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Progress in Research on the Antitumor Mechanisms and Clinical Applications of Active Compounds from Phellinus igniarius

Guiping Xuan, Qunfang Li, Tianping Li*

Hunan Polytechnic of Environment and Biology, Hengyang 421000, China

Abstract: Phellinus igniarius, a medicinal fungus with significant antitumor potential, exerts its inhibitory effects through multiple mechanisms, including the induction of apoptosis and immune modulation. However, its molecular mechanisms, signaling pathways, dose-response relationships, and the feasibility of clinical translation remain to be systematically elucidated. This essay reviews the latest research advancements in the antitumor effects of Phellinus igniarius, and identifies key challenges in areas such as synergistic effects and clinical applications. It aims to provide a reference for further research and development of Phellinus igniarius in the field of cancer therapy.

Keywords: Phellinus Igniarius; Polysaccharide; Anti-Tumor; Immunomodulation; Nanocarriers

Traditional Chinese medicine Phellinus igniariushas garnered widespread attention in medical research due to its unique bioactive components and significant pharmacological effects. Phellinus igniarius, belonging to the genus Phylloporia within the family Polyporaceae, is a perennial, woody, sessile fruiting body. Traditional Chinese medicine believes that Phellinus igniariusis associated with the liver and kidney meridians, possessing the effects of promoting blood circulation, hemostasis, resolving phlegm, and stopping diarrhea. Modern research has discovered that Phellinus igniariusfruiting bodies and mycelia are mainly composed of three core components: polysaccharides, flavonoids, and polyphenols, supplemented by triterpenoids, sterols, and unique pyranone compounds, forming a multi-target, synergistic "forest gold" active system. Studies have shown that Phellinus igniariuscan exert anti-tumor effects by changing cancer cells (SGC-7901) from flat to spherical, reducing cell adhesion, and increasing their elastic modulus, while having no effect on normal gastric epithelial cells (Wang et al., 2023). Phellinus igniariuspolysaccharides and flavonoids can regulate immune responses and inhibit tumor growth (Zapora et al., 2016), while also possessing antioxidant activity and significantly affecting the content of gut microbiota and short-chain fatty acids (Zhu et al., 2023). Although current research has provided some understanding of the anti-tumor effects of Phellinus igniariusand its mechanisms, further systematic clarification is needed regarding its specific action pathways, active ingredients, and the safety and efficacy of clinical applications. This will provide a systematic basis for its scientific application in anti-tumor therapy. Based on this, this article will conduct an in-depth discussion on the anti-tumor effects of the active components of Phellinus igniariusand its research progress.

1. Overview of Phellinus igniarius Chemical Components:

Phellinus igniarius, a medicinal fungus, boasts a diverse array of chemical components contributing to its therapeutic potential. These constituents can be broadly categorized into polysaccharides, polyphenols, terpenoids and alkaloids, and furan and pyranone derivatives, among others.

1.1 Polysaccharides

The polysaccharides present are primarily water-soluble heteropolysaccharides. These are composed of numerous sugar units linked by glycosidic bonds, with a typical main chain of β-(1→3)-D-glucan. The monosaccharide composition includes glucose, mannose, galactose, fucose, arabinose, and xylose. The detailed structural characteristics of Phellinus igniarius polysaccharides, such as varying sugar unit ratios, branching structures, and sulfation degrees, significantly impact their bioactivity. These substances exhibit a wide range of biological activities, including significant immune enhancement, anti-tumor, and anti-oxidation effects (Jin, 2024).

1.2 Polyphenols

Polyphenolic compounds, represented by flavonoids, Hispolon, ellagic acid, and 4-(3,4-dihydroxyphenyl)-3-buten-2-one, can induce

apoptosis in nasopharyngeal carcinoma, prostate cancer, and leukemia cells via the MAPK pathway. Over 20 flavonoid compounds have been isolated from Phellinus igniarius, including 5,7,4′-trihydroxy-6-o-hydroxybenzyl dihydroflavone, naringenin, 7-methylnaringenin, 3,7-dimethoxyquercetin, Phellinus igniariussu, and taxifolin. Among these, 3,7-dimethoxyquercetin plays a crucial role in anti-oxidation and free radical scavenging. Hispolon and other polyphenols induce nasopharyngeal carcinoma cell apoptosis by regulating the MAPK pathway, demonstrating potential anti-tumor applications (Huang GJ, 2011).

1.3 Terpenoids and Alkaloids

Terpenoids in Phellinus igniarius include triterpenoids and steroids. Triterpenoids, primarily of the oleanane and lupane types, are secondary metabolites with anti-tumor, anti-inflammatory, and anti-viral activities. Steroidal components, such as lanosterol, can inhibit lipopolysaccharide-induced NO production in macrophages, demonstrating anti-inflammatory potential. Alkaloids, nitrogen-containing organic compounds with mono-, bi-, or polycyclic structures, are present in low concentrations in Phellinus igniarius. However, their effects on the body are significant, particularly in anti-tumor, anti-inflammatory, and immunomodulatory aspects.

1.4 Furans, Pyranones, and Other Compounds

Furan and pyranone derivatives, such as Inoscavin A and 5-hydroxymethyl-2-furaldehyde, have been proven to have anti-complementary and anti-diabetic effects, representing a unique class of signaling molecules in Phellinus igniarius that expands its medicinal applications. Phenolic acids and lignans, including phellibaumin D, protocatechuic acid, and syringic acid, exhibit antioxidant and synergistic anti-tumor activity and are included in the candidate list of quality markers (Q-Marker) for Phellinus igniarius.

2 Anti-tumor Mechanisms of Phellinus igniarius Effective Components

2.1 Direct Anti-tumor Effects

The active components of Phellinus igniarius can induce tumor cell apoptosis. For example, polysaccharide (PIP) activates caspase-3, triggering mitochondrial-dependent apoptosis by increasing reactive oxygen species (ROS) levels, enhancing p53 expression, and promoting cytochrome c release (Jin et al., 2024). The ethanol extract of Phellinus igniarius (TPI) can downregulate the Bcl-2/Bax ratio, induce mitochondrial membrane potential collapse, and activate caspase-9/-3 and PARP cleavage (Wang et al., 2018). In addition, components such as hispolon can induce G0/G1 phase cell cycle arrest by downregulating Cyclin D1, Cyclin E, and CDK2/4/6, while upregulating p21 and p27 (Wu et al., 2014). The phenolic compound OSC can induce G2/M phase arrest (Yang et al., 2022). Phellinus igniarius extracts can also concentration-dependently inhibit tumor cell migration and invasion, with mechanisms related to inhibiting the activity of matrix metalloproteinases (MMPs) and the epithelial-mesenchymal transition (EMT) process. Atomic force microscopy observations have found that Phellinus igniarius treatment can change the morphology and mechanical properties of cancer cells, reducing their malignant phenotype (Wang et al., 2023).

2.2 Immunomodulation and Indirect Anti-tumor Effects

Phellinus igniarius polysaccharides can promote the increase of immune organ indices, activate innate immune cells such as macrophages and NK cells, stimulate the secretion of cytokines such as IL-2, IL-6, IL-12, IL-18, and IFN-γ, and inhibit TNF-α expression (Gao et al., 2017). In addition, Phellinus igniarius components can regulate the composition of the intestinal flora, promote short-chain fatty acid metabolism, and improve the intestinal immune microenvironment (Zhu et al., 2023). Combined with chemotherapy drugs, it can reduce immunosuppression, increase IFN-γ levels, reverse the expression of multidrug resistance genes MDR1 and P-gp (Yang et al., 2022), and scavenge free radicals to reduce oxidative damage (Huang et al., 2011).

2.3 Regulation of Key Signaling Pathways

Phellinus igniarius terpenoids and phenolic components can regulate the MAPK pathway (JNK, p38, ERK) and inhibit survival signal-

ing pathways such as PI3K/Akt, thereby synergistically promoting apoptosis and cell cycle arrest (Hsiao et al., 2013).

2.4 Combined Therapeutic Strategies of Phellinus igniarius Effective Components

Phellinus igniarius effective components demonstrate the potential for multi-pathway synergistic enhancement and toxicity reduction in anti-tumor combination therapy. When used in combination with chemotherapeutic drugs, Phellinus igniarius polysaccharides can overcome drug resistance by reversing the expression of multidrug resistance gene MDR1 and P-glycoprotein (Yang et al., 2022), while its polyphenolic components can scavenge free radicals and reduce liver and kidney oxidative damage and chemotherapy side effects (Huang et al., 2011). In radiation therapy, Phellinus igniarius active ingredients can inhibit the expression of DNA damage repair proteins ATM/ATR, enhancing radiation sensitivity (Hsiao et al., 2013), and alleviate radiation-induced tissue damage through anti-inflammatory and antioxidant properties (Zapora et al., 2016). Combined with targeted drugs, it can inhibit alternative pathways such as PI3K/Akt to delay drug resistance (Hsiao et al., 2013) and reduce skin and gastrointestinal toxicity. Synergizing with immune checkpoint inhibitors can promote the activation of DC cells and T cells, transforming “cold tumors” into “hot tumors” and improving the immune microenvironment (Gao et al., 2017). In addition, the combination of Phellinus igniarius with Ganoderma lucidum (Lingzhi), Astragalus, and other traditional Chinese medicines can take into account immune regulation and strengthening the body’s resistance (An, 2024).

3 Preparations and Administration Routes of Phellinus igniarius Effective Components

Based on traditional dosage forms, modern techniques such as extraction, purification, and micronization can significantly improve the solubility and stability of Phellinus igniarius effective components (such as polysaccharides, flavonoids, and triterpenoids), thereby improving their bioavailability and therapeutic effects. Non-oral administration routes such as injection, transdermal, and inhalation have been actively explored. Modern technologies such as supercritical fluid extraction (Liu et al., 2022) and nanocarrier systems (Wei et al., 2023) can significantly improve the bioavailability and targeting of Phellinus igniarius active ingredients. Nanodelivery systems can enhance tumor tissue accumulation and reduce systemic toxicity.

4 Research Prospects and Challenges

Phellinus igniarius anti-tumor research still faces many challenges. The anti-tumor mechanism of its active ingredients has not been fully elucidated, especially the signal transduction network at the molecular level, the tumor microenvironment regulation mechanism, and the role in different tumor types still need to be further clarified. Systematic in vivo pharmacokinetic, bioavailability, and toxicology studies need to be carried out urgently. Future research should focus on the extraction and purification technology of high-purity active ingredients, the development of new preparations, the comprehensive evaluation of pharmacodynamic effects, and the design of standardized clinical trials. Key issues include establishing a reliable pharmacodynamic and safety evaluation system and optimizing the administration regimen. At the same time, with the increasing demand for medicinal use, *Phellinus igniarius*’s wild resources are facing tremendous pressure, and it is necessary to actively carry out artificial cultivation, germplasm resource protection and sustainable utilization research, and use modern biotechnology such as synthetic biology and cell culture to improve the production efficiency and quality of active ingredients to ensure the sustainable utilization of resources.

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