found that high-substituted CMPCP achieved an inhibition rate of 60.91% against *S. aureus*, significantly outperforming low-substituted CMPCP. It can disrupt the bacterial cell membrane through a high absolute Zeta potential and appropriate particle size dynamics (initially increasing then decreasing), indirectly inhibiting biofilm formation[14]. These results indicate that water-soluble CMPCP with different degrees of substitution exhibit certain antibacterial activities *in vitro*, and the antibacterial effect tends to increase gradually with higher substitution degrees. The inhibition against *S. aureus* and *E. coli* is particularly significant, demonstrating that chemical modification can effectively enhance its biological activity.

PCP may exert antibacterial effects by interfering with bacterial energy metabolism or carbon source utilization, reducing the production of key metabolites, and thereby inhibiting bacterial proliferation. Bai Pengbo *et al.* extracted PCP using an organic solvent method with 4 ℃, 0.30 mol/L NaOH immersion. They then prepared a composite membrane hydrogel by combining it with food-grade film-forming materials such as sodium alginate and hydroxypropyl methylcellulose. This composite membrane exhibi-

ted significant antibacterial effects against *E. coli* and *S. aureus*[15]. Wang *et al.* found that carboxymethyl *P. cocos* polysaccharide (CMPCP) mixed with lotus seedpod oligomeric proanthocyanidins (LSPC) at specific ratios exhibited good synergistic antibacterial effects against *E. coli* 10899. Low concentrations of LSPC could enhance the antibacterial activity of CMPCP, with the synergistic effect being particularly prominent when the CMPCP concentration was below a critical value of 1.35 mg/mL[16]. These results suggest that the composite system of CMPCP and LSPC can more readily insert into bacterial membrane structures, leading to membrane potential imbalance and ion leakage, thereby disrupting cell membrane integrity and exerting potent antibacterial effects.

5 Prospects

As a natural active ingredient, PCP possesses various pharmacological effects including anticancer, anti-inflammatory, and antibacterial activities. It is non-toxic, has no significant side effects, and is widely available, indicating promising development prospects. However, current research still faces the following limitations: Existing studies on PCP are predominantly *in vitro* cellular or animal experiments; clinical studies are lacking, leaving its clinical efficacy and safety unconfirmed; the mechanisms of multi-target synergy and combination therapies are not sufficiently elucidated; differences in extraction methods lead to structural variations (*e.g.*, molecular weight, branching degree, substituents), and the structure-activity relationship has not been fully clarified; although PCP has good water solubility, it is easily degraded by intestinal flora upon oral administration, resulting in low bioavailability, and there is insufficient development of novel dosage forms. Future research should focus on strengthening clinical studies to evaluate efficacy and safety, utilizing multi-omics technologies to decipher the multi-target mechanisms of action, optimizing extraction processes to enhance purity and activity for the identification of active structural motifs, developing novel dosage forms such as nanoparticles and liposomes to improve bioavailability, and combining precision medicine approaches with genotype-based treatment selection to achieve precision treatment.

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