Cellular and Physiological Effects of *Ganoderma lucidum* (Reishi)

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Abstract: In Asia, a variety of dietary products have been used for centuries as popular remedies to prevent or treat different diseases. A large number of herbs and extracts from medicinal mushrooms are used for the treatment of diseases. Mushrooms such as *Ganoderma lucidum* (Reishi), *Lentinus edodes* (Shiitake), *Grifola frondosa* (Maitake), *Hericium erinaceum* (Yamabushitake), and *Inonotus obliquus* (Chaga) have been collected and consumed in China, Korea, and Japan for centuries. Until recently, these mushrooms were largely unknown in the West and were considered "fungi' without any nutritional value. However, most mushrooms are rich in vitamins, fiber, and amino acids and low in fat, cholesterol, and calories. These mushrooms contain a large variety of biologically active polysaccharides with immunostimulatory properties, which contribute to their anticancer effects. Furthermore, other bioactive substances, including triterpenes, proteins, lipids, cerebrosides, and phenols, have been identified and characterized in medicinal mushrooms. This review summarizes the biological effects of *Ganoderma lucidum* upon specific signaling molecules and pathways, which are responsible for its therapeutic effects.

Keywords: mushroom, *Ganoderma lucidum*, polysaccharides, triterpenes, signaling pathways.

INTRODUCTION

Ganoderma lucidum (Fr.) Karst (Ganodermataceae), basidiomycetous fungi, has been used as a medical remedy in traditional Chinese medicine (TCM) and in many Asian countries during the past two millennia [1, 2]. This edible mushroom was thought to preserve human vitality and to promote longevity [3]. *Ganoderma lucidum* has been used to treat various human diseases such as allergy, arthritis, bronchitis, gastric ulcer, hyperglycemia, hypertension, chronic hepatitis, hepatopathy, insomnia, nephritis, neurasthenia, scleroderma, inflammation, and cancer. In addition to having immunostimulatory effects, *Ganoderma lucidum* has been reported to have a variety of other pharmacological effects, which include analgesic, anti-aging, anti-atherosclerotic, anti-bacterial, anticancer, anti-fibrotic, anti-hypertensive, anti-inflammatory, anti-nociceptive, anti-oxidative, anti-platelet, anti-thrombotic, anti-ulcer, anti-viral, chemopreventive, hepatoprotective, hypoglycemic, hypolipidemic, and radioprotective effects [4-29]. Different compounds with various biological activities, including polysaccharides, triterpenes, proteins, lipids, cerebrosides, and phenols, have been extracted from mycelia, the fruiting bodies or spores of *Ganoderma lucidum,* and some of them have been linked to possible therapeutic effects (see below). Current research aimed at the identification and characterization of specific molecular targets for *Ganoderma lucidum* will add to our knowledge of the disease modifying properties of this dietary agent and will help direct its use as a therapeutic agent in Western medicine.

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EFFECTS OF POLYSACCHARIDE- AND SACCHARIDE-CONTAINING FRACTIONS IN VITRO

The biologically active compounds originally isolated from *Ganoderma lucidum* were identified as polysaccharides, and their ability to inhibit cancer was observed in subcutaneously transplanted sarcoma-180 cells in mice [30]. Although more than 100 types of polysaccharides have been isolated from *Ganoderma lucidum*, chemical analysis revealed that the most active polysaccharides are in the form of β-D-glucans, and the antitumor activity was exhibited mainly in the water-soluble branched [1→3]-β-D-glucans Fig. (**1**), which are usually isolated by extraction with hot water [9, 31]. The anticancer activity of polysaccharides from *Ganoderma lucidum* is felt to be mediated through complement receptor type 3 (CR3, $\alpha_M\beta_2$ integrin, CD11b/CD18), which binds β-glucan polysaccharides [32] (Table 1).

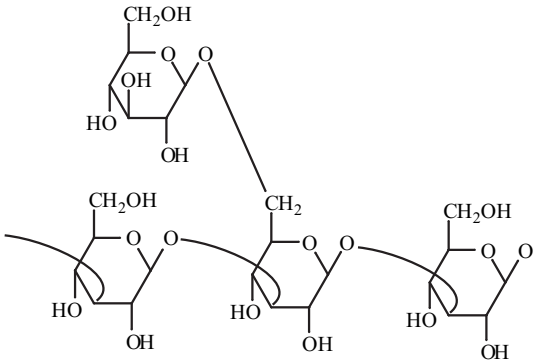

Fig. (1). Backbone structure of β-D-glucans from *Ganoderma lucidum*.

Ganoderma lucidum has been used for the treatment of a variety of different diseases; however, it's effects at the cellular and molecular levels remain elusive. The polysaccharide fraction of *Ganoderma lucidum* (PS-G)

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Table 1. ***In vitro*** **Effects of Polysaccharides Isolated from** ***Ganoderma lucidum***

Fraction	Biological Effect	Cell Type	Ref.
PS-G (polysaccharides)	Inhibition of growth[a], induction of differentiation[a]	U937 (leukemia)	33
	Induction of apoptosis[a]	HL-60, U937 (leukemia)	4
	Stimulation of production of IL-1β, TNF-α, IL-6	monocyte-macrophages	4
	Stimulation of production of IFN-γ	T-lymphocytes	4
	Inhibition of apoptosis through the activation of PI3K/Akt pathway	neutrophils	34
	Stimulation of phagocytosis and chemotaxis through the activation of PI3K, PKC, Src, p38 MAPK	neutrophils	35
	Activation of GST	NCTC-1469 (liver)	17
	Induction of neuronal differentiation, prevention of apoptosis, phosphorylation of Erk1, Erk2, CREB	PC12 (neuron)	36
G009 (amino-polysaccharides)	Antioxidant	HL-60 (leukemia)	18
Glycoprotein, (with fucose)	Stimulation of expression of IL-1, IL-2, IFN-γ, and cell proliferation	spleen cells	38
GLIS (proteoglycans)	Stimulation of cell proliferation, induction of IL-2 secretion, stimulation of expression of PKCα and PKCγ	B-lymphocytes	39
APBP (acidic protein bound polysaccharide)	Antiviral activity	vero cells	40
Cerebrosides	Inhibition of DNA polymerase		41

[a] – indirect effect of conditioned media from human blood mononuclear cells stimulated by PS-G (PSG-MNC-CM)

indirectly effects the growth of leukemia cells U937 [33]. Conditioned media from human blood mononuclear cells stimulated with PS-G (PSG-MNC-CM) significantly inhibit the growth of U937 cells. Furthermore, PSG-MNC-CM induces the differentiation of U937 cells into mature monocytes/macrophages. However, this effect is only present in conditioned media (PSG-MNC-CM) and PS-G itself, does not affect U937 cells [33]. In other studies, PSG-MN-CM induces apoptosis in HL-60 and U937 leukemia cells. Moreover, PS-G directly stimulates production of interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 from human monocyte-macrophages and interferon (IFN)-γ from T lymphocytes [4]. These PS-G–induced cytokines suppress clonogenicity of human leukemia cells. Therefore, these effects of polysaccharides from *Ganoderma lucidum* are mainly the result of activation of immune cell responses.

PS-G also enhances immune responses and elicits antitumor effects from human neutrophils by inhibiting spontaneous and Fas-mediated apoptosis through activation of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, independent of the extracellular signal-regulated kinase (Erk) pathway [34]. In addition, PS-G stimulates phagocytosis and chemotaxis of neutrophils through the mitogen-activated protein kinase (MAPK) and protein kinase C (PKC) pathways [35].

Polysaccharides from *Ganoderma lucidum* demonstrate chemopreventive effects in normal mouse liver cells (NCTC-1469), which were mediated by the induction of the activity of the detoxification enzyme glutathione S-transferase (GST) [17]. Although the mode of action of polysaccharides from *Ganoderma lucidum* on the activity of GST is not clearly characterized, the induction of GST activity appears to be related to the amount of protein present in polysaccharide-protein complexes in *Ganoderma lucidum* [17].

Water extracts containing polysaccharides from *Ganoderma lucidum* induce neuronal differentiation and prevent nerve growth factor–dependent apoptosis of rat pheochromocytoma PC12 neuronal cells [36]. These effects are probably mediated through the Ras/Erk and cAMP-response element binding protein (CREB) signaling pathways because *Ganoderma lucidum* extracts induce phosphorylation of Erk1, Erk2, and CREB [36]. Therefore, *Ganoderma lucidum* contains neuroactive compounds that mediate the neuronal differentiation and neuroprotection of PC12 cells [36].

In addition to polysaccharides with the β-glucan structure, other biologically active saccharides have been isolated from *Ganoderma lucidum*. Complexes of saccharides with amino acids, peptides, or proteins demonstrate different biological activities in various cell systems. For example, the amino-polysaccharide fraction (G009) from *Ganoderma lucidum* inhibits reactive oxygen species (ROS) [18]. G009 reduces oxidative DNA damage, inhibits iron-induced lipid peroxidation, and inactivates hydroxyl radicals and superoxide anions in rat brain homogenates and human promyelocytic leukemia HL-60 cells [18]. Since the activity of ROS has been directly linked to carcinogenesis and the pathophysiology of cancer [37], the amino-polysaccharide fraction of *Ganoderma lucidum* may have cancer chemopreventive potential.

A fucose-containing glycoprotein fraction from the water-soluble extract of *Ganoderma lucidum* stimulates the proliferation of spleen cells and the expression of cytokines [38]. While the active fraction contains mostly D-glucose,

D-mannose, and D-galactose, the only active component was identified in the glycopeptide fraction containing fucose residues. Furthermore, the crude extract of *Ganoderma lucidum* does not stimulate expression of cytokines, whereas the expression of IL-1, IL-2, and IFN-γ is stimulated by the glycoprotein fraction [38].

A proteoglycan composed of D-glucose, D-galactose, and D-mannose in a carbohydrate : protein ratio of 11.5 : 1 was isolated from the fruiting body of *Ganoderma lucidum* (GLIS). This fraction stimulates the proliferation and activation of B-lymphocytes [39]. GLIS induces secretion of IL-2, but does not affect the secretion of IL-4. GLIS also enhances the expression of PKCα and PKCγ in B cells [39].

Antiviral and antiherpetic activities have been identified in protein-bound polysaccharide fractions of *Ganoderma lucidum* [24, 40]. Acidic-bound polysaccharide (APBP) demonstrates antiviral activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in the plaque reduction assay [40]. Moreover, the combination of APBP with acyclovir possesses potent synergistic effects, suggesting the possible use of APBP as a new antiherpetic agent [40].

Two cerebrosides, glycosphingolipids consisting of D-glucose, sphingosine, and, respectively, 2-hydroxypalmitoyl or 2-hydroxystearoyl fatty acid moieties, were isolated from the fruiting body of *Ganoderma lucidum* [41]. Both cerebrosides inhibit DNA polymerases, which are crucial for the replication of DNA, and therefore these cerebrosides could potentially be used for anticancer therapy [41].

EFFECTS OF POLYSACCHARIDE- AND SACCHARIDE-CONTAINING FRACTIONS *IN VIVO*

The anticancer activity of polysaccharides isolated from *Ganoderma lucidum* was originally tested *in vivo* using subcutaneously transplanted sarcoma-180 cells growing in mice [30] (Table 2). The anticancer effects of *Ganoderma lucidum* were attributed to the activity of β-glucans [31], which were also isolated from other mushrooms and demonstrated potent immunostimulatory activity [42]. Therefore, stimulation of immune effector cells (lymphocytes, macrophages and NK cells) leads to the subsequent production of cytokines and contributes to the anticancer activity of *Ganoderma lucidum* [9].

While effectiveness of *Ganoderma lucidum* in mouse sarcoma-180 cell model is evident, polysaccharide extracts of *Ganoderma lucidum* also inhibit the growth of Lewis lung carcinoma (LLC) cells in mice [9, 43]. Interestingly, sulfate derivatives of D-glucans demonstrate significantly higher antitumor activity against Ehrlich ascites carcinoma [44]. Furthermore, water-soluble extracts from cultured medium of *Ganoderma lucidum* prevent azoxymethane-induced colon cancers in rats [26, 45]. Finally, a *Ganoderma lucidum* polysaccharide extract (Ganopoly) stimulates immune functions in patients with advanced-stage cancer, including lung, colon, breast, liver, prostate, bladder, and brain [46]. Twelve weeks of treatment with Ganopoly resulted in a significant increase in the plasma concentrations of IL-2, IL-6, and IFN-γ and enhanced NK activity, whereas the levels of IL-1 and TNF-α were significantly decreased [46].

In addition to anticancer effects, polysaccharides also demonstrate other biological activities *in vivo*. Intragastric application of polysaccharide fractions isolated from fruiting bodies of *Ganoderma lucidum* (GLPS) prevents indomethacin- and acetic acid–induced gastric mucosal lesions in the rat [22]. The antiulcerogenic effects are associated with the suppression of TNF-α expression and increased activity of ornithine decarboxylase (ODC) [22]. The anti-ulcer effects were confirmed in cell cultures of rat gastric cells (RGM-1), where GLPS stimulated cell proliferation, protein expression of ODC and c-myc, and mucus synthesis [22].

The hepatoprotective effects of *Ganoderma lucidum* polysaccharide (GLP) were evaluated in a mouse infection model utilizing Bacillus Calmette-Guerin (BCG) [47]. Treatment with GLP diminished histological changes of injury such as hemorrhage and necrosis in hepatic lobules and inflammatory infiltration of lymphocytes and Kupffer

Table 2. ***In vivo*** **Effects of Polysaccharides Isolated from** ***Ganoderma lucidum***

Fraction	Outcome	Model	Ref.
Animal studies			
β-glucans	Inhibition of tumor growth	sarcoma –180 ascites in mice	30
Polysaccharide extracts	Inhibition of tumor growth	Lewis lung carcinoma in mice	9, 43
Sulfated D-glucans	Inhibition of tumor growth	Ehrlich ascites carcinoma in mice	44
Polysaccharide extracts	Prevention of cancer	chemically induced colon cancers in rats	26, 45
Polysaccharides (GLPS)	Mucosal healing	chemically induced gastric ulcers in rats	22
Polysaccharide (GLP)	Hepatoprotective effects	hepatic inflammation in mice	47
Protein-bound polysaccharides	Hepatoprotective effects	cirrhosis induced by biliary obstruction	10
Glycans (ganoderan A and B)	Hypoglycemic activity	alloxan-induced diabetic mice	28, 48
Polysaccharides (*Gl*-PS)	Hypoglycemic activity	alloxan-induced diabetic mice	49
Polysaccharide extracts	Antihypertensive effects	rabbits and rats	12
Preclinical studies			
Ganopoly (polysaccharide extracts)	Stimulation of immune system, increased plasma concentration of IL-2, IL-6, IFN-γ	advanced-stage cancer of lung, colon, breast, liver, prostate, bladder and brain	46

cells around the central vein [47]. Immunohistochemistry showed that GLP inhibited the expression of inducible nitric oxide synthase (iNOS), suggesting that the protective effect of GLP was mediated by the inhibition of nitric oxide (NO) production [47]. Protein-bound polysaccharides from *Ganoderma lucidum* also reduced serum aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and total bilirubin in rats with cirrhosis induced by biliary obstruction [10]. Furthermore, both the content of collagen and liver morphology were improved [10].

Hypoglycemic activity was identified in glycans called ganoderan A and B, which were isolated from fruiting bodies of *Ganoderma lucidum* [48]. Both ganoderan A and B significantly reduced plasma glucose levels in normal and alloxan-induced hyperglycemic mice [48]. Ganoderan B increased the level of insulin in plasma but did not have any effect on insulin binding to isolated adipocytes [28]. Ganoderan B significantly increased the activities of hepatic glucokinase, phosphofructokinase, and glucose-6-phosphate dehydrogenase; decreased hepatic glucose 6-phosphatase and glycogen synthetase activities; and had no effect upon the activities of hexokinase and glycogen phosphorylase [28]. Finally, ganoderan B reduced the glycogen content of the liver but had no influence on total cholesterol and triglyceride levels in the plasma and liver [28]. Polysaccharides isolated from the fruiting body of *Ganoderma lucidum* (*Gl*-PS) demonstrate protective effects against alloxan-induced damage to insulin-producing pancreatic β cells [49]. *Gl*-PS increased the viability of and protected pancreatic β cells from necrosis [49]. Pretreatment with *Gl*-PS also inhibited alloxan-induced activation of NF-κB [49].

The water extract of mycelia from *Ganoderma lucidum* was also assessed for cardiovascular activity in rabbits and rats [12]. Although *Ganoderma lucidum* decreased systolic and diastolic blood pressure, there was no difference in the heart rate of the tested animals [12]. *Ganoderma lucidum*–dependent hypotension was felt to result from central inhibition of sympathetic nervous system activity [12].

EFFECTS OF TRITERPENES *IN VITRO*

We now consider another major compound isolated by extraction of *Ganoderma lucidum* with organic solvents: triterpenes. About 130 highly oxygenated and pharmacologically active lanostane-type triterpenes Fig. (**2**) have been isolated from *Ganoderma lucidum* [3, 50]. Some of these triterpenes, isolated more than 20 years ago and originally called ganoderic acids U, V, W, X, and Y, demonstrate cytotoxicity against hepatoma cells *in vitro* [51]. In addition, ganoderic aldehyde A exhibits cytotoxic effects against human hepatoma and nasopharynx carcinoma cells [52]. Recently, new triterpenes isolated from the spores of *Ganoderma lucidum* were tested for their cytotoxicity against mouse sarcoma (Meth-A) and mouse Lewis lung carcinoma (LLC) cells. The ganoderic alcohols lucidimols A and B, ganodermanondiol, ganoderiol F, and ganodermanontriol demonstrated cytotoxic effects on both tumor cell lines [53]. However, ganoderic acids γ, δ, ε, ζ, η, and θ did not show any activity against cancer cells [53]. In additional studies, ganodermanol, ganodermadiol, and aldehydes lucilaldehyde B and C showed cytotoxic effects against mouse LLC, Meth-A, sarcoma 180, and human breast cancer cells T-47D [54]. Some studies have also examined triterpenes or alcohol extracts from *Ganoderma lucidum* (containing triterpenes) for their effects on specific signaling pathways in particular cell lines (Table 3). An alcohol extract of *Ganoderma lucidum* inhibited proliferation of breast cancer cells (MCF-7) by inducing cell-cycle arrest in the G1 phase of the cell cycle. This effect resulted from upregulation of the cell-cycle inhibitor p21/Waf-1 and by downregulation of cyclin D1 [55]. Furthermore, the alcohol extract also induced apoptosis of breast cancer cells, which was mediated through the upregulation of the proapoptotic Bax protein [55]. Interestingly, a triterpene-enriched extract of *Ganoderma lucidum* inhibited proliferation of hepatoma cells by cell-cycle arrest at the G2 phase [56]. This inhibitory effect was linked to the suppression of PKC and activation of c-Jun N-terminal kinase (JNK) and p38 MAPK [57]. However, triterpene extract did not affect a normal human liver cell line [56]. Extracts from the alcohol-extracted spores subjected to silica gel chromatography, which is used to isolate triterpenes [9], inhibited the growth of HeLa cells (human cervical carcinoma), with cell-cycle arrest in the G1 phase [57]. These extracts also markedly decreased the level of intracellular calcium, suggesting that triterpene-dependent changes in the calcium transport system might alter signal transduction involved in the regulation of the cell cycle [57]. Furthermore, triterpenes inhibited the Ras oncoprotein, which is responsible for cancer cell transformation [58]. Ganoderic acids A and C inhibited farnesyl protein transferase (FPT), which catalyzes post-translational farnesylation of Ras oncoprotein and is essential for the cell-transforming activity of Ras [58].

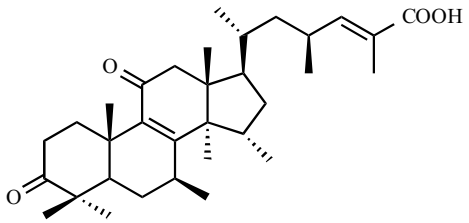

Fig. (2). Schematic structure of lanostane triterpenes from *Ganoderma lucidum*.

In addition to their cytotoxic and anticancer effects, triterpenes isolated from *Ganoderma lucidum* also demonstrate activity against the HIV virus. Ganoderiol F and ganodermanontriol inhibit HIV 1–induced cytopathic effects in MT-4 cells, whereas ganoderic acids A, B, C1, and H have no inhibitory activity upon HIV-1 replication [23]. Moreover, ganolucidic acid A, ganodermanondiol, ganodermanontriol, lucidimol B, and ganoderic acid β significantly inhibit HIV-1 protease, an essential enzyme required for the proliferation of HIV [23, 59].

Ganoderiol F, ganodermanondiol, and ganodermanontriol also demonstrate strong anticomplement activity against the classical pathway of the complement system [60]. Ganodermic acid S (GAS) alters the signaling pathways in human platelets [61]. GAS inhibits calcium mobilization and phosphorylation of myosin light chain and pleckstrin. It inhibits the platelet response to thromboxane-A, an effect

Table 3. Triterpenes in *Ganoderma lucidum*

Compound	Biological Effect	Ref.
Ganoderic acids U, V, W, X, Y	Cytotoxic against hepatoma cells	51
Ganoderic acids A, B	Inhibition of farnesyl protein transferase	58
Ganoderic acid F	Prevention of invasion of metastatic cells *in vivo*	62
Ganoderic acid β	Inhibition of HIV-1 protease	59
Ganolucidic acid A	Inhibition of HIV-1 protease	59
Ganodermic acid S	Inhibition of Ca^{2+} mobilization in platelets	61
Ganoderic aldehyde A	Cytotoxic against hepatoma and nasopharyx carcinoma cells	52
Lucilaldehyde B, C	Cytotoxic against Lewis lung carcinoma (LLC), mouse sarcoma Meth-A, sarcoma 180, and breast cancer cells T-47D	55
Lucidimol A, B; ganodermanondiol, ganodermanontriol, ganoderiol F	cytotoxic against LLC and Meth-A cancer cells	53
Ganodermanol, ganodermadiol	cytotoxic against LLC, Meth-A, sarcoma 180, and T-47D cells	53
Ganodermanontriol, ganoderiol F	HIV-1 inhibitors	23
Lucidimol B, ganodermanondiol, ganodermanontriol	Inhibition of HIV-1 protease	59
Ganodermanondiol, ganodermanontriol, ganoderiol F	Anticomplement activity	60

felt to be mediated by the inactivation of the phospholipase C pathway [61].

EFFECTS OF TRITERPENES *IN VIVO*

The *in vivo* antitumor activity of polysaccharides and *in vitro* cytotoxicity of triterpenes was reported more than 20 years ago [3, 30, 50]. The *in vivo* antitumor effects of terpenoid fractions of *Ganoderma lucidum* were demonstrated only recently. Oral administration of the triterpenoid fraction of the fruiting body of *Ganoderma lucidum* inhibited the growth of intrasplenic implants of Lewis lung carcinoma in mice [62]. In addition, the triterpenoid fraction prevented the invasion of metastatic tumor cells into the white pulp of the spleen and hepatocytes [62]. Furthermore, Matrigel-induced neovascularization was also inhibited, and the biologically active compound responsible for the suppression of angiogenesis was identified as ganoderic acid F [62]. Combined treatment with lovastatin and an oxygenated triterpenoid fraction from *Ganoderma lucidum* inhibited the growth of human hepatoma Hep 3B cells [63]. Moreover, lovastatin and triterpenoid fraction reduced the growth of tumors in nude mice with orthotopically inoculated human hepatoma Hep 3B/T2 cells. These data suggest that triterpenoids from *Ganoderma lucidum* may have potential as adjuvant therapy for the treatment of cancer [63].

OTHER BIOLOGICALLY ACTIVE COMPONENTS OF *GANODERMA LUCIDUM*

Although the major components isolated from *Ganoderma lucidum* are polysaccharides and triterpenes, other biologically active compounds have also been isolated [9]. A protein derived from *Ganoderma lucidum* (LZ-8) demonstrated mitogenic activity *in vitro* on mouse spleen cells and prevented the production of antibody to hepatitis B surface antigen (HBs Ag) *in vivo* [64]. LZ-8 also demonstrated immunosuppressive properties by delaying rejection of transplanted allografted pancreatic rat islets [65]. Phenols isolated by methanolic extraction of *Ganoderma lucidum* demonstrated antioxidant activity by inhibiting lipid peroxidation. This effect was comparable to the antioxidant activity of phenols isolated from other medicinal mushrooms [66]. Oleic acid (but not other saturated fatty acids) extracted from *Ganoderma lucidum* effectively inhibited histamine release from rat peritoneal mast cells [14]. Cyclooctasulfur isolated by sequential fractionation of the culture medium of *Ganoderma lucidum* demonstrated antiallergic activity by inhibiting histamine release, suggesting that the inhibitory effect of cyclooctasulfur may be through its interaction with membrane proteins [15]. Lipids extracted from the germinating spores of *Ganoderma lucidum* inhibited the growth of mouse hepatoma, sarcoma S-180, and reticulocyte sarcoma L-II cells in mice, suggesting that the biological activity of *Ganoderma lucidum* could be enhanced by the germination of dormant spores [67] (Table 4).

THE WHOLE MUSHROOM

The isolation, identification, and characterization of biologically active compounds of *Ganoderma lucidum* may provide new and important future therapies for a variety of diseases. However, *Ganoderma lucidum* is an edible mushroom and is available as a dietary supplement in the form of water or alcohol extracts and in the form of un-fractionated fruiting bodies and/or collected spores. While the intact mushroom and spores are non-toxic, some of the isolated components can be toxic. Furthermore, certain components in the product may reduce the cytotoxicity of

Table 4. Other Biologically Active Fractions from *Ganoderma lucidum*

Fraction/Compound	Biological effect/mechanism of action	Reference
Alcohol extract	Inhibition of proliferation, induction of apoptosis, cell cycle arrest at G1, upregulation of p21/Waf-1, Bax, downregulation of cyclin D1 in human breast cancer cells.	55
Alcohol extract	Inhibition of growth, cell cycle arrest at G1, decrease of the intracellular calcium in human cervical carcinoma cells.	57
Triterpene-enriched extract	Inhibition of proliferation, cell cycle arrest at G2, activation of JNK and MAPK, inhibition of PKC in hepatoma cells.	56
Oxygenated triterpenoid fraction	Adjuvant effect with lovastatin for the inhibition of growth of human hepatoma tumors in nude mice.	63
LZ-8 (protein)	Immunosupresive, delayed rejection of transplants in rats.	64, 65
Phenols	Antioxidant properties, inhibition of lipid peroxidation.	66
Oleic acid, cyclooctasulfur	Antiallergic activity, inhibition of histamine release from mast cells.	14, 15
Lipids	Inhibition of growth of hepatoma and sarcoma cells in mice.	67
Spores/fruiting bodies	Inhibition of cell adhesion, migration and invasion, inhibition of AP-1 and NF-κB, downregulation of uPA and uPAR in human breast and prostate cancer cells.	69, 72

the whole product, and the interaction between different biologically active compounds can increase their effects [68]. Thus, it is important to study the whole mushroom and spores, in addition to isolated components.

By using the commercially available dietary supplement *Ganoderma lucidum* in the form of spores (GS) and fruiting bodies (GFB), we recently demonstrated that *Ganoderma lucidum* inhibited constitutively active transcription factors AP-1 and NF-κB in highly invasive breast and prostate cancer cells [69]. One of the characteristics of highly metastatic cancer cells is the constitutive activation of AP-1 and NF-κB. We have also shown that the inhibition of AP-1 and NF-κB results in the suppression of secretion of urokinase-type plasminogen activator (uPA) and the inhibition of cell migration of highly invasive breast cancer cells [70, 71]. *Ganoderma lucidum* downregulated the expression of uPA and its receptor uPAR as well as secretion of uPA, resulting in the inhibition of the cell motility of breast and prostate cancer cells [69]. In addition, *Ganoderma lucidum* also suppressed cell adhesion and cell invasion, suppressing the metastatic potential of highly invasive cancer cells.

One of the disadvantages of using whole mushrooms or dietary supplements from *Ganoderma lucidum* is the lack of information about the active compounds in the particular preparations. The biological activity of *Ganoderma lucidum* reflects the concentration of the active ingredients, which are variable and dependent on the harvesting techniques, age, manipulation, and storage of the mushrooms and spores. For example, the contents of triterpenes and their compositions isolated from *Ganoderma lucidum* varied among the specimens obtained from different strains, cultivating areas (China, Vietnam, Japan, or Korea), or mushroom forms [50].

Ganoderma lucidum is currently available from different sources and because the quality and composition of each source are unknown and not characterized, the biological effect of *Ganoderma lucidum* on cancer cells can be variable. For this reason, we compared the activity of a number of preparations of *Ganoderma lucidum* that were available in the form of dietary supplements. We demonstrated that the potency for inhibiting cancer cell migration was directly linked to the inhibition of constitutively active NF-κB. We found that the various preparations displayed different activities upon NF-κB expression and cancer cell migration [72]. For example, dietary supplements containing spores of *Ganoderma lucidum*, which are usually more expensive than the supplements containing the ground mushroom (fruiting bodies), demonstrated diverse inhibitory activities, and one sample containing purified spores was virtually inactive, while another containing fruiting bodies was very active against cancer cells [72]. Therefore, the activity of *Ganoderma lucidum* as a whole mushroom or dietary supplement may vary, and its use for therapy should be evaluated by biological methods.

SUMMARY AND FUTURE DIRECTIONS

Chemopreventive and therapeutic studies in Asia have demonstrated the beneficial effects of herbal supplements upon a variety of different diseases. The popular edible mushroom *Ganoderma lucidum* has been used to treat cancer and is linked to lower rates of mortality and increased longevity. Biologically active components, mostly containing polysaccharides and triterpenes, have been isolated from *Ganoderma lucidum* and their chemical structures characterized. Furthermore, *Ganoderma lucidum* demonstrates activity against specific molecular targets for a variety of diseases, and some polysaccharides and triterpenes have also been evaluated in studies *in vivo.* Because some of the triterpenes isolated from *Ganoderma lucidum* demonstrate cytotoxicity against cancer cells and because polysaccharides stimulate the immune system, it is possible that the whole mushroom or dietary supplement (spores or fruiting bodies) achieves cumulative biological effects that exceed those of fractionated components. Future studies evaluating the effects of both whole mushroom/spores and fractionated components in animal and clinical studies are needed to justify the broader use of *Ganoderma lucidum* as an adjuvant to the systematic therapy for different diseases.

Alternatively, such studies could also scientifically justify the use of *Ganoderma lucidum* as a health-promoting dietary supplement.

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