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## Antitumor Properties of *Ganoderma lucidum* Polysaccharides and Terpenoids

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### Abstract

Camargo MR, Kaneno R. Antitumor Properties of *Ganoderma lucidum* Polysaccharides and Terpenoids. *ARBS Annu Rev Biomed Sci* 2011;13:1-8. *Ganoderma lucidum* is an edible medicinal mushroom with immunomodulatory and antitumor properties, which are mainly attributed to polysaccharides and triterpenes that can be isolated from mycelia, fruiting bodies and spores. *G. lucidum* has been used in a powdered form, as a medicinal beverage and a nutraceutical food (usually dried). In the present review we report some historical facts and the experimental evidence that polysaccharides and triterpenes obtained from this mushroom present potential antitumor activity. Direct effects on tumor cells include induction of apoptosis and interference in the cell cycle, whereas indirect effects are based on the modulation of immune response, usually impaired by cancer cells. Data indicate that *G. lucidum* can be used as a complementary tool for treatment of cancer patients.

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**Keywords:** Immunomodulation; Mushroom; Polysaccharides; Triterpenes; Tumor.

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## 1. Introduction

The edible mushroom *Ganoderma lucidum* (*G. lucidum*), popularly known as Lingzhi in China and Reishi or Mannentake in Japan, belongs to the Fungi kingdom, order Polyporales and family Ganodermataceae. Due to its intrinsic immunomodulatory and antitumor properties, it has been widely used

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for the general promotion of health and longevity in Asian countries. During the Ming Dynasty, this basidiomycete was known as “the mushroom of immortality” and/or “the marvelous herb”, and it was used as a tonic to cure several human diseases, such as hepatopathy, hypertension, nephritis, bronchitis, and cancer (Sliva *et al.*, 2002; 2003; Zhang *et al.*, 2002; Chan *et al.*, 2005; Lin, 2005). In the Imperial Court of ancient China, its dried powder was especially popular as a cancer chemotherapeutic agent (Mizushima *et al.*, 1998). Nowadays, *G. lucidum* is commercialized in a powdered form, as a medicinal beverage, as well as a nutraceutical food.

Most of the different compounds, with several biological activities, extracted from the mycelia, fruiting bodies or spores are associated with antitumor effects (Chiu *et al.*, 2000). One of the first scientific reports on antitumor effects of *G. lucidum* was published by Maruyama *et al.* (1989), who observed that aqueous but not ethanolic extract of this mushroom was remarkably effective at inhibiting the subcutaneous growth of murine sarcoma 180. This effect was mainly attributed to a carbohydrate-rich fraction obtained by ion-exchange chromatography, and produced the highest effect when the animals were inoculated intraperitoneally.

Extracts obtained from powdered spores and fruiting bodies can inhibit the active transcription factors AP-1 enzyme and NF- $\kappa$ B in breast and prostate cancer cells, by inhibiting the expression of urokinase-type plasminogen activator (uPA) and its receptor. In fact, increased levels of urokinase expression were shown to be associated with malignancy and it was observed that inhibition of this enzyme suppresses metastasis of breast and prostate cancer cells (Sliva *et al.*, 2002). Ingestion of 1.5 g/day of a water-soluble extract, obtained from mycelia grown in liquid culture medium, is able to significantly diminish the colorectal adenomas of patients after 12 months of treatment (Oka *et al.*, 2010).

Zhuang *et al.* (2009) reported that patients with different types of cancer, under chemotherapy and/or radiotherapy, who ingested a dietary complex with *G. lucidum* for 6 weeks showed decreases of leukopenia and neutropenia, as well as a delay in the decrease of NK-cell and CD4 lymphocyte counts. The maintenance of NK cells by the dietary complex was attributed to the activity of the *G. lucidum* polysaccharides. However, the fact that this complex was prepared with many other phytotherapeutic species precludes any conclusion that the final effect was due to Ganoderma.

Among the compounds showing pharmacological and immunomodulatory properties, special attention has been directed to polysaccharides and triterpenes.

## 2. Immunomodulatory Effects of *G. lucidum* Polysaccharides

The main bioactive compounds originally isolated and purified from *G. lucidum* were identified as polysaccharides (GL-PS). The extensive immunomodulatory effects of GL-PS include the activation of mononuclear phagocyte functions, humoral and cellular immunity, and the proliferation and differentiation of immune precursor cells to effector cells (Cao & Lin, 2002) while (1 $\rightarrow$ 6)- $\beta$ -glucans of GL-PS extract was shown to be the most immunogenic polysaccharide fraction (Chan *et al.*, 2007). The main properties of polysaccharides are summarized at the Table 1.

Early reports by Lieu *et al.* (1992) indicated that a polysaccharide fraction of this mushroom is able to induce, by in vitro stimulation, the production of soluble “factors” by human mononuclear cells. This conditioned medium, but not polysaccharide solution alone, induced the proliferation of the U937 monocytic leukemia cell line and induced their differentiation to monocytes/macrophages. This view was further supported by Wang *et al.* (1997), who showed that the addition of Ganoderma polysaccharides to human macrophage cultures increases the in vitro production of cytokines such as IL-1 $\beta$ , TNF- $\alpha$  and IL-6. In addition, T lymphocytes were stimulated to release IFN- $\gamma$ . Supporting the previous report by Lieu *et al.* (1992), these authors also observed that T cell- or macrophage cultures supernatants stimulated with polysaccharides induced the differentiation of U937 cells into mature monocyte/macrophage phenotype (expression of CD14 and CD68). In contrast to the former authors, it was observed that the fraction suppresses the proliferation and clonogenicity of U937 and HL60 cells, probably by inducing their apoptosis, as demonstrated both by flow cytometry and DNA electrophoresis. The authors have further demonstrated that the main antitumor cytokines were IFN- $\gamma$ . and TNF- $\alpha$ .

With regard to its effects on dendritic cells (DC) it was observed that addition of polysaccharides to murine DC culture increases the co-expression of CD11c and I-A/I-E (MHC class II) molecules by these cells, both promoting the mRNA expression and increasing the production of IL-12 p40. This study showed that GL-PS promote not only the maturation of cultured murine bone marrow-derived DC, but also their functions, indicating that GL-PS are able to enhance the priming of T lymphocytes (Cao & Lin, 2002). Phenotypic and functional signs of DC maturation were observed after incubation of murine cells with GL-

PS, which showed significant production of both IL-12 and IL-10 (Chan *et al.*, 2007). This finding indicates that mushroom polysaccharides can influence the development of the immune response by affecting very early steps of specific immunity.

Treatment of sarcoma 180-bearing mice with a bioactive fraction of *G. lucidum* inhibited the tumor growth by 60%, a reduction followed by the proliferation and differentiation of spleen B lymphocytes that produced a large concentration of IgM. Polysaccharide fraction also activated bone marrow-derived macrophages, which, in turn, produced IL-1 $\beta$ , TNF- $\alpha$  and reactive nitrogen intermediates, augmented phagocytosis and raised the macrophage-mediated tumor cytotoxicity (Zhang *et al.*, 2010).

Chan *et al.* (2007), found that purified polysaccharides from *G. lucidum* mycelium can induce the proliferation of human peripheral blood mononuclear cells (PBMC). Effects on innate immunity include the activation of TLR4, a key receptor for innate immune response, expressed by both murine macrophages and human DC, as well as murine B cells (Hsu *et al.*, 2004; Shao *et al.*, 2004).

Analysis by DNA microarray has shown that although transcription of phagocytic cell markers (CD36, CD206 and CD209) had been decreased, the transcription of genes associated with pro-inflammatory chemokines (CCL20, CCL5 and CCL19), cytokines (IL-27, IL-23A, IL-12A and IL-12B), and co-stimulatory molecules (CD40, CD54, CD80 and CD86) was elevated after mushroom treatment, showing that GL-PS can effectively promote the activation and maturation of DCs, thereby favoring the development of Th1 response (Lin *et al.*, 2006).

The polysaccharide fraction is able to directly affect tumor cells. In fact, Jiang *et al.* (2004) showed that *G. lucidum* inhibits the growth of breast cancer cells through cell cycle arrest at G0/G1, which was mediated by suppression of NF- $\kappa$ B signaling and down-regulation of cyclin D expression. *G. lucidum* also induced cell cycle arrest at the G2/M phase in ovarian cancer cells, inducing apoptosis by activating caspase 3 and increasing p53 molecule, and strongly decreased the cell numbers in a dose-dependent manner (Zhao *et al.*, 2011). Nanotechnology has enabled the preparation of chitosan nanospheres loaded with GL-PS that showed significant antitumor efficacy in vitro against HepG2, HeLa and A549 cancer cell lines, through both direct cytotoxic effects on tumor cells and growth-promoting effects on spleen cells (Li *et al.*, 2010).

The chemopreventive potential of carbohydrate compounds contained in *G. lucidum* was evaluated through a chemical colon carcinogenesis model. It was observed that the development of colonic aberrant crypt foci, induced in rats by s.c inoculation of azoxymethane (Lu *et al.*, 2001, 2003) or dimethylhydrazine (Lu *et al.*, 2002), can be prevented by dietetic treatment with mycelium-derived water-soluble extract. The colon is especially susceptible to inflammation-associated carcinogenesis while the generation of reactive oxygen species (ROS) is associated with carcinogenesis in some tissues. Therefore, it is possible to suggest that the ability of *G. lucidum* amino-polysaccharides to protect against oxidative damage induced by ROS can be one mechanism for chemopreventive activity against the development of colon cancer. In fact, it was reported that this fraction dose-dependently inactivates hydroxyl radicals and superoxide anions, and reduces DNA strand breaks caused by hydrogen peroxidase (Lee *et al.*, 2001).

These results were supported by Lakshmi *et al.* (2003) who observed that ethanol extract of *G. lucidum* mycelia inhibits the Fe<sup>++</sup>-induced lipidic peroxidation in rat liver and croton oil-induced peroxidation in mouse skin. This extract was also able to reduce the acute and chronic inflammatory reactions induced by carrageenan and formalin, respectively, which were associated with antimutagenic activity for changes induced by sodium azide or methyl nitrosoguanidine.

One of the main polysaccharide fractions is F3, which contains fucose (Chen *et al.*, 2004). This fraction works as an immunomodulator and is able to stimulate spleen cell proliferation and the expression of cytokines, especially IL-1, IL-2 and INF- $\gamma$ , suggesting a possible NK cell activation and antitumor activity (Wang *et al.*, 2002). It has been also proposed that F3 binds to TLR4 on macrophages in order to activate proteins such as extracellular signal-regulated kinase (ERK) – involved in the regulation of meiosis, mitosis and post-mitotic functions – as well as c-Jun N-terminal kinase (JNK) and p38, involved in apoptosis, cell differentiation, proliferation, inflammatory conditions and cytokine production (Chen *et al.*, 2004). This polysaccharide modulates Th1 response by inducing high expression of INF- $\gamma$ . DNA microarray allows us to state that the product can induce death receptor ligands (TNF- $\alpha$  and TRAIL) leading to cell shrinkage and apoptosis, thus demonstrating the efficacy of F3 fractions against tumor development (Cheng *et al.*, 2007).

Feeding mice fermented wheat flour supplemented with *G. lucidum* for 3 months caused both immunostimulatory and immunosuppressive effects in their peritoneal macrophages and spleen lymphocytes. An increase in the IFN- $\gamma$  concentration was observed simultaneously with decreases in NO

production, TNF- $\alpha$  release and the numbers of CD3+ and CD8+ T spleen cells, and a rise in IL-10 production. These data suggest that *G. lucidum* metabolites can act not only to enhance specific immune response against tumor cells or pathogenic microorganisms, but also to mitigate the adverse effects of the immune system such as autoimmune diseases and the inflammatory process (Rubel *et al.*, 2010).

Table 1: Antitumor effects of Polysaccharides.

	<b>Antitumor effects</b>	<b>References</b>
	Increase INF- $\gamma$	Cheng <i>et al.</i> , 2007
<b>Citokines, kemokines</b>	Increase IL-1 $\beta$ , TNF- $\alpha$ , IL-6	Wang <i>et al.</i> , 1997
	Stimulate spleen cells proliferation and IL-1, IL-2 and INF- $\gamma$ expression	Wang <i>et al.</i> , 2002
	Increase INF- $\gamma$ and IL-10, decrease TNF- $\alpha$ , NO production and CD3 and CD8 spleen cells	Rubel <i>et al.</i> , 2010
	Increase IL-12	Cao & Lin 2002
	Increase IL-1 $\beta$ , TNF- $\alpha$ , NO production and phagocytosis	Zhang <i>et al.</i> , 2010
	Production of IL-12 and IL-10	Chan <i>et al.</i> , 2007
	Induce IL-1 expression	Chen <i>et al.</i> , 2004
	Suppress proliferation and clonogenicity of U937 and HL 60 cells, by inducing their apoptosis	Lieu <i>et al.</i> 1992; Wang <i>et al.</i> , 1997
<b>Prolif., different., maturation</b>	Decrease by 60% tumor growth in sarcoma-bearing mice, proliferation and differentiation of spleen B cells	Zhang <i>et al.</i> , 2010
	Induce differentiation of monocytic leukemia cell line to monocyte/macrophage cells	Lieu <i>et al.</i> , 1992
	Growth promotion of spleen cells	Li <i>et al.</i> , 2010
	Increase cytotoxicity mediated by macrophages, humoral and cellular immunity, proliferations and differentiation of effector cells	Cao & Lin 2002; Zhang <i>et al.</i> , 2010; Chan <i>et al.</i> , 2007
	Promote DC maturation and activation	Cao & Lin 2002;; Lin <i>et al.</i> , 2006; Chan <i>et al.</i> , 2007
	Stop cell cycle at G0/G1 phase, decrease NF- $\kappa$ B and D cyclin	Jiang <i>et al.</i> , 2004
<b>Cell cycle</b>	Stop cell cycle at G2/M phase, activate caspase-3, induce apoptosis of ovarian cancer cells	Zhao <i>et al.</i> , 2011
	Prevent the development of colonic aberrant crypt foci in chemical colon carcinogenesis	Lu <i>et al.</i> , 2001, 2002, 2003
	Activate TLR4 in murine macrophage and B cells, and human DC cells	Hsu <i>et al.</i> , 2004; Shao <i>et al.</i> , 2004
<b>Ligands</b>	Polysaccharides bind to TLR4 on macrophages and activate ERK, JNK and p38	Chen <i>et al.</i> , 2004
	Induce death receptor ligands (TRAIL)	Cheng <i>et al.</i> , 2007
	Increase the ability to enhance priming of T lymphocytes	Cao & Lin 2002
<b>Other effects</b>	Increase IgM and activate macrophage	Zhang <i>et al.</i> , 2010
	Induce cytotoxic effects against HepG2, HeLe and A549 tumor cells	Li <i>et al.</i> , 2010
	Inactivate hydroxyl radicals, superoxide anion and reduce DNA strand breaks	Lu <i>et al.</i> , 2001
	Decrease acute and chronic inflammatory reaction	Laksmi <i>et al.</i> , 2003

### 3. Terpenoids from *Ganoderma lucidum*

The ganoderic acids (GAs), a highly oxygenated type of lanostane-type triterpenoid constitute another group of compounds isolated from *G. lucidum* studied by some authors. Six ganoderic acids – denominated  $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\zeta$ ,  $\eta$  and  $\tau$  – were isolated from spores and chemically characterized by Min *et al.* (2000), and showed cytotoxic effects against Meth-A (sarcoma) and LLC (lung) tumor cell lines. Terpenoid types and their main effects are summarized at the Table 2.

Ha *et al.* (2000) also isolated 2 lanosteroids from the basidiocarpe (fruiting body) of this mushroom, one of which markedly increased the activity of NAD(P)H:quinone-oxidoreductase. Since this enzyme takes part in xenobiotic metabolism, the determination of its activity can be used to detect the antitumor chemopreventive potential of the product.

Submerged fermentation of *G. lucidum* is viewed as a promising technology for production of these triterpenes, and substantial efforts have been devoted in the last decade towards improving their production (Xu 2010). Up to the year 2000, over 120 types of triterpenoids were isolated from *G. lucidum* and other species of the genus *Ganoderma*.

Ganoderic acids A ( $\alpha$ ), F ( $\phi$ ) and H ( $\eta$ ) can inhibit the growth (cell proliferation and colony formation) and invasive behaviors (adhesion, migration and invasion) of human breast cancer cells through the down-regulation of cyclin-dependent kinase 4 (Cdk4) expression and the suppression of uPA secretion by these cells (Jiang, 2008). In addition, it was demonstrated that ganoderic acid X ( $\xi$ ) and T ( $\tau$ ) induced respectively, apoptosis in human hepatoma and metastatic lung tumor cells mediated by mitochondrial dysfunctions and stimulation of the caspase-3 activity (Li *et al.*, 2005; Tang *et al.*, 2006).

Extracts of *G. lucidum* triggered the killing of human gastric carcinoma AGS cells through the activation of the intrinsic apoptosis pathways by down-regulating the anti-apoptotic Bcl-2 protein and consequently elevating the Bax/Bcl-2 ratio. The extract also increased the enzymatic activity of caspase cascades, such as caspases 8 and 9, thereby decreasing the levels of total Bid expression. Since the products of Bid cleavage can bind to Bax, they promote conformational changes in this protein and activate caspases 9 and 3. Moreover, *G. lucidum* extracts were shown to inactivate phosphatidylinositol-3 kinase (PI3K)/Akt, which plays a critical role in the regulation of cell survival or death in many physiological and pathological settings (Jang *et al.*, 2010). Lee *et al.* (2011), showed that ergosta-7,22-diene-2 $\beta$ ,3 $\alpha$ ,9 $\alpha$ -triol (EGDT), extracted from the fruiting bodies of this edible mushroom, can activate apoptosis by DNA fragmentation and caspase-3 activation. In vivo, EGDT significantly decreased the Lewis lung carcinoma (LLC) growth, indicating that this triterpene fraction is one of the apoptotic parts of *G. lucidum* mushroom.

Methanol extract containing total terpenoids (GLme) and purified methanol extract containing mainly acidic terpenoids (GLpme) can both inhibit tumor growth of B16 mouse melanoma cells and reduce the viability of B16 cells in vitro. This must occur because GLme inhibit cell proliferation and induce caspase-dependent apoptotic cell death mediated by upregulated p53 and inhibited Bcl-2 expression. They showed that GLme was associated with intensified production of reactive oxygen species, and its neutralization resulted in partial recovery of tumor cell viability (Harhaji *et al.*, 2009).

Yue *et al.* (2010) showed that the ganoderic acids F( $\phi$ ), K( $\kappa$ ), B( $\beta$ ), D( $\delta$ ) and AM1 might exert their cytotoxicity on HeLa cells. Treatment of such cells with these ganoderic acids induces several proteins, 12 of which show the same tendency after treatment with different acids. The authors grouped these proteins according to their main functional features as being associated with: a) cell proliferation/death, b) carcinogenesis, c) oxidative stress or d) calcium signaling and endoplasmic reticulum stress. Therefore, even though some of such proteins as IL-17E, TPM4-ALK and ribonucleoprotein K are correlated with carcinogenesis process, the treatment of tumor cells with those acids induces other proteins that play a protective role, including ubiquitin 2 (associated with antigen processing machinery), 14-3-3 $\beta\alpha$ , (cell cycle control and apoptosis), peroxiredoxin 2, (control of oxidative stress), and nucleobinding-1 and reticulocalbin 1 (calcium signaling and RE stress).

Ganodermanontriol (GNDT), a purified triterpene from GL, was shown to inhibit the proliferation of HCT-116 and HT-29 colon cancer cells in vitro by inhibiting: transcriptional activity of  $\beta$ -catenin, protein expression of cyclin D1(target gene) in a dose-dependent manner and the expression of Cdk-4 and PCNA. A dose-dependent increase was even observed in protein expression of E-cadherin and  $\beta$ -catenin in HT-29 cells, an important pathway of progression of colorectal cancer. In addition, Jedinak (2011) demonstrated suppressed tumor growth in a xenograft model of these cells implanted in nude mice without any side-effects.

Table 2: Antitumor effects of Ganoderic Acids.

	Antitumor effects	References
	Acids X ( $\xi$ ) and T ( $\tau$ ) induce apoptosis in human hepatoma and metastatic lung tumor cells, mitochondrial dysfunctions and stimulation of the caspase-3 activity	Li <i>et al.</i> , 2005; Tang <i>et al.</i> , 2006
Proliferation and apoptosis	Down-regulate the anti-apoptotic Bcl-2 protein, raise the Bax/Bcl-2 ratio, increase caspase-8 and 9, decrease the levels of total Bid expression, activate caspase-9 and 3, and inactivate PI3K/Akt of human gastric carcinoma AGS cells	Jang <i>et al.</i> , 2010
	EGDT activates apoptosis, promotes DNA fragmentation and caspase-3 activation, and significantly decreases LLC growth	Lee <i>et al.</i> , 2011
	GLme inhibits cell proliferation of B16 mouse melanoma cells,	Harhaji <i>et al.</i> , 2009
	GNDT inhibits the proliferation of HCT-116 and HT-29 colon cancer cells <i>in vitro</i> , and suppresses tumor growth in nude mice	Jedinak, 2011
	Acids A ( $\alpha$ ), F ( $\phi$ ) and H ( $\eta$ ) can inhibit the cell proliferation, colony formation, adhesion, migration and invasion of uPA of human breast cancer cells	Jiang, 2008
	Down-regulate Cdk4 expression and the suppression of uPA of human breast cancer cells	Jiang, 2008
Ligands	Lanosteroids increase activity of NAD(P)H quinone oxidase	Ha <i>et al.</i> , 2000
	Up-regulate p53 molecule, inhibit Bcl-2 expression and intensifies the production of reactive oxygen species	Harhaji <i>et al.</i> , 2009
	Inhibit transcriptional activity of $\beta$ -catenin and the protein expression of cyclin D1, Cdk-4 and PCNA, and increase protein expression of E-cadherin and $\beta$ -catenin,	Jedinak, 2011
	Acids $\gamma$ , $\delta$ , $\epsilon$ , $\zeta$ , $\eta$ and $\tau$ show cytotoxic effect against Meth-A and LLC tumor cell lines	Min <i>et al.</i> , 2000
Other effects	Acids F( $\phi$ ), K( $\kappa$ ), B( $\beta$ ), D( $\delta$ ) and AM1 present cytotoxicity against HeLa cells	Yue <i>et al.</i> , 2010
	Induce the production of IL-17E, TPM4-ALK, ribonucleoprotein K, ubiquitin 2, 14-3-3ba, peroxiredoxin 2, nucleobinding-1 and reticulocalbin-1	Yue <i>et al.</i> , 2010

## 4. Conclusion

Different compounds of *G. lucidum* produce distinct effects on human and murine immune cells, thus enhancing the functions of lymphocytes, monocytes, macrophages, dendritic cells, neutrophils and NK cells. As reported by some authors, polysaccharides from this edible mushroom constitute the main immunomodulatory compound and produce a direct antitumor effect. On the other hand, triterpenes kill tumor cells by inducing apoptosis and interfering with the cell cycle.

In conclusion water-soluble and water-insoluble fractions of this mushroom exhibit diverse effects and are able to both improve the anticancer immuneresponse and minimize the collateral effects of chemotherapeutic treatments.

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