

Ganoderma Lucidum Bioactive Compounds and the Antitumor Mechanisms Current Advances

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Abstract: At present, radiotherapy and chemotherapy are commonly used in clinical practice to treat tumors, but these therapies often cause severe side effects that compromise human health. Being a traditional Chinese herbal medicine, *Ganoderma lucidum* (lingzhi) has garnered significant attention of late years for the antitumor activity of its components. Relevant studies have revealed that its bioactive compounds, including *Ganoderma lucidum* polysaccharides, *Ganoderma lucidum* triterpenes, *Ganoderma lucidum* active proteins, sterols and nucleosides, exhibit antitumor effects through multiple mechanisms such as immune regulation, induction of tumor cell apoptosis as well as attenuation of tumor cell proliferation and metastasis, and demonstrate synergistic effects combining with various antitumor drugs. Notably, they exhibit promising efficacy with minimal toxicity. This paper reviews the major bioactive substances of *Ganoderma lucidum*, analyzing their molecular structures and mechanisms of action. It summarizes current research progress and clinical applications, discusses existing challenges and limitations in related studies, and explores future prospects for developing *Ganoderma*-based antitumor drugs, providing a theoretical foundation for subsequent research and application of *Ganoderma* bioactive compounds in antitumor drug development.

Keywords: *Ganoderma lucidum*, Active ingredients, Antitumor, Adjuvant therapy.

1. Introduction

Based on the data statistics disclosed by IARC in 2022, the number of Chinese cancer cases approximately one-quarter of global cancer incidence, and 26.5% of global mortality cases. Of all carcinoma, lung cancer is the most common and virulent, with other frequent tumors are female breast cancer, prostatic cancer gastrointestinal tumors (e.g. colorectal cancer, stomach cancer) and so on [1]. At present, the main methods for treating cancer in clinical are radiotherapy and chemotherapy, but these methods have adverse side-effect, and impact patient's quality of life [2]. Choosing cis-platinum, a platinum-based anti-cancer drug commonly used in clinical practice as an example, the toxic adverse caused by it affect kidney, nervous system, digestive system, blood system, etc. For specific performance are renal dysfunction, dizziness, tinnitus, vomiting, diarrhea, and cytopenia [3]. As a result, the introduction of update medicine has become a clinical indispensable.

As documented in the 2020 ChP, *Ganoderma lucidum* exhibits the function of calming the spirit, regulating energy, relieving cough and ease breathing difficulties, with indications including palpitations, insomnia, pulmonary weakness and fatigue-induced respiratory weakness [4]. Pharmacological research has established that the primary bioactive constituents of *Ganoderma lucidum*, including polysaccharides and triterpenoids, demonstrate immunoregulatory functions and exhibit antitumor activity [5,6].

Belong to the member of the Polyporoid fungi family, *Ganoderma lucidum* displays significant medicinal potential and health-promote function with both its fruiting bodies and spores. These medicinal applications are owing to its distinct bioactive profile and pharmacological activities [7]. Experimental studies have confirmed that *Ganoderma* polysaccharides and triterpenes exhibit inhibitory effects against malignant tumor including liver cancer, lung cancer and cervical cancer. Their pathway involves inducing tumor cell apoptosis, stopping cell multiplication and immune modulation etc [8].

Until now, there is limited related research about *Ganoderma lucidum* active component of against tumor mechanism. This review comprehensively summarizes the active component, its tumor-suppressive actions, explored it undetected in oncotherapy, and lays the theoretical groundwork for advancing new drug therapies.

2. The anti-cancer mechanism of the main active components of *ganoderma lucidum*

2.1. Polysaccharides

Ganoderma lucidum polysaccharides are active components extracted from *Ganoderma lucidum* spores or fruiting bodies, which have significant anti-tumor effects. Their structures are diverse, comprising β -D-glucan, α -D-glucan, α -D-galactan, and heteropolysaccharides, etc. These molecules exhibit structure-dependent biological functions, with their (β 1,3)-linked main chain and (β 1,6)-branched configuration serving as critical determinants of their pharmacological activity.

β -1,3-glucan engages with pattern recognition receptors (PRRs) on immune cells, initiating immunostimulatory signaling cascades, including Dectin-1 and TLR2., activating macrophages, neutrophils, dendritic cells, and other immune cells, and enhancing their ability to phagocytize pathogens and tumor cells [8]. β -1,6 polysaccharides remodel the tumor immune microenvironment, favoring CD8⁺ T cell and Th1 cell expansion over Tregs, thus strengthening T cell-dependent tumor immunity [9]. *Ganoderma lucidum* polysaccharides exert indirect antitumor effects through immunomodulation. They enhance immune function by activating macrophages, T cells and NK cells, improving lymphocyte transformation rates, stimulating immunoglobulin production, and boosting immune recognition and elimination of tumor cells, thereby strengthening the body's antitumor immune response [10]. *Ganoderma lucidum* polysaccharides can not only indirectly inhibit tumor growth by activating immune cells but also directly act on tumor cells, inducing their apoptosis, inhibiting proliferation and metastasis. For example, *Ganoderma lucidum* polysaccharide GL-B can significantly inhibit the growth of transplanted sarcoma S180 in mice, but it has no direct anti-tumor effect. Its anti-tumor effect is achieved by promoting the expression of TNF- α (Tumor Necrosis Factor-alpha mRNA) and INF- γ (Interferon-gamma mRNA) and increasing the secretion of TNF- α and INF- γ . *Ganoderma lucidum* polysaccharides can also enhance immune responses and regulate the functions of immune cells. They can activate macrophages, dendritic cells (DCs), and natural killer cells (NK cells), promote the secretion of cytokines such as IL-2 (Interleukin-2) and IFN- γ , and enhance anti-tumor immunity. In the adjuvant treatment of lung cancer patients, combined with chemotherapy, it can significantly elevate the CD4⁺/CD8⁺ T cell ratio while mitigating immunosuppressive mechanisms [11,12].

2.2. Triterpenoids

Ganoderma lucidum triterpenoids are a class of triterpenoids found in Ganoderma lucidum, scientifically known as total triterpenoids of Ganoderma lucidum. They are highly oxidized lanostane derivatives and are the main chemical and pharmacological components of Ganoderma lucidum. They are tetracyclic triterpenoids with lanostane as the basic skeleton. Their structures are complex, with relative molecular weights generally ranging from 400 to 600 daltons. They have good lipid solubility but poor water solubility, and most of them have a bitter taste. The structural characteristics of Ganoderma lucidum triterpenoids include A/B, B/C, and C/D rings being trans, β -CH₃ at C10 and C13, a β -side chain at C17, α -CH₃ at C14, and R configuration at C20 [13].

Ganoderma lucidum triterpenoids exhibit direct antitumor activity by suppressing neoplastic cell proliferation. For instance, ganoderic acids A, B, and D can block tumor cells in the G0/G1 or G2/M phase by regulating cyclins and cyclin-dependent kinases (CDKs), thereby inhibiting their proliferation. For example, ganoderic acid D induces tumor cell apoptosis through mitochondrial pathways, inhibition of survival signaling pathways, and cell cycle arrest, exerting anti-tumor effects. Ganoderma lucidum triterpenoids activate the apoptotic pathway of tumor cells by up-regulating pro-apoptotic proteins (Bax, Bak), down-regulating anti-apoptotic proteins (Bcl-2, Bcl-xL), inducing mitochondrial membrane potential collapse, releasing cytochrome C, and activating the Caspase-9/3 cascade reaction [14]. Ganoderma lucidum triterpenoids exert anti-tumor effects through multiple mechanisms, which work in synergy to act on the processes of tumor occurrence, development and metastasis.

2.3. Protein

Ganoderma lucidum protein active ingredients exist in many shapes, most of which serve as a vital determinant in modulating the immune mechanism of the body directly or indirectly. Among these proteins, Fungal immunomodulation proteins (FIPs) are the major bioactive proteins of Ganoderma lucidum, which are small protein with immunoregulatory activity [15]. The earliest FIPs were first isolated from Ganoderma lucidum mycelium extract by Kino et.al. and named Lingzhi-8(LZ-8) [16]. Up to now, researcher have found various FIPs from different fungi. Ganoderma microsporum immunomodulatory protein (GMI)and LZ-8 are two FIPs that share structural and sequence similarities. Studies have displayed that these two FIPs have significant antitumour activity. For instance, Hsin, I. L et al. found that GMI can stimulates autophagy pathways in non-small cell lung carcinoma rather than apoptosis, while Ching-Hsiung Lin et al. proved GMI's ability to suppress epidermal growth factor (EGF) moderated transference and infiltration in A549 lung carcinoma cells [17,18]. Chien-Ting Wu et al. found that LZ-8 inhibit proliferation of lung carcinoma cells by mediating p53-dependent growth arrest through the ribosomal protein S7-MDM2-p53 pathway [19]. Lin T Y et al. found that both LZ-8 and GMI can inhibit lung cancer LLC1 cells transfer and significantly induce apoptosis in vitro by down -regulation of small heat shock protein (HSPs) expression [20]. Guan Huimin found through experiment that GMI exhibits strong anti-metastatic activity both in vivo and vitro, and it mechanism may be related to decline the expression of N-cadherin and β -catenin, and thereby reverse the migration of liver cancer cells [21].

2.4. Other components

Sterols and nucleosides found in Ganoderma lucidum, such as ergosterol, cholesterol, adenosine, uridine and guanosine, have also demonstrated antitumor activity. These compounds exert immunomodulatory, anti-angiogenic, antioxidant, anti-inflammatory and tumor cell apoptosis-inducing effects, indirectly exerting antitumor effects by synergizing with other antitumor components or influencing the tumor microenvironment.

The sterol components in *Ganoderma lucidum* share a steroid nucleus as their basic structural backbone, featuring a fatty side chain at the C17 position and some specific functional groups. Sterols can inhibit the proliferation of tumor cells [22]. For example, Li Xiangmin examined gene expression in tumor cells treated with ergosterol and peroxyergosterol by PCR analysis, followed by Western blotting to assess corresponding protein levels. The study revealed that ergosterol upregulated Foxo3a (forkhead rhabdomyosarcoma like 1,FKHRL1) expression in breast cancer cells, promoting downstream target genes Bim and FasL (Fas ligand) and inducing apoptosis via the death receptor and mitochondrial pathways, while peroxyergosterol suppressed the activity of oncogenic factors pAKT (Ser473) and c-Myc, increased Foxo3a levels in liver cancer cells, enhanced the expression of Puma and Bax proteins, start the apoptotic pathway, triggering the apoptosis of liver cancer cells [23]. Additionally, peroxyergosterol also inhibits angiogenesis [24].

The nucleoside components in *Ganoderma lucidum* are formed by glycosidic bonds linking a base to ribose, often with unique modifications such as *Ganoderma*-specific purines and 2'-deoxyuridine. *Ganoderma* nucleosides primarily exert indirect antitumor effects by modulating biological processes to alter the tumor microenvironment. For instance, adenosine inhibits platelet aggregation, delaying or eliminating some of the life-threatening hematological complications in advanced-stage malignancies [25]. Due to their supportive role, nucleosides are typically used as adjuvant agents in combination with other antitumor compounds.

3. *Ganoderma lucidum* as an adjuvant to other drug treatments for tumors

In modern clinical applications, targeted therapies primarily utilize active compounds derived from *Ganoderma lucidum*. Structural modifications of these bioactive components combination with other drugs, and use of *Ganoderma lucidum* extracts as adjuvant drugs are all employed for tumor treatment. *Ganoderma lucidum* belongs to the category of fungal polysaccharide drugs. Over the past few years, it has been discovered that the polysaccharide ingredients of this type of drug have multiple pharmacological effects in the clinical treatment of tumors. They are excellent biological response modifiers (BMRs) and have been proven to actively participate in the anti-tumor immune response in the body, enhance tolerance to chemotherapy, eliminate fatigue, promote protein synthesis, reduce bleeding and infection, inhibit the development and deterioration of lesions, and prolong survival time. *Ganoderma lucidum* spore powder capsules are effective adjuvants for chemotherapy, enhancing its efficacy and reducing toxicity. They are used as adjuvant drugs for chemotherapy and as an adjuvant treatment for tumors in clinical practice, and have high application value [26].

4. Challenges in the development of *ganoderma*-based antitumor drugs

The unique antitumor mechanisms of *Ganoderma lucidum* bioactive components offer novel therapeutic strategies for cancer treatment. However, the molecular mechanisms and specific targets of certain *Ganoderma* active compounds such as nucleosides remain poorly understood with limited experimental evidence and numerous research gaps, impeding the development of related drugs, especially targeted antitumor drugs and still warrants further research. In addition, due to a variety of factors, the potency and concentration may decline in the process of extracting bioactive compounds from *Ganoderma lucidum*, affecting their antitumor effect. The extraction process is in need of optimization and innovation to obtain bioactive compounds with higher activity and concentration. For instance, low-temperature continuous phase extraction has demonstrated higher yields of solids, polysaccharides, and triterpenes compared to traditional water extraction [27]. The bioactive components of *Ganoderma lucidum* may also cause adverse effects or drug resistance issues, such as increasing hepatic burden, and certain constituents exhibit poor bioavailability in human body, requiring structural modifications of active compounds or specialized drug delivery systems (e.g.,

targeted delivery systems and controlled-release formulations) to be employed to enhance targeted drug delivery efficiency while minimizing effects on normal cells. For instance, nano-formulation of Ganoderma active components can increase their exposed surface area in solvents, improve extraction yields and enhance their tumor cell proliferation inhibitory effects [28]. Furthermore, developing multi-target antitumor drugs could help prevent therapeutic resistance as well. Combination therapy using Ganoderma-based antitumor agents with other pharmacological agents can also help overcome these problems.

5. Conclusion

In recent years, bioactive components derived from traditional Chinese medicinal herbs have been increasingly applied in the treatment of tumor. The active constituents of Ganoderma lucidum mainly include Ganoderma lucidum polysaccharides, Ganoderma lucidum triterpenes and some proteins, peptides, sterols and nucleosides. These compounds exhibit significant medicinal value in killing tumor cells, inhibiting tumor growth, proliferation and metastasis as well as synergizing with other antitumor drugs. They demonstrate efficacy against various cancers such as liver, lung and breast cancer with strong anticancer effects, minimal side effects and multiple therapeutic targets. Clinically, Ganoderma bioactive components are mainly used for immune regulation and adjuvant therapy of cancer patients. Currently, research on Ganoderma-based antitumor drugs still faces certain challenges and limitations. With further advancements in related fields, Ganoderma active ingredients are expected to play an even greater role in cancer treatment. With the rapid development of information technology, it is also possible to combine the analysis of Ganoderma's bioactive components and their mechanisms with data-driven tools and artificial intelligence (AI) system(e.g., AlphaFold, Monocle, Space Ranger) could enhance drug development efficiency and lead to novel antitumor drugs with improved efficacy and reduced toxicity.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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