REVIEW ARTICLE

Research progress on antitumor effects of active proteins, polysaccharides, and triterpenoids in *Ganoderma lucidum*

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Cancer is a serious threat to human life and health, and treatment options include operation, chemicals, intervention, immunotherapy, and radiotherapy. However, these methods often come with serious side effects, drug resistance, and exorbitant costs. As such, scientists are turning to natural products as a potential alternative for cancer treatment due to their safety and multi-target pharmacological efficacy. *Ganoderma lucidum* (GL), also known as "Lingzhi", is a beneficial medicinal fungus and regarded as one of the best vegetarian foods for tumor patients. The purpose of this review is to investigate and summarize the bioactivity and mechanism of *Ganoderma lucidum* polysaccharide (GLP), *Ganoderma lucidum* triterpenoids (GLT), and *Ganoderma lucidum* active protein (GLAP). The results demonstrated that these natural products had potent anti-tumor effects including immune response regulation, inhibition of cancer oncogenesis, inhibition of cancer cell invasive metastasis, generation of cytotoxicity, regulation of signaling pathways, and inhibition of malignant phenotypes of tumor cells. Notably, these natural products had the ability to modulate the immune response, which was critical for cancer treatment. Through the buildup of reactive oxygen species and the activation of caspase, GLAP could cause the lung tumor A549 cells to undergo apoptosis. It could also actively prevent the growth of human glioma cells U251 by causing cell cycle arrest and encouraging cancer cell death. GLP and GLT had been found to boost autoimmune reaction by boosting cytokine production. Additionally, these natural compounds could impede tumor angiogenesis, inhibiting cancer cell development and spread. GLT could limit cancer cell invasion by inhibiting the activity of matrix metalloproteinases, which played an important role in tumor cell invasion. Finally, because of its safety and multi-target pharmacological performance, GL had been identified as a viable natural product for cancer treatment. This review shed light on the anti-tumor activities of GLAP, GLP, and GLT, as well as their potential as natural cancer treatments.

Keywords: *Ganoderma lucidum*; polysaccharide; triterpenoids; active protein.

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Introduction

Ganoderma lucidum (GL), a well-known medicinal and edible fungus, is a member of the families of *Basidiomycetes*, *Toadobacteria*, and *Poraceae* [1]. It is also known as “Linhchi” in Vietnam, “Yeongji” in South Korea, “Reishi” in Japan, and "fairy grass" in China, and was first mentioned in the ancient Chinese medical encyclopedia "Shennong Bencao Jing" more than 2,000 years ago [2, 3]. Recent research has isolated and identified over 600 effective components from more than 20 types of GL including polysaccharides, triterpenoids, proteins, alkaloids, and nucleosides [4]. GL has comparatively high levels of *Ganoderma lucidum*

polysaccharide (GLP), *Ganoderma lucidum* triterpenoids (GLT), and *Ganoderma lucidum* active protein (GLAP) concentrations, which all have greater biological activities and functions than that of the other components. It has been demonstrated *via* studies that GL possesses anti-tumor, immunological modulation, liver protection, lowering blood sugar and lipid levels, anti-aging, anti-inflammation, antibacterial, suppressing pigmentation, heart protection, anti-atherosclerosis, anti-androgen, and enhancing the weak body effects [5, 6].

Cancer is a serious threat to human health, and its morbidity and mortality rates are rising over the world [7]. Chemotherapy is an important part of cancer treatment, yet it can harm the body's immune system. Furthermore, chemotherapy drugs like doxorubicin and cisplatin might result in significant adverse effects and treatment resistance [8]. GL's natural ingredients have shown promise as a medicinal agent. Because of their low toxicity, minimal side effects, and wide variety of therapies, these natural products are gaining popularity due to their safety and effectiveness [9]. However, the biological activity and potential value of GLP, GLAP, and GLT as natural anticancer substances have not been evaluated in the current research literature. This review study focused on the anti-tumor actions and mechanisms of GL active proteins, polysaccharides, and triterpenes. The findings could provide a theoretical foundation for the development of novel anti-tumor medications based on natural ingredients [10].

Biological activity and structural characteristics of *Ganoderma lucidum*

Recent pharmacological studies have revealed that GL contains a plethora of active substances that exhibit potent therapeutic properties. The researchers used cutting-edge methodologies including high performance liquid chromatography, high performance anion exchange chromatography, and pulsed amperage detector to reveal the structural features and biological activities of GL. GL contains several active proteins, polysaccharides, and triterpenoids that exhibit inhibitory functions against tumor cells. These substances have been demonstrated to have pro actions *via* a variety of mechanisms including immune response regulation, angiogenesis suppression, and apoptosis induction. Furthermore, the structural properties of GL's active chemicals are critical in defining their biological activity. Polysaccharides produced from GL, for example, have distinct structural characteristics such as glucan linkages and high molecular weights, which contribute to their powerful immunomodulatory actions. Triterpenoids derived from GL also have a variety of biological actions such as anti-inflammatory, anti-tumor, and hepatoprotective properties. Overall, these results may pave the way for the creation of new therapeutic drugs for the management of diseases such as cancer [11].

Ganoderma lucidum active protein (GLAP)

(1) Lucidum regulatory protein

Currently, 12 types of fungal immunomodulatory proteins (FIPs) have been gradually discovered from different types of GL (Table 1). FIPs, enzymes, lectins, glycoproteins, and ribosome inactivating proteins (RIPs) are among the bioactive components found in GL. Among them, FIP is the main active protein that plays a critical role in regulating human immunity [12]. In 1989, FIP was secluded from GL and designated Lingzhi-8 (LZ-8). LZ-8 is a 13 kD protein with 110 amino acids that plays an important function in immune regulation and mitosis [13]. LZ-8 and other FIPs have some similarity with members of the immunoglobulin superfamily (IgSF). Yet, the physiological activity of LZ-8 was determined by the structure of the peptide rather than the spatial organization of the protein [14]. LZ-8 has been found to reduce the proliferation of human lung cancer cells A549 and caused autophagy death in SGC7901 gastric cancer cells *via* generating endoplasmic reticulum stress. Lectins are glycoproteins or polyvalent carbohydrate binding proteins that agglutinate cells or precipitate sugar complexes that are not

Table 1. Characteristic parameters and basic attributes of FIP in GL.

Name	Molecular weight (kD)	Amino acid	Biological activity	Reference
LZ-8	12.40	110	Inhibiting proliferation of A549 human lung cancer cells	[18]
LZ-9	13.10	111	lectin	[19]
FIP-gts	12.50	110	Anti hepatoma	[20]
FIP-gja	12.50	111	anticancer	[21]
FIP-gmi	15.90	111	Anticancer and bacteriostasis	[22]
FIP-gsi	12.40	111	——	[23]
FIP-gat	12.50	111	Anti-cancer and anti-inflammation	[24]
FIP-gap1	12.70	113	lectin	[25]
FIP-gap2	12.50	113	——	[26]
FIP-gte	12.52	——	——	[27]
FIP-gam	12.00	110	Induce endoplasmic reticulum stress in SGC7901 gastric cancer cells	[28]

immune-derived [15]. GL has yielded a number of lectins including a novel bioactive lectin with potent antifungal action. Anticancer and antiviral properties of RIPs have been demonstrated, whereas glycoproteins and enzymes play varied roles in metabolic and immunological control [16]. FIP, the major active protein in GL, is important in regulating human immunity and possesses anti-inflammatory and anticancer properties. Additional bioactive components with diverse biological activity and possible medical applications include lectins, RIPs, glycoproteins, and enzymes [17]. Further research is needed to investigate the mechanisms underlying these components' bioactivity and possible therapeutic uses.

(2) *Ganoderma lucidum* glycopeptide

Ganoderma lucidum (GL) glycopeptide is a key active substance in GL composed of one or more oligopeptide chains covalently linked to polysaccharide molecules. This complex structure contributes to its diverse biological functions [29]. GL glycopeptide GL-PS is obtained from the fruit body of GL and comprises 93.61% polysaccharides and 6.49% protein. When cultivated with rat abdominal cells, GL-PS was reported to increase M1-type macrophage polarization by raising the amounts of IL-12, IL-6, and TNF, while lowering M2-type macrophage IL-10 and arginaseI production [30]. GL glycopeptide GL-pp has also been found in studies to minimize the spread of mouse melanoma caused by sleep problems and to limit the proliferation of human glioma cell U251 by increasing cancer cell apoptosis [31, 32]. These findings demonstrated the potential of GL glycopeptide as a therapeutic agent for inflammatory diseases and cancer.

(3) Active peptide of *Ganoderma lucidum*

Active peptides generated from GL are secondary metabolites or protein hydrolysates that have many advantages including high potency, stability, and low toxicity, making them useful in the food and pharmaceutical industries [33]. Earlier research focused on the diverse functions of GL polypeptide components, but the structure and analysis of the components remained unknown. Nevertheless, GL mixed polypeptides derived from GL fruiting bodies, sporangium powder, and fermentation broth have anti-tumor, antioxidant, hypoglycemia, liver protection, blood pressure reduction, and immune boosting properties [34]. As research progresses, the major goal is to isolate specific GL peptides in order to investigate their biological activities and processes with the goal of developing functional targets for these peptides. GL active peptides, known as GL's major antioxidant component, have been found to reduce lipid peroxidation *via* antioxidant, metal chelation, and free radical scavenging properties [35]. Previous study discovered two forms of GL active peptides with more hydroxyl radical scavenging activity than Ganoderma

Table 2. Structural properties of polysaccharides from GL.

Type of polysaccharide	The main chain	Molecular weight (Da)	References
LZ-B-1	(1→6)-α-D-Galactose (1→2,6)-α-D-Galactose (1→6)-β-D-Glucose (1→3)-β-D-Glucose	1.12×10^4	[41]
LZ-C-1	(1→6)-α-D-Galactose (1→6)-β-D-Glucose (1→3)-β-D-Glucose (1→2,6)-α-D-Galactose	7.00×10^3	[42]
LZ-D-1	(1→6)-α-D-Galactose (1→2,6)-α-D-Galactose	2.80×10^4	[43]
PSG-1	(1→6)-α-D-Galactose	1.013×10^6	[44]
PSG-2	(1→6)-α-D-Galactose	6.90×10^4	[45]
GLPCW-II	(1→6)-α-D-Galactose	1.20×10^4	[46]
GLSA50-1B	(1→6)-β-D-Glucose	1.03×10^5	[47]
GLSB50-A-III-1	(1→3)-β-D-Glucose (1→6)-β-D-Glucose (1→4)-β-D-Glucose (1→3,6)-β-D-Glucose (1→4,6)-β-D-Glucose	1.93×10^5	[48]
LBPI	(1→4,6)-β-Glucose (1→3,6)-β-Glucose (1→6)-β-Galactose (1→3)-β-Mannose	9.17×10^4	[49]
LBPII	(1→3,6)-β-Glucose (1→4,6)-β-Glucose (1→3)-β-Glucose (1→6)-β-Glucose (1→3)-β-Mannose (1→6)-β-Mannose (1→6)-β-Galactose	1.86×10^4	[49]
GLP1a	(1→6)-β-D-Galactose	1.12×10^6	[50]
GLP1b	(1→6)-β-D-Galactose	1.21×10^5	[50]

polysaccharide, which were Ser-Asp-Gly-Ser tetrapeptide and Leu(Ile)-Leu(Ile)-Thr-Phe-His-Ala heptapeptide [36]. Another oligopeptide (C18) discovered in GL could bind to the formyl peptide receptor and limited superoxide generation, reducing chemotactic cell damage [37]. Active peptides from GL are high in amino acids including Phe, Asp, Pro, His, and Ile, which contribute to their antioxidant effects. GL active peptides can directly act on important areas due to their small molecular size and tissue permeability, making them particularly efficient against a range of malignancies. The low molecular weight of GL active peptides, on the other hand, makes them susceptible to breakdown in the gastrointestinal tract, limiting their stability and bioavailability. As a result, new strategies must be developed to strengthen their stability and inhibit digestion, so boosting their efficacy and bioavailability. The use of nano-carriers or sustained-release bodies such as nano-liposomes to improve the bioavailability of GL active peptides is one intriguing strategy. However, more research is required to optimize these carriers' transport technology and mechanisms.

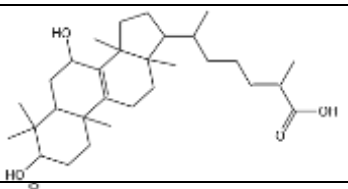
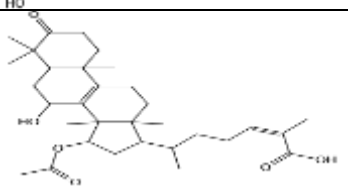
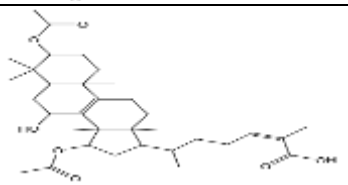
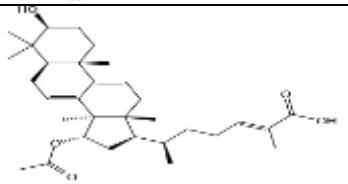
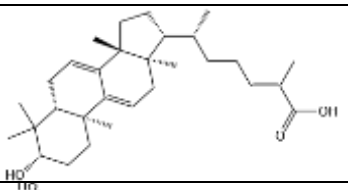
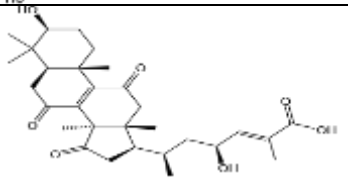
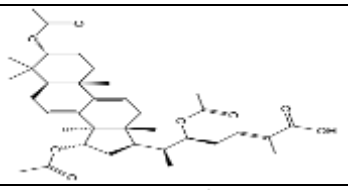
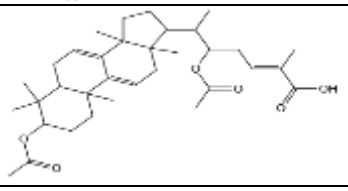
***Ganoderma lucidum* polysaccharides (GLP)**

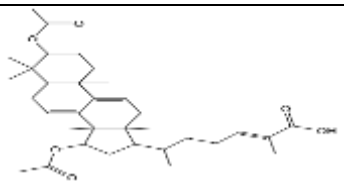
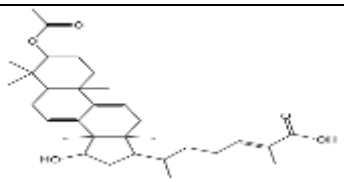
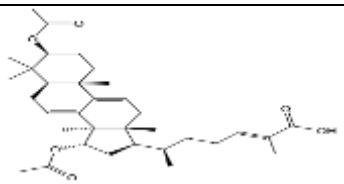
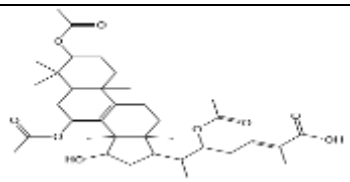
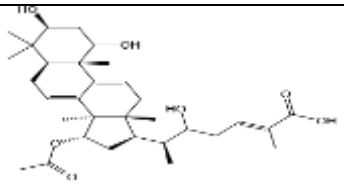
Polysaccharides from GL are noted for their complex and variable structures, which are mostly made of -glucan as the predominant form [38]. Table 2 showed a full list of GL polysaccharide key components and characteristic analyses. Water extraction, alcohol extraction, membrane separation, freezing pretreatment, coenzyme treatment, and ultrasonic catalytic cellulose separation are some of the extraction technologies that have been developed. The changes in the main chain and side chain architectures of GLPs influence their physiological activities. The more biological activity, the longer the primary chain structure. However, due to the complicated spatial organization and variety of heteropoly sugars contained in GL extract, analyzing its polysaccharide structure is difficult. The main chain of GLP is composed primarily of glucose, galactose, and mannose, whereas the branch chain is composed primarily of fucose, xyantang, and arabinose [39]. Furthermore, the fundamental structure of GLP serves as the basis for their investigation. However, determining the primary structure is difficult due to factors such as polysaccharide molecular weight, sugar group order and configuration, composition ratio, uronic acid type and proportion, connection between the sugar chain and the non-sugar component, and the external group of sugar residues. Yan, *et al*. performed acidolysis on GL and discovered seven types of monosaccharides with the molar ratios of arabinose as fucose:galactose:glucose:mannose:rhamnose:xylose being 31.96:5.34:1.89:72.64:5.90:5.24:1.00, respectively [40]. While over 200 different forms of GLP have been identified, only a limited analysis of their repeating units has been done, prompting additional research on their secondary, tertiary, and spatial conformation.

***Ganoderma lucidum* triterpenoids (GLT)**

Formerly, the scarcity of triterpenoids derived from GL hampered study into their anticancer efficacy and underlying processes. The principal components of GLT with anticancer activities were summarized in Table 3. Toth, *et al*. identified six different types of ganoderic acid from GL mycelium, which were discovered to suppress the multiplication of hepatocellular carcinoma cells *in vitro*, indicating a promising direction for triterpenoids in future anti-tumor research. Liu, *et al*. discovered that ganoderic acid T, Mk, Me, S, Mf, and O might decrease the proliferation of several tumor cell types, including transitional cell carcinoma and squamous cell carcinoma, by producing cytotoxicity [51, 52]. These findings shed light on the potential of triterpenoids from GL as antitumor agents. Ganoderic acid Me was found to have substantial anti-tumor action in C57BL/6 mice Lewis lung carcinoma. A 28 mg/kg intraperitoneal injection of ganoderic acid Me demonstrated to dramatically improve the activity of natural killer cells as well as the production of IL-2 and interferon-Y (IFN-Y) [53]. Ganoderic acid Me has also been shown to trigger apoptosis in wild-type human P53 tumor cells. T cell death, CD8+ T cell inactivation, and Treg-mediated immunosuppression all contribute to the formation of a tolerant environment in lung cancers. Ganoderic acid Me has been proved to raise the amount of KB-A-1/Dox in multi-drug resistant cancer cells by 60%, which was thought to promote multi-drug resistance cell sensitivity to adriamycin *via* influencing the activity of membrane protein P-gp [54]. Ganoderic acid T, a triterpenoid produced from GL, has been widely investigated and has demonstrated the substantial anti-tumor effect. *In vitro* investigations demonstrated that ganoderic acid T caused dose-dependent cytotoxicity in a variety of cancer cell lines from humans including lung carcinoma cells PC9, PC9-IR, H1650, and H1975, 95-D, colon cancer cells HCT-116, and lung cancer Lewis cells. Furthermore, it was discovered that ganoderic acid T inhibited 95-D metastasis in lung cancer cells by lowering the expression of MMP-2 and MMP-9 [55]. Furthermore, by modulating the innate immune system and blocking the G1 phase of the cell cycle, ganoderic acid T significantly reduced 95-D cell proliferation. The chemical induced apoptosis in metastatic lung cancer cells *via* an intrinsic route involving

Table 3. Structural parameters of triterpenoids in GL.

Name of compound	Molecular formula	Molecular weight	Chemical structure	References
Ganoderic acid U	$C_{30}H_{48}O_4$	472		[60]
Ganoderic acid V	$C_{32}H_{48}O_6$	528		[60]
Ganoderic acid W	$C_{34}H_{52}O_7$	572		[60]
Ganoderic acid X	$C_{32}H_{48}O_5$	512		[60]
Ganoderic acid Y	$C_{30}H_{46}O_3$	454		[60]
Ganoderic acid Z	$C_{30}H_{48}O_3$	456		[60]
Ganoderic acid T	$C_{30}H_{46}O_3$	612		[61]
Ganoderic acid Mk	$C_{34}H_{50}O_7$	570		[62]

Ganoderic acid Me	$C_{34}H_{50}O_6$	554		[62]
Ganoderic acid Mf	$C_{32}H_{48}O_5$	512		[63]
Ganodermic acid S	$C_{34}H_{50}O_6$	554		[64]
7-O-Ethyl ganoderic acid O	$C_{36}H_{54}O_9$	658		[64]
Ganoderic acid T1	$C_{34}H_{50}O_7$	570		[65]

mitochondrial malfunction and p53 activation [56]. Ganoderic acid T has also been shown to suppress tumor cell HCT-116 growth by inhibiting cell growth, migration, and adherence to the cell membrane and promoting cell homogeneity clustering. The cytotoxicity induced by ganoderic acid T was found to be dependent on the p53 gene, as observed by comparing the results of ganoderic acid T treatment in p53+/+ and p53−/− cell types of HCT-116. The results showed that ganoderic acid T could be a good target for suppressing human cancer cell invasion [57]. Ganoderic acid T has been shown *in vivo* to prevent the growth and spread of Lewis lung cancer tumors. Subcutaneous injection of ganoderic acid T (28 mg/kg) into C57BL/6 mice significantly inhibited Lewis lung cancer tumor development (63.35%) and lung metastasis (78.33%). Quantitative reverse transcription polymerase chain reaction (qRT-PCR) examination of mRNA collected from tumor tissues demonstrated that ganoderic acid T inhibited the production of MMP-2 and MMP-9 mRNA *in vivo*, showing its promise as a tumor metastasis therapy [55]. Lai, *et al*. found that ganoderic acid T has substantial anticancer action against A549 lung adenocarcinoma cells, reducing tumor development and metastasis *in vivo*. The researchers compared the weight, tumor size, survival rate, tumor weight, and metastatic tumor colonies in mouse liver and lung following therapy, confirming the efficacy of ganoderic acid T [58]. Interestingly, the C-26 carboxyl group of ganoderic acid T has been discovered as an active modification site, resulting in increased selectivity for cell cycle arrest in tumor cells comparing to carboxy-terminal derivatives. These data pointed ganoderic acid T as a potentially anticancer treatment option.

Mechanisms of *Ganoderma lucidum* anti-tumor action

Recent research has revealed that GL contains polysaccharides, triterpenoids, and active protein components that perform a variety of biological functions, including inhibiting tumor cell growth and reducing metastatic potential. GL's active constituent has an inhibitory effect on a range of cancers. These effects are achieved primarily through altering the cell cycle, triggering apoptosis, creating cytotoxins that preferentially target tumor cells, preventing angiogenesis, lowering cancer cell growth and invasive metastasis, and controlling signaling pathways.

Regulation of immune response

Current research in the treatment of lung cancer has indicated that the function of lymphocytes is closely related to the expression of perforin and granulosin B. The expression of these proteins in lymphocytes is inhibited in lung cancer patients. GL polysaccharide (GLP), on the other hand, has been discovered to reverse this inhibition, implying that it may have a role in avoiding plasma-induced lymphocyte inhibition in patients with lung cancer [65]. Furthermore, the Caspase family has been identified as a major enzyme involved in cell apoptosis. The mitochondrial apoptosis pathway's cleaved caspase, caspase 3, has been recognized as the most important regulator of cell apoptosis [66]. These findings could shed light on the molecular pathways underlying lung cancer and the possible therapeutic effects of GLP. Chen, *et al*. used an A549 xenograft tumor model to examine the anticancer effects of GL extract *in vivo*. The findings demonstrated that GL extract significantly suppressed the growth of xenografted tumors in nude mice *in vivo* while having no negative side effects. GL extract dramatically raised the production of Bcl-2 and decreased the amount of Bax in lung cancer cells *in vivo* compared to the control group, enhancing apoptosis in lung cancer cells. GL extract also showed to boost cleaved caspase-3 protein levels *in vivo*, implying that GL extract increased caspase-3 activation, lending credence to its anti-tumor actions [67, 68]. GLPs were discovered to offer therapeutic potential in the treatment of liver cancer in a separate investigation. The study found that GLPs improved intestinal flora and microbial metabolic dysfunction in HepG2-induced hepatocellular cancer mice. Further, in mice with liver cancer, GLPs were reported to lower mortality and provide an anti-tumor effect by modulating cecal microbiota and tumor-related genes such as Acaa1b, Fabp4, Mgll, and Scd1 [69]. Overall, GL extract and GLPs had the potential to be effective treatment agents for lung and liver cancer, respectively [70], which might be related to an increase in the ratio of effector to regulatory T cells. GLP was observed to abolish the inhibitory effects of CD4+CD25+Treg on CD4+CD25-TEFF proliferation and boost IL-2 release. The researchers discovered that administering GLP increased the expression of the target MicroRNA-125b (miRNA125b) in hepatocellular cancer mice intracellular factors, which implied that GLP worked to prevent liver cancer by increasing the expression of miRNA125b. Interestingly, the study found that GLP had little influence on tumor-bearing mice's body weight and caused minimal damage to normal liver cells, which implied that GLP was a risk-free therapeutic option for liver cancer [71].

It was discovered that total GLT could alter the levels of cyclinD1, Bcl-2, Bcl-xl, Bax, and Caspase-9 in breast cancer cells by evaluating the expression levels of various key enzymes in the cell apoptosis pathway and studying the apoptosis mechanism of breast cancer cells [72]. Importantly, Caspase-9 activation could lead to the activation of additional caspases as well as the breakage of DNA, the activation of apoptosis in cancer cells, and the suppression of carcinogen activation, which might be the underlying mechanisms for its anti-breast cancer efficacy [73]. The findings indicated that GLT might have possible therapeutic effects on breast cancer, emphasizing the necessity of targeting the cell apoptotic pathway [74].

Production of cytotoxins to tumor cells

GL has been shown in studies to have direct cytotoxicity against cancer cells. GL extract has been reported to dramatically suppress the release of cancer-promoting chemicals such as IL-6, IL-8, MMP2, and MMP9 in a pro-inflammatory condition, resulting in decreased cancer cell survival and migration [75]. Some GLTs such as ganoderic acid N and ganoderic acid A have demonstrated substantial cytotoxicity against cancer cells Hep-G2 and P388 [76]. In BALB/c mice, oral administration of GL extract increased the secretion of cytokines IL-6 and IFN- by type 1 T helper cells and macrophages, enhanced NK cell activity, and stimulated phagocytosis [77]. GLP has been demonstrated to bind to the TLR-4 receptor and activate signaling pathways of ERK, JNK, and p38MAPK. In mouse spleen cells, GLPs were discovered to promote the expression of cytokines GMCSF, GCSF, and M-CSF [78]. These data implied that GLP has a lot of potential in cancer treatment by inducing apoptosis in cancer cells, modulating immune response, and blocking cancer-promoting chemicals [79]. Treatment with 2.5 mg/kg GLP for an extended period resulted in faster recovery of spleen NK cells and NK cells as well as increased T cell and B cell proliferations. Importantly, macrophage phagocytosis was also boosted without any negative consequences, which could be useful in cancer treatment.

Inhibition tumor cells induced angiogenesis

Angiogenesis is important in tumor pathogenesis. Since the concept of "tumor growth has vascular dependence" arose, researchers discovered that, in addition to chemotherapy, radiation, and surgical resection, preventing the development of tumor neovascularization could be a possible technique for decreasing tumor proliferation and spread [80]. *In vivo* research has shown that GLP could prevent angiogenesis generated by matrix gel and heparin. Active compounds of GLT such as ganoderic acid F have been discovered as powerful inhibitors of angiogenesis caused by Martigel using IR, H-1, C-13-NMR, and MS, implying that GLT's efficacy may be connected to tumor angiogenesis suppression. In addition, *Ganoderma* spore powder has been found in nude mice to limit subcutaneous tumor growth of SMMC-7721 cells, potentially *via* reducing tumor angiogenesis [81]. Yang, *et al*. found that ganoderic acid A at 0.5 mmol/L successfully inhibited the development of glioma C6 cells in glioma model rats. The researchers discovered a decrease in CD31 expression, indicating suppression of tumor angiogenesis, which ultimately led to tumor growth inhibition [82]. In a study by Liu, *et al*., a nude mouse model of A549 tumor cells was utilized to evaluate the anti-tumor effects of GLT. In comparison to the control group, the combination of GLT and gefitinib significantly reduced the expression of the vascular endothelial growth factor receptor 2 (VEGFR2) gene and protein while increasing the expression of angiostatin and endostatin [83]. Taken together, those results demonstrated that GLT could effectively limit tumor blood vessel growth, resulting in anti-cancer benefits. The combination of GLT and gefitinib represented a viable technique for treating lung cancer with fewer side effects. These findings point to promising new avenues for cancer treatment.

Cell cycle arrest induction

GL water extract has been demonstrated to reduce the growth of bowel cancer HCT116 cells by causing a cell cycle halt and encouraging apoptosis in the treatment of pancreatic cancer. It can also boost 5-fluorouracil's anticancer efficacy by decreasing integrin 1 and E-cadherin mRNA expression [84]. Similarly, GL water extract has been shown to suppress human pancreatic cancer SW1990 cell proliferation, migration, and invasion by upregulating spleen tyrosine kinase [85]. Zolj, *et al*. investigated the effect of total GLT on lung cancer cell growth and apoptotic protein levels in the setting of lung cancer treatment. These findings implied that GLT induced apoptosis and reduced lung cancer cell growth *via* an increase in Bax/large molecule B lymphoblastic tumor protein (Bcl-xl) [86]. In terms of liver cancer treatment, Ruan, *et al*. confirmed that GLT could hinder cellular proliferation by blocking the transition from the

G0 stage of the cell cycle to the early phase of DNA synthesis (G1), resulting in cell cycle arrest [87]. GL has been widely examined for its possible anti-tumor activities in cancers ranging from pancreatic through lung, liver, cervical, and prostate. The aqueous extract of GL was discovered to decrease the growth of bowel cancer HCT116 cells by causing cell death and improving the anticancer activity of 5-fluorouracil in pancreatic cancer [88]. Similarly, GL extract showed to suppress human pancreatic cancer SW1990 cell growth, motility, and invasive by upregulating spleen tyrosine kinase. Total GLT was discovered to cell cycle arrest and decreasing lung cancer cell proliferation in the treatment of lung cancer. GLT was discovered to suppress the proliferation of liver cancer cells by preventing the transition from the G0 phase of the cell cycle to the early phase of DNA synthesis in the treatment of liver cancer [89]. GLP has been shown in cervical cancer treatment to preserve immunological organs, boost oxidative alpha amylase, and limit tumor growth with substantial anti-tumor effectiveness and low adverse effect. Similarly, GLP was discovered to increase tumor cell apoptosis by controlling the expression of cellular senescence proteins. GLP has been demonstrated to limit the proliferation of prostate cancer cells, mostly by decreasing the transformation of cancer cells from the G1 to the DNA synthesis phase and lowering apoptotic proteins. Furthermore, GLT was discovered to decrease the utterance of anti-apoptotic proteins, boost the production of top player enzymes, impede the development of prostate cancer cells by inhibiting the expression of matrix metalloproteinases, and inhibit their migration and invasion, inducing cell apoptosis. These data imply that GL could be a promising alternative or supplemental treatment for several forms of cancer [90, 91].

Regulate signal transduction pathways

The extracellular signal-regulating protein kinase signaling pathway (ERK) is a key control over cell growth, invasion, motility, differentiation, and apoptosis in the setting of hepatoma therapy [92]. GLP has shown to decrease the production and phosphorylation of ERK-related proteins in a dose-dependent manner, resulting in the induction of apoptosis and the prevention of lung cancer cell growth. Another significant mechanism that governs tumor cell biological processes is the PI3K/Akt signaling system. After phosphorylation, activated PI3K connects to downstream molecule Akt, activating downstream apoptosis-related proteins [93]. GLP has shown to prevent PI3K and Akt activation with a greater inhibitory impact at higher concentrations as well as down-regulate the transcriptional activity of p-PI3K and p-Akt [94]. Therefore, GLP's inhibitory effect on the malignant phenotype of hepatocellular carcinoma cells was linked to the inhibition of the PI3K/Akt transcription factor. Jin, *et al*. examined the expression and phosphorylation levels of signal transduction and transcription activator 5 (STAT5) and Janus kinase (JAK) in human cervical cancer cells in a study on the therapy of cervical cancer [95]. GLP was proved in studies to effectively lower phosphorylated STAT5 and JAK levels while maintaining STAT5 and JAK expression in cervical cancer cells. These data implied that GLP inhibited the JAK/STAT5 signaling pathway in cervical cancer cells, resulting in decreased viability and apoptosis [96]. Cao, *et al*. revealed that GLP reduced tumorigenesis and immune evasion in mice with cervical cancer by using an ICOS inhibitor. GLP was discovered to decrease intestinal cancer cell proliferation in rectal cancer *via* modulating the p-Akt1/p-ERK signaling pathway and Bax/Bcl-2 protein production [97]. Li, *et al*. also conducted *in vitro* and *in vivo* studies to evaluate the anti-cancer effects of GL neutral triterpenoids and acidic triterpenoids.

Conclusion

In recent years, the incidence and mortality of cancer are still rising year by year. In 2022, there were 24.68 million new cancer cases worldwide. However, there are few effective treatment measures for cancer at present, and existing treatment methods also have problems such as

strong drug resistance, large side effects, and high cost. *Ganoderma lucidum* has attracted much attention from researchers because of its high safety, low cost, and great hope for efficient treatment of cancer. In this study, the main components of GL including active protein, polysaccharides, and triterpenoids were reviewed. It was found that they played a powerful anti-tumor effect through immune regulation, inhibition of cytotoxicity, inhibition of tumor angiogenesis, and inhibition of tumor cell proliferation, providing a reference for efficient treatment of tumor.

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