Ganoderma lucidum (Reishi) in Cancer Treatment

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The popular edible mushroom *Ganoderma lucidum* (Reishi) has been widely used for the general promotion of health and longevity in Asian countries. The dried powder of *Ganoderma lucidum* was popular as a cancer chemotherapy agent in ancient China. The authors recently demonstrated that *Ganoderma lucidum* inhibits constitutively active transcription factors nuclear factor kappa B (NF-κB) and AP-1, which resulted in the inhibition of expression of urokinase-type plasminogen activator (uPA) and its receptor uPAR. *Ganoderma lucidum* also suppressed cell adhesion and cell migration of highly invasive breast and prostate cancer cells, suggesting its potency to reduce tumor invasiveness. Thus, *Ganoderma lucidum* clearly demonstrates anticancer activity in experiments with cancer cells and has possible therapeutic potential as a dietary supplement for an alternative therapy for breast and prostate cancer. However, because of the availability of *Ganoderma lucidum* from different sources, it is advisable to test its biologic activity.

Keywords: **Ganoderma lucidum; *Reishi; breast and prostate cancer; signaling pathways; AP-1; NF-κB; uPA; uPAR***

Traditional Chinese medicine (TCM) has been practiced in many Asian countries during the past 2 millennia. In TCM, foods play an important role for maintaining and improving health and for preventing and treating disease.[1] Even with the progress of modern Western medicine in the fields of surgery, radiation therapy, and chemotherapy for cancer treatment, many malignancies can be prevented or treated with proper nutrition. The general use of dietary supplements in the United States significantly increased during the past 10 years, and the use of dietary supplements and herbal therapies by cancer patients continues to increase.[2] By tracing the multistep process of carcinogenesis at the cellular levels, it is possible to understand the molecular mechanisms through which the components of foods and botanical dietary supplements affect the development of cancer.[3] Therefore, we can identify specific molecular targets, which can eventually be modulated in the prevention and/or treatment of cancers by the dietary supplements.

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Ganoderma lucidum

Ganoderma lucidum (Fr.) Karst. (Ganodermataceae), basidiomycetous fungi, has been used as a medical remedy in China, Korea, and Japan for centuries.[4] This edible mushroom was considered to preserve the human vitality and to promote longevity.[5] In addition, *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. Different compounds with various biological activities were extracted from mycelia, the fruiting bodies or spores of *Ganoderma lucidum*, and some of them were linked to possible therapeutic effects (Table 1).

Polysaccharides

Antitumor effects of polysaccharides isolated from *Ganoderma lucidum* were originally observed in subcutaneously transplanted sarcoma-180 ascites growing in mice.[6] The biologically active polysaccharides were mainly in the form of β-D-glucans, and the antitumor activity from *Ganoderma lucidum* was exhibited mainly by the branched (1→3)-β-D-glucans.[7] The activity of polysaccharides from *Ganoderma lucidum* was suggested to be mediated through the complement receptor type 3 (CR3 receptor), which binds β-glucan polysaccharides.[8] In addition to (1→3)-β-D glucans isolated from *Ganoderna lucidum*,[7] other polysaccharides were isolated from *Ganoderma applanatum* (Pers.) Pat.,[9,10] *Ganoderma japonicum* (Fr.) Lloyd,[11] and *Ganoderma tsugae* Murrill.[12,13] Therefore, antitumor activity was demonstrated with glucuronoglucan, mannogalactoclucan, arabinoglucan, and glucogalactan from *Ganoderma* species. However, the mushroom used and studied the most among the *Ganoderma* species is *Ganoderma lucidum*.

Polysaccharides from the mushroom were demonstrated to prevent oncogenesis and tumor metastasis

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Table 1. Biologically Active Compounds in *Ganoderma lucidum*

Compound	*Function/Outcome*	*References*
Polysaccharides		
(1→3)-β-D-glucans	Inhibition of growth of sarcoma S 180 tumor in mice	7
PS-G, protein-bound polysaccharides (95% polysaccharides and 5% peptides)	Activation of immune response, stimulation of the IL-1β, IL-6, TNF-α, and IFN-γ production by macrophages and T lymphocytes	15
	Inhibition of neutrophil apoptosis	16
	Induction of neutrophil phagocytosis	17
	Induction of GST	18
G009, aminopolysaccharides	Antioxidant	20
Glycoproteins (with fucose)	Stimulation of IL-1, IL-2 and IFN-γ expression in spleen cells	21
GLIS, proteoglycans	Activation of B-lymphocytes	22
Cerebrosides	Inhibition of DNA-polymerase	23
Triterpenes		
Ganoderic acid (U, V, W, X, Y)	Cytotoxic for hepatoma cells	24
Ganoderic acid (A, C)	Inhibition of farnesyl protein transferase	25
Lucidimol (A, B), ganodermanondiol, ganoderiol F, ganodermanontriol	Cytotoxic for sarcoma and lung carcinoma cells	27, 28, 29
Ganoderic acid F	Inhibition of angiogenesis	30
Phenols	Antioxidant	31
Lipids	Growth inhibition of hepatoma, sarcoma S-180 and reticulocyte sarcoma L-II in vivo	32

indirectly, via the activation of the immune response of the host organism by the stimulation of natural killer cells, T cells, B cells, and macrophage-dependent immune system responses.[14] Polysaccharides isolated from the fresh fruiting body of *Ganoderma lucidum* (PS-G) stimulated production of interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 from human monocyte-macrophages and interferon (IFN)-γ from T lymphocytes.[15] Furthermore, these PS-G-induced cytokines suppressed the proliferation and clonogenicity of human leukemic cells.[15] PS-G also enhanced the immune responses and elicited antitumor effects from human neutrophils by inhibiting spontaneous and Fas-mediated apoptosis through the activation of the phosphatidylinositol (PI) 3-kinase/Akt pathway.[16] In addition, PS-G enhanced phagocytic activity of neutrophils through the mitogen-activated protein kinase (MAPK) and protein kinase C (PKC) pathways.[17] Finally, polysaccharides from *Ganoderma lucidum* demonstrated a chemopreventive effect, which was mediated by the induction of glutathione S-transferase (GST) activity.[18]

Saccharide-Containing Fractions

The aminopolysaccharide fraction (G009) from *Ganoderma lucidum* demonstrated the inhibition of reactive oxygen species, which have been implicated in the pathophysiology of cancer.[19] G009 inhibited iron-induced lipid peroxidation and inactivated hydroxyl radicals and superoxide anions.[20] Furthermore, G009 also reduced oxidative DNA damage, suggesting that the aminopolysaccharide fraction of *Ganoderma lucidum* possesses chemopreventive potential.[20]

A fucose-containing glycoprotein fraction from the water-soluble extracts of *Ganoderma lucidum* stimulated spleen cell proliferation and cytokine expression.[21] Although the active fraction contained the majority of D-glucose, D-mannose, and D-galactose, the only active component was identified in the glycopeptide fraction containing fucose residues. In addition, the crude extract of *Ganoderma lucidum* did not stimulate expression of cytokines, whereas glycoprotein fraction significantly induced the expression of IL-1, IL-2, and interferon (IFN)-γ.[21]

A proteoglycan isolated from the fruiting body of *Ganoderma lucidum* (GLIS) is predominantly composed of D-glucose, D-galactose, and D-mannose in a carbohydrate:protein ratio 11.5:1.[22] GLIS stimulated the proliferation and activation of B lymphocytes, resulting in the increased production of IL-2, whereas the secretion of IL-4 was not changed. Furthermore, GLIS also enhanced the expression of PKCα and PKCγ in B cells.[22]

Two cerebrosides, glycosphingolipids consisting of D-glucose, sphingosine, and 2-hydroxypalmitoyl or 2-hydroxystearoyl fatty acid moiety, respectively, were isolated from the fruiting body of *Ganoderma lucidum*.[23] Interestingly, both cerebrosides inhibited DNA polymerases, suggesting their possible use for cancer therapy by inhibiting DNA replication.

Triterpenes

More than 100 highly oxygenated and pharmacologically active lanostane-type triterpenes have been isolated from *Ganoderma lucidum*.[24] Some of these triterpenes, isolated more than 20 years ago and originally named ganoderic acids U, V, W, X, and Y,

demonstrated cytotoxicity against hepatoma cells in vitro.[25] More recently, ganoderic acids A and C inhibited farnesyl protein transferase, an enzyme that is crucial for activation of the Ras oncoprotein responsible for cell transformation.[26] Furthermore, 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.[27-29] However, the new isolated ganoderic acids γ, δ, ε, ζ, η, and θ did not show any activity against cancer cells.[29]

The triterpenoid fraction of the fruiting body of *Ganoderma lucidum* inhibited primary solid-tumor growth in the spleen, liver metastasis, and secondary metastatic tumor growth in the liver, which were originally induced by the intrasplenic implantation of the LLC in mice.[30] In addition, the triterpenoid fraction inhibited Matrigel-induced neovascularization, and the biologically active compound responsible for the inhibition of angiogenesis was identified as ganoderic acid F.[30]

Phenols isolated by the methanolic extraction from *Ganoderma lucidum* demonstrated antioxidant activity in the inhibition of lipid peroxidation, which was comparable to the antioxidant activity of phenols isolated from *Ganoderma tsugae*.[31] Lipids extracted from the germinating spores of *Ganoderma lucidum* remarkably inhibited the growth of mouse hepatoma, sarcoma S-180, and reticulocyte sarcoma L-II cells in mouse, suggesting that the biological activity of *Ganoderma lucidum* could be enhanced by the germination of dormant spores.[32]

Signaling Pathways

Ganoderma lucidum is available as a dietary supplement in the form of spores, fruiting body, or water or alcohol extracts. Although the identification of biologically active components of *Ganoderma lucidum* is important for characterizing their specific activity, some of these components can be toxic. Furthermore, certain components in the herbal products can reduce the cytotoxicity of the whole product, and the interaction between different biologically active compounds can increase their effects.[33] Therefore, some studies demonstrated the effect of the whole product or the unfractionated extracts from *Ganoderma lucidum* on specific signaling pathways in cancer cells.

One of the characteristics of highly metastatic cancer cells is the constitutive activation of transcription factors AP-1 and NF-κB. We have shown that the inhibition of AP-1 and NF-κB results in the suppression of secretion of urokinase-type plasminogen activator (uPA) following the inhibition of cell migration of highly invasive breast cancer cells.[34,35] By using commercially available dietary supplements in the form of spores (GS) and fruiting body (GFB) of *Ganoderma lucidum*, we have recently demonstrated that *Ganoderma lucidum* inhibits constitutively active AP-1 and NF-κB in highly invasive breast and prostate cancer cells.[36] Furthermore, both GS and GFB downregulated the expression of uPA and its receptor uPAR as well as secretion of uPA, resulting in the inhibition of cell motility of breast and prostate cancer cells.[36] In addition, *Ganoderma lucidum* also suppressed cell adhesion to fibronectin (FN), which binds to the $\alpha_3\beta_1$ integrin receptor, and to vitronectin (VN), which binds to the $\alpha_v\beta_3$ integrin receptor (Figure 1). Our data suggest that *Ganoderma lucidum* inhibits the formation of uPA-uPAR-FN-$\alpha_3\beta_1$ and uPA-uPAR-VN-$\alpha_v\beta_3$ complexes, resulting in the inhibition of cell adhesion and cell motility of highly invasive breast and prostate cancer cells (Figure 2). Therefore, we propose the mechanism (on the molecular level) by which *Ganoderma lucidum* inhibits invasion and metastasis of breast and prostate cancers.

An alcohol extract of *Ganoderma lucidum* inhibited proliferation of breast cancer cells by cell-cycle arrest at the G1 phase of the cell cycle by upregulating the cell-cycle inhibitor p21/Waf-1 and by downregulating cyclin D1.[37] Furthermore, the alcohol extract also induced apoptosis of breast cancer cells, which was mediated through the upregulation of expression of proapoptotic Bax protein.[37] A triterpene-enriched extract of *Ganoderma lucidum* inhibited growth of hepatoma cells but not a normal human liver cell line.[38] The inhibitory effect was caused by a decrease in the activity of PKC and activation of the c-Jun N-terminal kinase (JNK) and p38 MAPK, resulting in G2 cell-cycle arrest.[38] A water extract from *Ganoderma lucidum* induced the neuronal differentiation and prevented apoptosis of rat pheochromocytoma PC12 cells derived from a tumor of adrenal medulla, suggesting the presence of neuroactive compounds in *Ganoderma lucidum*.[39] These effects were probably mediated through the ras/extracellular signal-regulated kinase (Erk) and cAMP-response element binding protein (CREB) signaling pathways because *Ganoderma lucidum* induced activation of Erk1, Erk2, and CREB.[39]

Taken together, the antitumor activity of *Ganoderma lucidum* is caused by the inhibition or activation of specific mechanisms and pathways (Table 2). As mentioned above, some of the effects on cancer cells are indirect and are caused by stimulation of the immune system by polysaccharides and the release of cytokines from activated macrophages and T lymphocytes.[15] Other effects of *Ganoderma lucidum* are targeted

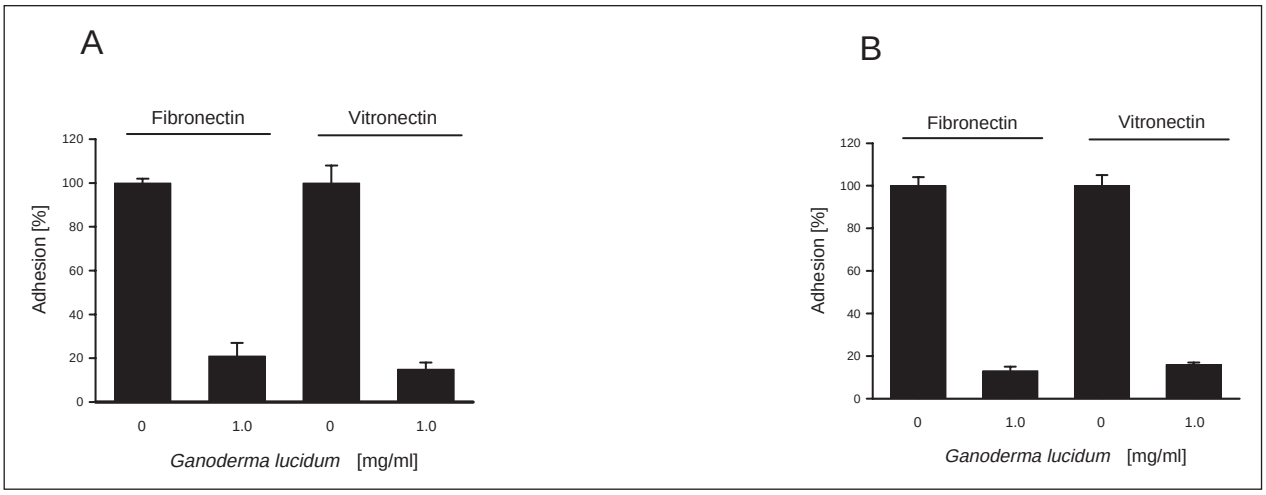

Figure 1 Ganoderma lucidum *inhibits adhesion to vitronectin and fibronectin. (A) Adhesion of breast cancer cells to fibronectin and vitronectin. MDA-MB-231 cells were incubated with* Ganoderma lucidum *(1.0 mg/ml) for 24 hours and harvested, and adhesion to fibronectin and vitronectin (VN) was assessed after an additional 1.5 hours of incubation. (B) Adhesion of prostate cancer cells to fibronectin and vitronectin. PC-3 cells were incubated with* Ganoderma lucidum*, and adhesion was determined as described above. The proportion of adherent cells was counted as a percentage of the control. Data points represent the average ± SD of 3 parallel wells within 1 representative experiment repeated at least twice.*

directly to the cancer cells by modulating their intracellular signaling and can affect the behavior of cancer cells.[36-39]

The Sources of *Ganoderma lucidum* and Its Biological Activity

The usefulness of the edible mushroom *Ganoderma lucidum* as a preventive/therapeutic dietary supplement has been justified in TCM for thousands of years and has recently gained some interest also in Western medicine. However, because *Ganoderma lucidum* is currently available from different sources and because the quality and composition are unknown and not characterized, the biological effect of *Ganoderma lucidum* on cancer cells can be variable. Therefore, we have compared the activity of some of the samples of *Ganoderma lucidum* that are available in the form of dietary supplements. Because we have recently demonstrated that the potency to inhibit cancer cell migration is directly linked to the inhibition of constitutively active NF-κB, we evaluated the potency of fruiting body, spores, and their mixture to inhibit NF-κB and migration of highly invasive breast and prostate cancer cells.[40] Although our data demonstrated that *Ganoderma lucidum* inhibits breast and prostate cancer cells with the same potency, suggesting the involvement of common signaling pathways, the composition of tested samples did not correlate with their inhibitory activity.[40] For example, the dietary supplements containing spores of *Ganoderma lucidum*, which are usually more expensive than the supplements containing the ground mushroom (fruiting body), demonstrated diverse inhibitory activity, and one sample containing fruiting body was more active than another containing spores (Table 3). Because the biological activity of the dietary supplement *Ganoderma lucidum* reflects the concentration of the active ingredients, which are variable and dependent on the harvesting, age, manipulation, and storage of mushrooms and spores, it is advisable to test each new sample for its biological activity. For example, the contents of triterpenes and their compositions isolated from *Ganoderma lucidum* varied among the specimen obtained from different strains, cultivating areas (China, Vietnam, Japan, or Korea), or mushroom forms.[41] Furthermore, because the dietary supplements are not approved or regulated by the Food and Drug Administration (FDA), some of them can be without any effect because the producers of dietary supplements do not have to provide the evidence that the FDA relies on to substantiate safety or effectiveness of a product or substance.[42] However, we and others have clearly demonstrated the anticancer activity of the dietary supplement *Ganoderma lucidum* at the molecular and cellular levels.

Summary and Future Directions

The chemopreventive and therapeutic studies in Asia have demonstrated the effect of herbal supplements on different diseases, including cancer. The popular edible mushroom *Ganoderma lucidum* has been used mainly against cancer and linked to lower rates of mortality.[1] Various signaling pathways

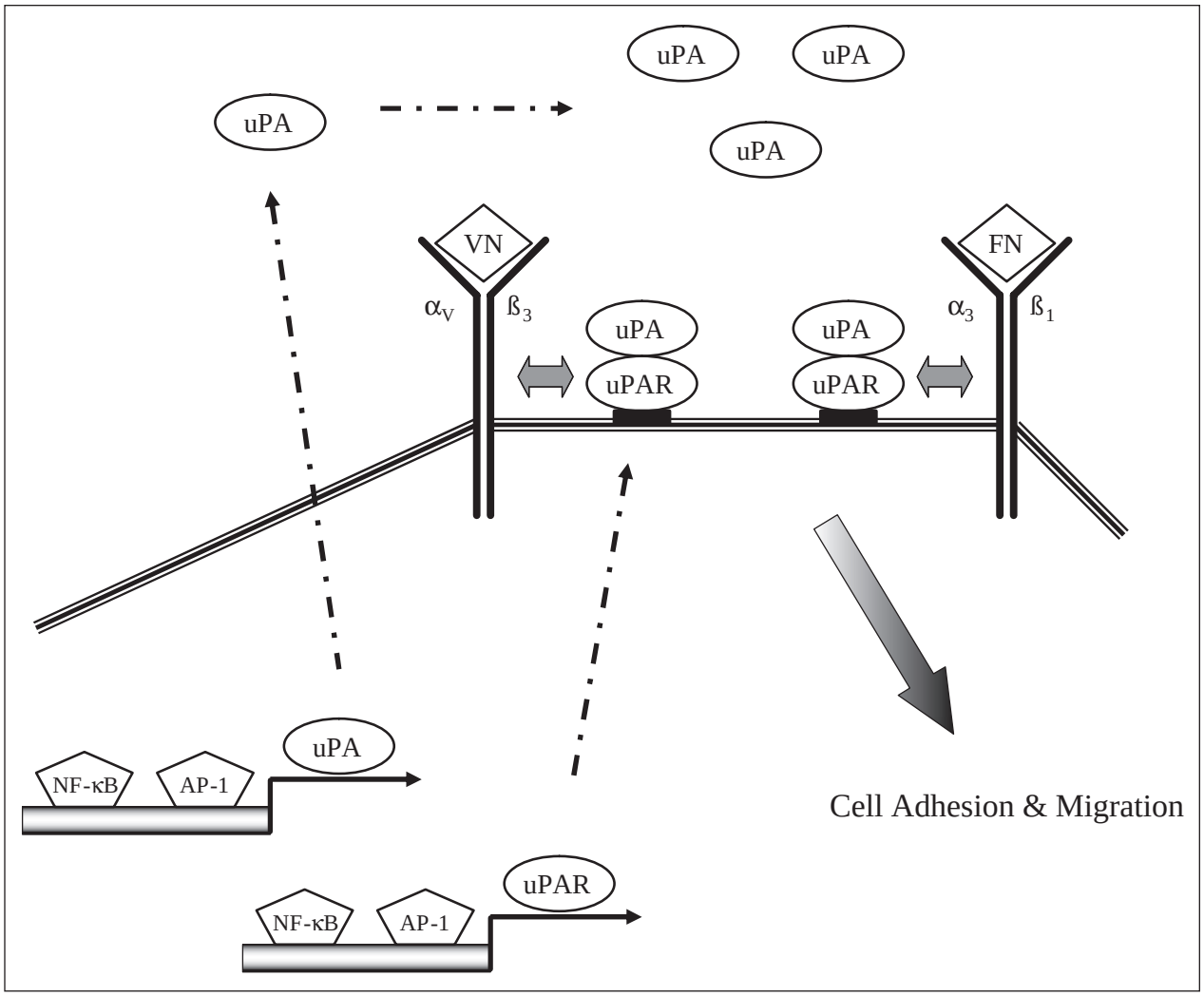

Figure 2 Scheme depicting the role of Ganoderma lucidum *in the inhibition of a uPA-uPAR-integrin complex. Urokinase plasminogen activator (uPA) binds to uPA receptor (uPAR) and forms a complex with $\alpha_v\beta_3$ integrin, which binds vitronectin (VN). uPA and uPAR can also form the complex with $\alpha_3\beta_1$ integrin, which binds fibronectin (FN).* Ganoderma lucidum *inhibits constitutively active AP-1 and NF-κB, resulting in the inhibition of expression of uPA and uPAR and secretion of uPA. The impaired formation of VN-$\alpha_v\beta_3$-uPA-uPAR and FN-$\alpha_3\beta_1$-uPA-uPAR will result in the inhibition of cell adhesion and cell migration of breast and prostate cancer cells.*

Table 2. Mechanisms of *Ganoderma lucidum* Action in Cancer Cells

Target Molecule		*Biological Effect*	*Cell Type*	*References*
NF-κB	↓	Inhibition of cell adhesion and cell migration	Breast cancer, prostate cancer	36, 40, Figure 1
AP-1	↓			
uPA	↓			
uPAR	↓			
p21/Waf-1	↑	G1 cell cycle arrest	Breast cancer	37
Cyclin D1	↓			
Bax	↑	Induction of apoptosis		
PKC	↓	G2 cell cycle arrest	Hepatoma	38
JNK	↑			
p38 MAPK	↑			
Erk1	↑	Prevention of apoptosis	Pheochromocytoma	39
Erk2	↑			
CREB	↑			

NF-κB = nuclear factor κB; AP-1 = activator protein-1; uPA = urokinase plasminogen activator; uPAR = uPA receptor; PKC = protein kinase C; JNK = c-Jun N-terminal kinase; MAPK = mitogen-activated protein kinase; Erk = ras/extracellular signal-regulated kinase; CREB = camp-response element binding protein.

Table 3. Inhibitory Effects of *Ganoderma lucidum* on Breast and Prostate Cancer Cells

	Breast Cancer Cells Inhibition (%)		Prostate Cancer Cells Inhibition (%)	
Composition (Source)	*Cell Migration*	*NF-κB*	*Cell Migration*	*NF-κB*
Spores A (China)	90 ± 3.7	71 ± 4.6	84 ± 1.1	65 ± 14.5
Spores B (China)	10 ± 5.2	3 ± 3.9	17 ± 7.4	17 ± 0.5
Fruiting body A (Taiwan)	87 ± 3.6	82 ± 9.2	94 ± 1.3	66 ± 3.0
Fruiting body B (China)	54 ± 2.2	32 ± 13.7	39 ± 7.2	25 ± 0.9
Powdered extracts with spores (US)	99 ± 1.0	87 ± 1.9	89 ± 1.8	97 ± 0.8

For more details, see reference 40.

responsible for aberrant characteristics of cancer cells were modulated by *Ganoderma lucidum*, resulting in cell-cycle arrest, induction of apoptosis, inhibition of growth, and suppression of metastatic behavior. *Ganoderma lucidum* also inhibits constitutively active transcription factors NF-κB and AP-1, which were suggested as potential therapeutic targets for cancer treatment.[43,44] Because NF-κB controls the expression of proteins involved in cell adhesion, migration, and invasion (uPA, uPAR)[45,46]; proteins protecting against cell death (Bcl-2, Bcl_{XL})[47]; oncoproteins stimulating dysregulation of the cell cycle and tumor formation (cyclin D1)[48]; and angiogenic factors that stimulate tumor growth (VEGF, FGF2, TGF-β, MMP-9, and COX-2),[49] the inhibition of NF-κB by *Ganoderma lucidum* is especially important for the prevention and treatment of cancer. Moreover, this dietary supplement has the potential to be used, after evaluation in animal and clinical studies, as an adjuvant to the systematic therapy against cancer.

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References

1 Yun TK. Update from Asia: Asian studies on cancer chemoprevention. *Ann N Y Acad Sci.* 1999;889:157-192.

2. Go VL, Wong DA, Resnick MS, Heber D. Evaluation of botanicals and dietary supplements therapy in cancer patients. *J Nutr.* 2001;131(1):179S-180S.
3. Heber D, Blackburn GL, Go VL. *Nutritional Oncology.* New York, NY: Academic Press; 1999.
4. Kim SS, Kim YS. *Korean Mushrooms.* Seoul: Yupoong; 1990:298-299.
5. Shiao MS, Lee KR, Lin LJ, Wang CT. Natural products and biological activities of the Chinese medical fungus, *Ganoderma lucidum.* In: Ho CT, Osawa T, Huang MT, Rosen RT, eds. *Food Phytochemicals for Cancer Prevention. II. Teas, Spices, and Herbs.* Washington, DC: American Chemical Society; 1994:342-354.
6. Miyazaki T, Nishijima M. Studies on fungal polysaccharides. XXVII. Structural examination of a water-soluble, antitumor polysaccharide of *Ganoderma lucidum. Chem Pharmacol Bull.* 1981;29(12):3611-3616.
7. Sone Y, Okuda R, Wada N, Kishida E, Misaki A. Structure and antitumor activities of polysaccharides isolated from fruiting body and the growing culture of mycelium of Ganoderma lucidum. *Agric Biol Chem.* 1985;49:2641-2653.
8. Yan J, Vetvicka V, Xia Y, Coxon A, Carroll MC, Mayadas TN, Ross GD. Beta-glucan, a "specific" biologic response modifier that uses antibodies to target tumors for cytotoxic recognition by leukocyte complement receptor type 3 (CD11b/CD18). *J Immunol.* 1999;163(6):3045-3052.
9. Sasaki T, Arai Y, Ikekawa T, Chihara G, Fukuoka F. Antitumor polysaccharides from some polyporaceae, *Ganoderma applanatum* (Pers.) Pat and *Phellinus linteus* (Berk. et Curt) Aoshima. *Chem Pharm Bull.* (Tokyo) 1971;19(4):821-826.
10. Nakashima S, Umeda Y, Kanada T. Effect of polysaccharides from *Ganoderma applanatum* on immune response. I. Enhancing effect on the induction of delayed hypersensitivity in mice. *Microbiol Immunol.* 1979;23(6):501-513.
11. Ukai S, Kiho T, Hara C, et al. Polysaccharides in fungi. XIII. Antitumor activity of various polysaccharides isolated from *Dictyophora indusiata, Ganoderma japonicum, Cordyceps cicadae, Auricularia auricula-judae,* and *Auricularia* species. *Chem Pharm Bull.* (Tokyo) 1983;31(2):741-744.
12. Wang G, Zhang J, Mizuno T, et al. Antitumor active polysaccharides from the Chinese mushroom Songshan Lingzhi, the fruiting body of *Ganoderma tsugae. Biosci Biotechnol Biochem.* 1993;57(6):894-900.
13. Zhang J, Wang G, Li H, et al. Antitumor active protein-containing glycans from the Chinese mushroom Songshan Lingzhi, *Ganoderma tsugae* mycelium. *Biosci Biotechnol Biochem.* 1994;58(7):1202-1205.
14. Wasser SP. Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. *Appl Microbiol Biotechnol.* 2002;60(3),258-274.
15. Wang SY, Hsu ML, Hsu HC, Lee SS, Shiao MS, Ho CK. The antitumor effect of *Ganoderma lucidum* is mediated by cytokines released from activated macrophages and T lymphocytes. *Int J Cancer.* 1997;70(6):699-705.
16. Hsu MJ, Lee SS, Lin WW. Polysaccharide purified from *Ganoderma lucidum* inhibits spontaneous and Fas-mediated apoptosis in human neutrophils through activation of the phospatidylinositol 3 kinase/Akt pathways. *J Leuokoc Biol.* 2002;72(1):207-216.
17. Hsu MJ, Lee SS, Lee ST, Lin WW. Signaling mechanisms of enhanced neutrophil phagocytosis and chemotaxis by the polysaccharide purified from *Ganoderma lucidum. Brit J Pharmacol.* 2003;139(2):289-298.
18. Kim HS, Kacew S, Lee BM. In vitro chemopreventive effects of plant polysaccharides (*Aloe barbadendis Miller, Lentis edodes, Ganoderma lucidum* and *Coriolus versicolor*). *Carcinogenesis.* 1999;20(8):1637-1640.
19. Pincemail JJ. Free radicals and antioxidants in human diseases. In: Favier AE, Cadet J, Kalyanaraman B, Fontecave M, Pierre JL, eds. *Analysis of Free Radicals in Biological Systems.* Berlin, Germany: Birkhauser Verlag; 1995:83-98.

20. Lee JM, Kwon H, Jeong H, et al. Inhibition of lipid peroxidation and oxidative damage by *Ganoderma lucidum*. *Phytother Res*. 2001;15(3):245-249.
21. Wang YY, Khoo KH, Chen ST, Lin CC, Wong CH, Lin CH. Studies on the immuno-modulating and antitumor activities of *Ganoderma lucidum* (Reishi) polysaccharides: functional and proteomic analysis of a fucose-containing glycoprotein fraction responsible for the activities. *Bioorg Med Chem*. 2002;10(4):1057-1062.
22. Zhang J, Tang Q, Zimmerman-Kordman M, Reutter W, Fan H. Activation of B lymphocytes by GLIS, a bioactive proteoglycan from *Ganoderma lucidum*. *Life Sci*. 2002;71(6):623-638.
23. Mizushina Y, Hanashima L, Yamaguchi T, et al. A mushroom fruiting body-inducing substance inhibits activities of replicative DNA polymerases. *Biochem Biophys Res Commun*. 1998; 249(1):12-22.
24. Shiao MS, Lee KR, Lin LJ, Wang CT. Natural products and biological activities of the Chinese medical fungus, *Ganoderma lucidum*. In: Ho CT, Osawa T, Huang MT, Rosen RT, eds. *Food Phytochemicals for Cancer Prevention. II: Teas, Spices, and Herbs*. Washington, DC: American Chemical Society; 1994:342-354.
25. Toth JO, Luu B, Ourission G. Les acides ganoderiques T & Z: triterpenes cytotoxiques de *Ganoderma* lucidum (Polyporacee). *Tetrahedron Lett*. 1983;24(10):1081-1084.
26. Lee S, Park S, Oh JW, Yang C. Natural inhibitors for protein prenyltransferase. *Planta Medica*. 1998;64(4):303-308.
27. Min BS, Nakamura N, Miyashiro H, Bae KW, Hattori M. Triterpenes from the spores of *Ganoderma lucidum* and their activity against HIV-1 protease. *Chem Pharm Bull*. 1998; 46(10):1607-1612.
28. El-Mekkawy S, Meselhy MR, Nakamura N, et al. Anti-HIV-1 and antiHIV-1-protease substances from *Ganoderma lucidum*. *Phytochemistry*. 1998;49(6):1651-1657.
29. Min BS, Gao JJ, Nakamura N, Hattori M. Triterpenes from the spores of *Ganoderma lucidum* and their cytotoxicity against Meth-A and LLC tumor cells. *Chem Pharm Bull*. 2000; 48(7):1026-1033.
30. Kimura Y, Taniguchi M, Baba K. Antitumor and antimetastic effects on liver triterpenoid fractions of *Ganoderma lucidum*: mechanism of action and isolation of an active substance. *Anticancer Res*. 2002;22(6A):3309-3318.
31. Mau JL, Lin HC, Chen CC. Antioxidant properties of several medicinal mushrooms. *J Agric Food Chem*. 2002;50(21):6072-6077.
32. Liu X, Yuan JP, Chung CK, Chen XJ. Antitumor activity of the sporoderm-broken germinating spores of *Ganoderma lucidum*. *Cancer Lett*. 2002;182(2):155-161.
33. Wilasrusmee C, Kittur S, Siddiqui J, Bruch D, Wilasrusmee S, Kittur DS. In vitro immunomodulatory effects of ten commonly used herbs on murine lymphocytes. *J Altern Complement Med*. 2002;8(4):467-475.
34. Sliva D, English D, Lyons D, Lloyd FP Jr. Protein kinase C induces motility of breast cancers by upregulating secretion of urokinase-type plasminogen activator (uPA) through the activation of AP-1 and NF-κB. *Biochem Biophys Res Commun*. 2002; 290(1):552-557.
35. Sliva D, Rizzo MT, English D. Phosphatidylinositol 3-kinase and NF-κB regulate motility of invasive MDA-MB-231 human breast cancer cells by the secretion of urokinase-type plasminogen activator. *J Biol Chem*. 2002;277(5):3150-3157.
36. Sliva D, Labarrere C, Slivova V, Sedlak M, Lloyd FP Jr, Ho NWY. *Ganoderma lucidum* suppresses motility of highly invasive breast and prostate cancer cells. *Biochem Biophys Res Commun*. 2002;298(4):603-612b.
37. Hu H, Ahn NS, Yang X, Lee YS, Kang KS. *Ganoderma lucidum* extract induces cell cycle arrest and apoptosis in MCF-7 human breast cancer cell. *Int J Cancer*. 2002;102(3):250-253.
38. Lin SB, Li CH, Lee SS, Kan LS. Triterpene-enriched extracts from *Ganoderma lucidum* inhibit growth of hepatoma cells via suppressing protein kinase C, activating mitogen-activated protein kinases and G2-phase cell cycle arrest. *Life Sci*. 2003; 72(2):2381-2390.
39. Cheung WMW, Hui WS, Chu PWK, Chiu SW, Ip NW. Ganoderma extract activates MAP kinases and induces the neuronal differentiation of rat pheochromocytoma PC12 cells. *FEBS Lett*. 2000;486(3):291-296.
40. Sliva D, Sedlak M, Slivova V, Valachovicova T, Lloyd FP Jr., Ho NWY. Biologic activity of *Ganoderma lucidum* for the inhibition of highly invasive breast and prostate cancer cells. *J Altern Complement Med*. 2003;9(4):491-497.
41. Hattori M. Recent studies on the bitter principles of *Ganoderma lucidum*—isolation of novel triterpenes, their biological activity and pharmacokinetics. Proceedings of the Int. Symposium Ganoderma Sci.; April 27-29, 2001; Auckland, New Zealand.
42. http://www.cfsan.fda.gov.
43. Wang CY, Cusack JC Jr, Liu R, Baldwin AS Jr. Control of inducible chemoresistance: enhanced anti-tumor therapy through increased apoptosis by inhibition of NF-kappaB. *Nature Med*. 1999;5(4):412-417.
44. Ludes-Meyers JH, Liu Y, Munoz-Medellin D, Hilsenbeck SG, Brown PH. AP-1 blockade inhibits the growth of normal and malignant breast cells. *Oncogene*. 2001;20(22):2771-2780.
45. Lengyel E, Gum R, Stepp E, Juarez J, Wang H, Boyd D. Regulation of urokinase-type plasminogen activator expression by an ERK1-dependent signaling pathway in a squamous cell carcinoma cell line. *J Cell Biochem*. 1996;61(3):430-443.
46. Wang Y. The role and regulation of urokinase-type plasminogen activator receptor gene expression in cancer invasion and metastasis. *Med Res Rev*. 2001;21(2):146-170.
47. Schorr K, Li M, Krajewski S, Reed JC, Furth PA. Bcl-2 gene family and related proteins in mammary gland involution and breast cancer. *J Mam Gland Biol. Neoplasia*. 1999;4(2):153-164.
48. Biswas DK, Cruz AP, Gansberger E, Pardee AB. Epidermal growth factor-induced nuclear factor κB activation: a major pathway of cell cycle progression in estrogen-receptor negative breast cancer cells. *Proc Natl Acad Sci USA*. 2000;97(15):8542-8547.
49. van Moorselaar RJA, Voest EE. Angiogenesis in prostate cancer: its role in disease progression and possible therapeutic approaches. *Mol Cell Endocrinol*. 2002;197(1-2):239-250.