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Title:

Pachymic Acid: A Promising Natural Agent for Cancer Therapy

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Abstract

Cancer remains a leading cause of death worldwide. Current treatment modalities, including surgery, chemotherapy, and radiotherapy, often suffer from limitations such as toxicity, drug resistance, and limited efficacy. As a result, there is growing interest in identifying novel anticancer agents from natural sources. Pachymic acid (PA), a triterpenoid compound derived from the medicinal fungus Poria cocos, has demonstrated broad pharmacological activities, including anti-inflammatory and antioxidant effects. Notably, recent research has increasingly focused on PA's potential anticancer properties. This review provides a comprehensive summary of the anticancer mechanisms of PA. Evidence from both in vitro and in vivo studies indicates that PA can induce apoptosis, modulate the cell cycle, enhance the sensitivity of cancer cells to conventional drugs and radiotherapy, and impede tumor angiogenesis. Due to its relatively low toxicity and potent anticancer effects, PA shows promising potential for development as an effective cancer therapeutic agent.

1. Introduction

Cancer poses a significant burden on global health, with its incidence and mortality rates continuously rising [1]. Current standard treatments, including chemotherapy and radiotherapy, often face challenges of systemic toxicity, drug resistance, and unsatisfactory outcomes in advanced disease states [2,3].

Additionally, innovative strategies such as immunotherapies and gene therapies, while promising, face issues related to complex side effects, limited tumor infiltration, and high costs [4].

In recent decades, natural products derived from medicinal plants and fungi have attracted substantial attention for their potential in cancer treatment due to their multilevel mechanisms of action, favorable safety profiles, and relatively low costs [5–7]. Poria cocos, a well-known medicinal fungus in traditional Chinese medicine, has been used for centuries for its diuretic, tonic, and sedative properties [8,9]. Among the bioactive components extracted from Poria cocos, triterpenoids have emerged as key players in its therapeutic effects [10].

Pachymic acid (PA), a triterpenoid isolated from Poria cocos, exhibits anti-inflammatory, antioxidant, and immunomodulatory properties [11–14]. More recently, PA's anticancer effects have garnered attention. Studies suggest that PA not only induces apoptosis and modulates the cell cycle of various cancer cells but also enhances the efficacy of conventional drugs and radiotherapy [15–20]. This review aims to elucidate the mechanisms underlying PA's anticancer activities, summarize the current findings, and highlight future research directions.

2. Apoptotic Activity of Pachymic Acid

Apoptosis, or programmed cell death, is essential for maintaining cellular homeostasis and is often dysregulated in cancer [21,22]. PA has been shown to induce apoptosis in multiple cancer cell lines through both intrinsic and extrinsic pathways [15,19,23]. Mechanistically, PA alters the expression of Bcl-2 family proteins and promotes caspase activation, ultimately leading to mitochondrial outer membrane permeabilization and release of cytochrome c [24–27].

PA also triggers endoplasmic reticulum (ER) stress and activates unfolded protein response (UPR)-related proteins, including ATF4, CHOP, and XBP-1, to induce apoptosis [28–30]. Moreover, PA can inhibit JAK2/STAT3 signaling and enhance reactive oxygen species (ROS) generation, further contributing to cancer cell apoptosis [29,31,32]. These multifaceted actions make PA a potent inducer of cancer cell death.

3. Cell-Cycle Modulation by Pachymic Acid

Dysregulated cell-cycle progression is a hallmark of cancer [33]. PA arrests cancer cells at various phases of the cell cycle, thereby inhibiting proliferation. Studies demonstrate that PA upregulates p53 and p21, while downregulating cyclin and CDK complexes essential for G1-to-S and G2/M transitions [34–37]. PA's ability to block cancer cells in the G0/G1 or G2/M phases halts their proliferation and sensitizes them to other treatments.

Furthermore, PA's modulation of signaling pathways, such as AKT/ERK and COX-2/β-catenin, contributes to cell-cycle arrest [36,38]. By interfering with multiple cell-cycle regulatory nodes, PA emerges as an effective agent to curb uncontrolled cancer cell division.

4. Enhancing the Efficacy of Conventional Therapies with Pachymic Acid

Combining PA with standard anticancer drugs or radiotherapy can improve therapeutic outcomes. PA reduces drug resistance by inhibiting P-glycoprotein expression and enhancing the metabolic stability of coadministered drugs [39,40]. These actions reverse multidrug resistance (MDR) and increase the accumulation of chemotherapeutic agents in cancer cells.

Additionally, PA sensitizes cancer cells to radiotherapy. By suppressing hypoxia-inducible factor-1α (HIF-1α) and upregulating pro-apoptotic proteins, PA enhances radiosensitivity and promotes more effective DNA damage under radiation [20]. Combining PA with biomaterials such as multi-walled nanotubes also inhibits angiogenesis, limiting nutrient supply to tumors [41].

5. Safety and Future Perspectives

Preclinical studies indicate that PA does not cause significant toxicity in animals [20,36]. Its ability to target multiple oncogenic pathways and synergize with existing therapies makes PA a promising candidate for anticancer drug development. Future research should focus on refining PA formulations, investigating optimal dosing regimens, and conducting clinical trials to confirm its therapeutic potential and safety profiles.

Additionally, understanding PA's pharmacokinetics and molecular targets in greater detail would support the rationale for combination strategies and guide personalized treatment approaches. The integration of PA into current cancer therapies could reduce side effects, overcome drug resistance, and ultimately improve patient outcomes.

6. Conclusion

PA demonstrates a broad spectrum of anticancer activities, including inducing apoptosis, modulating the cell cycle, enhancing drug efficacy, and sensitizing tumor cells to radiotherapy. With a growing body of evidence supporting its safety and efficacy, PA holds promise as a novel natural anticancer agent. Further clinical research and development of PA-based therapeutics may offer more effective and safer cancer treatment options.

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