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Pharmacological Values of Medicinal Mushrooms for Prostate Cancer Therapy: The Case of *Ganoderma Lucidum*

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Prostate cancer (PCa) is the most common male malignancy in many Western countries. Primary PCAs is hormone dependent and is manageable by hormonal therapy. However, it rapidly develops to hormone-refractory tumors due to the accumulation of mutations in the androgen receptor and/or the acquisition of alternative cellular pathways that support proliferation and inhibit apoptosis of prostate cancer. To date, no effective therapy is available for clinically hormone-insensitive or hormone-refractory stages of prostate cancer.

Whereas prostate cancer is very common in Western countries, its levels are very low in Asia, providing evidence for a potential link between diet, environmental factors, and cancer incident. Natural products have been used as a source of new pharmaceuticals including anticancer drugs. The medicinal properties of mushrooms have been well known in Eastern Asia for thousands of years. Of special interest is the implication of several mushrooms in prostate cancer prevention including the popular mushroom *Ganoderma lucidum* (Ling Zhi or Reishi) that has been widely used for the general promotion of health and longevity in Asia. Dried powder of *G. lucidum* was popular as a cancer chemotherapy agent in ancient China. The pharmaceutical activities of *G. lucidum* substances targeting signal transduction pathways or molecular targets implicated in prostate carcinogenesis are reviewed.

**OVERVIEW**

For thousands of years, natural products have played an important role throughout the world in treating and preventing human diseases. Natural product medicines have originated from various source materials including plants, fungi, microorganisms, and animals. Such natural bioactive substances possess an enormous structural and chemical diversity, unsurpassable by any synthetic library; they are evolutionally optimized as drug-like molecules and might be considered biologically validated. Moreover, these molecules can serve as templates for semisynthetic and fully synthetic modifications.

An analysis of the origin of drugs developed between 1981 and 2002 showed that natural products or natural product-derived drugs comprised 28% of all novel chemical entities (NCEs) launched onto the market (1). In addition, 24% of these NCEs were synthetic or natural mimic compounds based on a study of pharmacophores related to natural products. This combined percentage (52% of all NCEs) suggests that natural products are important sources for new drugs and are also good lead compounds suitable for further modification during drug development (2). In the case of anticancer agents, natural products have made significant contributions as either direct treatments or templates for synthetic modification. In this category, there are some 140 anticancer agents available to Western countries and Japan; 62% of them are nonsynthetic agents.

It is estimated that there are approximately 1.5 million species of fungi in the world, of which approximately 82,000 are
Prostate Cancer

Prostate cancer is the most common male malignancy in many Western countries and the third leading cause of cancer deaths in men worldwide. The age-standardized incidence rate of prostate cancer is highest in the United States (137 per 100,000 in Black men), lower in European countries (28 and 31 per 100,000 in England and Denmark, respectively), and lowest in Asia (10 and 2.3 per 100,000 in Japan and China, respectively) (15).

The epithelium of the prostate gland is under the hormonal control of androgens, the production of which depends on the hypothalamic-pituitary-testicular axis. Leydig cells of the testes produce 95% of total androgens, and the adrenal glands produce the remaining 5%. In the prostate, free testosterone diffuses directly into the epithelial or stromal cells where it is converted into the functionally active androgen, dihydrotestosterone (DHT), by the action of 5α-reductase enzyme system located on the nuclear membrane. Dihydrotestosterone action is mediated by the androgen receptor (AR) (16), which functions to preserve the normal function and structure of the prostate. The androgen receptor is a structurally conserved member of the nuclear receptor superfamily of ligand-activated transcription factors. Androgen ablation therapy has been shown to produce the most beneficial responses in patients with hormone-responsive prostate cancer (19). Castration, either surgically or chemically, remains the standard treatment option for most patients. Combined with antiandrogens that interfere with androgen receptor function, these methods significantly prolong the survival of prostate cancer patients (20). Androgen deprivation therapy is initially effective in repressing primary prostate tumors. However, progression to the clinically hormone-insensitive stage is usually inevitable. To date, no effective therapy is available for hormone-insensitive or hormone-refractory stages of prostate cancer (21).

Prostate cancer has a complex etiology; currently age, ethnicity, obesity, and family history are the most consistently reported risk factors associated with the disease. Other potential risk factors, such as environmental (17) and dietary (18) factors, have also been suggested. Conversion of a normal cell into the malignant state is often linked to genetic alterations of the cell (22,23). The known tumor-suppressor genes, Retinoblastoma (Rb) and p53, were reported to play an important role in the progression of prostate cancer (24). Both genes appear to be early events in prostate carcinogenesis (25,26). In addition, mutations or deletions of pTEN, a tumor suppressor gene, have been found in 30% of primary prostate cancers and 63% of malignant cases, ranking it as one of the most common determinants of prostate tumor progression (27,28,57). The abnormal expression of growth factors and their receptors including the epidermal growth factor (EGF) (29), the transforming growth factor-β (TGF-β) (30), the transforming growth factor-α (TGF-α) (31), HER-2/neu, and c-erbB-3 oncogenes (32) may also contribute to the growth and development of both local and metastatic prostate cancer. The progression of prostate tumors to a hormone-refractory state is frequently associated with the increased expression of the antiapoptotic gene Bcl-2 (33), and the mutation of pTEN (34).

Androgen Receptor in Prostate Cancer

Like all steroid hormone receptors, the androgen receptor consists of 4 distinct regions in the expressed receptor that have specific functions (35), including the DNA-binding domain, which is responsible for the interaction with hormone-responsive elements of the target gene promoters (36), and the ligand binding region, which is located at the carboxyl terminus of the receptor and contains the activation function 2 (AF2) domain and regulates ligand-dependent receptor function. Furthermore, the ligand-binding domain is thought to be important in the function of coactivator proteins (37) and in regulating transcription (38). The androgen receptor remains cytoplasmic until ligand binding occurs, and the dissociation of heat-shock proteins (HSPs) is thought to allow conformational change in the androgen receptor and mediate translocation to the nucleus. In the absence of ligand, the androgen receptor in the cytoplasm is rapidly degraded. In the presence of ligand, the androgen receptor dimerizes, translocates to the nucleus, and initiates gene transcription by binding to specific androgen responsive elements (AREs) found in androgen-responsive promoters (39). During androgen-independent progression, prostate cancer relies on various cellular pathways, some involving the androgen receptor and others bypassing it. In the former type of pathways, a mutated androgen receptor may be activated by various ligands. In addition, deregulated growth factors and cytokines can activate the androgen receptor, usually with the help of androgen-receptor coactivators. Most of these growth factors, including EGF, insulin-like growth factor (IGF) and fibroblast growth factor (FGF), are potent mitogens and are upregulated by androgens, although the exact mechanisms are unknown. In contrast, TGF-β activity is downregulated by androgens (49). In the pathways that bypass the androgen receptor, the loss of pTEN reverses the inhibition of the PI3K/Akt pathway, permitting activated Akt to phosphorylate Bad. This activation results in the release of Bcl-2, which eventually leads to cell survival. In addition, androgen-independent cells may overexpress Bcl-2 (50). Recently, increasing evidence implicated the canonical Wnt signaling pathway in modulating the androgen signaling at multiple levels (51,52). β-catenin protein, a particularly
critical molecular component of canonical Wnt signaling, is now known to promote androgen signaling through its ability to bind to the androgen receptor protein in a ligand-dependent fashion and to enhance the ability of liganded androgen receptor to activate transcription of androgen-regulated genes (53). Furthermore, other components of the Wnt signaling pathway also augment androgen receptor function through diverse mechanisms (51–55).

**Historical and Contemporary Uses of Medicinal Mushrooms**

The medicinal use of fungi dates back thousands of years and is recorded in the histories of both traditional Western medicine (TWM) and traditional Chinese medicine (TCM) (72). Although fungi have often been marginalized in traditional Western medicine and have not been widely incorporated into Western diets, the use of fungi has been central to the cultures of most Asian countries since antiquity (73). In traditional Chinese medicine, fungi are used in their entirety, fresh or dried, to treat the patient (and the patient’s ailments) as a whole (72). In addition, certain fungi have been used in both traditional Western medicine and in traditional Chinese medicine to target specific conditions. Such is the case with *De Materia Medica (or Pen ts’ao king)* and *Ling chi (zhi)* (73). Anumber of ancient medicinal fungi discussed are still in use. These include *Ganderma lucidum*, *Poria cocos* (Schwein.) F.A. Wolf, *Grifola umbellata* (Pers.) Pilát, *Calvatia lilacina* (Berk et Mont.) Lloyd, and *Tremella fuciformis* Berk. Special attention is given to “chi” or “Ling chi (zhi)” varieties of *G. lucidum*, said to promote well-being and immortality (73). In Asia, this fungus has traditionally been used to treat age-related ailments such as coronary disease, hypertension, bronchial problems, and cancer (74).

**Fungal Secondary Metabolites**

Secondary metabolite production in fungi is a complex process coupled with morphological development (75). In most cases, the function of secondary metabolites for producing fungus is unknown but is inferred from several studies using mutants or enzyme inhibitors. These substances have their origins as derivatives from many intermediates in primary metabolism, but most can be classified according to 5 main metabolic sources: 1) amino acid-derived pathways, 2) the shikimic acid pathway for the biosynthesis of aromatic amino acids, 3) the acetate-malonate pathway from acetyl coenzyme A, 4) the mevalonic acid pathway from acetyl coenzyme A that functions in primary metabolism for the synthesis of sterols, and 5) polysaccharides and peptidopolysaccharides. The polyketide and mevalonic acid pathways are most often involved, and they produce a greater variety of compounds than the other pathways (11). Some of these compounds have tremendous importance to humankind in that they display a broad range of useful antibacterial, antiviral, and pharmaceutical activities as well as less desirable toxic activities.

Two major groups of secondary metabolites are responsible for toxic activities (the division is rather arbitrary): mycotoxins and mushroom poisons (76). All mycotoxins are low-molecular-weight natural products (i.e., small molecules) produced as secondary metabolites by filamentous microfungi, whereas mushrooms and other macroscopic fungi produce mushroom poisons. Depending on the definition used, and recognizing that most fungal toxins occur in families of chemically related metabolites, some 300 to 400 compounds are now recognized as mycotoxins (77). The second group of toxic metabolites is mushroom poisons. About 300 species of mushrooms are poisonous to humans. These species produce a wide spectrum of poisons that have been divided into the following 7 main categories (in brackets, an example of producing fungi): amanitin (*Amanita phalloides* [Vaill. : Fr.] Link, *Galerina autumnalis* [Peck] A.H. Sm. et Singer), orellanine (*Cortinarius orellanus* Fr.), gyromitrin (*Gyromitra esculenta* [Pers.] Fr.), muscarine (*Clitocybe dealbata* [Sowerby] Gillet), ibotenic acid (*Amanita cothurnata* G.F. Atk.), psilocybin (*Psilocybe baeocystis* Singer et A.H. Sm., *Panaeolus castaneifolius* [Murrill] A.H. Sm., *Conocybe cyanopus* [G.F. Atk.] Kühner) and coprine (*Coprinus atramentarius* [Bull.] Fr.) (78).

Among the fungal secondary metabolites are lectins, lactones, terpenoids, alkaloids, antibiotics, and metal chelating agents (6). Fungi also contain a number of enzymes such as lactase, superoxide dismutase, glucose oxidase, and peroxidases. It has been shown that such an enzyme therapy can also play an important role in cancer treatment preventing oxidative stress and inhibiting cell growth (79).

**Anticancer Activity of Fungal Substances**

It has been demonstrated that fungal metabolites can be used as inhibitors of molecular targets in malignant cells in order to combat certain cancers. Fungal anticancer substances can be roughly divided into two groups of high- and low-molecular-weight molecules. The major difference between these two groups is their mechanism of action. Most of the high-molecular-weight compounds are polysaccharides or protein-bound polysaccharides (80). It appears that these compounds are capable of interacting nonspecifically with the immune system to upregulate or downregulate many aspects of the host response (81). The second group comprises low-molecular-weight secondary compounds that can penetrate the cell membrane and act on specific signal-transduction pathways (11). These include mainly sesquiterpenes (which are the predominant secondary metabolites of Basidiomycetes), triterpenes, steroids and sterols,
and a few polyketides (abundantly produced by Actinomycetes).

**Anticancer Activity of *Ganoderma Lucidum***

*Ganoderma* is the most popular and intensely investigated genus among the medically active mushrooms. Plenty of its species are famous for their antiviral, antibacterial, antifungal, anticancer, and immunostimulating activities and have been used traditionally in the folk medicine of Eastern countries for centuries. These activities were due to the production of various metabolites such as proteins, terpenes, sterols, and so forth.

The genus *Ganoderma* belongs to the class of Hymenomycetes. Within the genus *Ganoderma*, over 250 taxonomic names have been reported worldwide (82) including *G. adspersum, G. applanatum, G. australe, G. lucidum,* and *G. tsugae,* to name a few. However, the majority of reports in the literature appear to refer to one species, *G. lucidum* (83).

*Ganoderma lucidum* (W. Curti: Fr.) P. Karst. (Ling Zhi or Reishi), an oriental medical mushroom, has been used widely in Asian countries for centuries to prevent or treat different diseases including cancer (Fig. 1). Dried powder of *G. lucidum,* which was recommended as a cancer chemotherapy agent, is currently used popularly worldwide in the form of dietary supplements.

*G. lucidum* extracts were reported to possess cytotoxic activity against various cancer cell lines including leukemia, lymphoma, multiple myeloma (84,112), human hepatoma PLC/PRF/5 and KB, human breast cancer MDA-MB-231 (85), human prostate cancer PC-3 (86), human breast cancer MCF-7 (87), human cervix uteri tumor HeLa (88), and low-grade bladder cancer MTC-11 (89) cell lines. The cytotoxic effects of *G. lucidum* as demonstrated by the studies of Jiang et al. (85,86) and Zhu et al. (88) were concentration dependent. This activity of *G. lucidum* can be attributed directly to specific compounds from experiments employing isolated and purified molecules. However, the molecular mechanism(s) responsible for the inhibitory effects have not been fully elucidated.

**Ganoderma Lucidum Inhibits Proliferation of Prostate Cancer Cells**

Proliferation is the multiplication or reproduction of cells resulting in the rapid expansion of a cell population. Cell proliferation is controlled by cell cycle regulatory elements.

Hsieh and Wu (92) tested the ability of extracts from individual herbs containing the herbal mixture PC-SPES, of which *Ganoderma lucidum* is one of its components, using amounts estimated to be equivalent to that present in the herbal mixture to suppress LNCaP, an androgen-dependent prostate cancer cell line, growth and/or lower prostate-specific androgen (PSA) expression, compared to cells treated with PC-SPES. Treatment of LNCaP cells with 5 microl/ml ethanol extracts of *Ganoderma lucidum* showed a 63.5% reduction in cell growth and exhibited a similar decrease in cell viability. Additional studies demonstrated the ability of *Ganoderma lucidum* extracts to also inhibit cell proliferation of AR-independent cancer cell lines such as PC-3 in a dose- and time-dependent manner (86). Growth inhibition of PC-3 cells by *Ganoderma lucidum* was mediated by the downregulation of expression of cyclin B and Cdc2 and by the upregulation of p21 expression. The inhibition of cell growth was also demonstrated by cell cycle arrest at the G2/M

![Ganoderma lucidum fruit bodies](image)
phase (86). Liu et al. (62) reported that the LNCaP growth inhibitory activity of *G. lucidum* extract is mediated by Ganoderol B isolated from *G. lucidum* fruiting body extract. Liu et al. (62) reported that Ganoderol B inhibits 5α-reductase activity and thereby causes inhibition of the proliferation of the androgen-dependent LNCaP cell line.

**Ganoderma Lucidum Induces Apoptosis in Prostate Cancer Cells**

Apoptosis is the predominant mechanism by which cancer cells die when subjected to chemotherapy or irradiation. However, cancer cells develop resistance to these therapies that may be due, at least in part, to the development of effective antiapoptotic mechanisms (103). Another mechanism allowing escape from apoptosis is the activation of survival signal transduction pathways, including Akt-dependent (104) and Akt-independent mechanisms (105). An Akt-independent example includes EGF-induced survival mechanisms (31). When LNCaP cells are treated with PI3K inhibitors and deprived of survival factors, they spontaneously undergo apoptosis. However, treatment with EGF or androgen can protect cells from apoptosis, although Akt activity remains inhibited. It was found that EGF can protect LNCaP cells from apoptosis induced via the mitochondrial pathway but not from apoptosis induced via the death-receptor pathway (106,107).

A large portion of prostate cancer cells contain deregulated Akt. For example, in LNCaP prostate cancer cell line, Akt is constitutively active as a result of a frame-shift mutation in the pTEN tumor suppressor gene, which encodes a phosphatase that inactivates the lipid products of PI3K. As a result, the lack of the pTEN protein in these cells resulted in a constitutively activated antiapoptotic NF-κB pathway (108). Thus, these cells are less sensitive to anticancer drugs whose mechanism of action is based on the induction of apoptosis (109).

*Ganoderma lucidum* induced apoptosis of PC-3 cells with a slight decrease in the expression of NF-κB-regulated Bcl-2 and Bcl-xL and the upregulation of the proapoptotic Bax protein, resulting in the enhancement of the ratios of Bax/Bcl-2 and Bax/Bcl-xL (86). Bemis et al. (110) studied the bioactivity of a unique preparation of concentrated soybean isoflavones fermented with *G. lucidum* mycelia named genistein combined polysaccharide (GCP). During fermentation, a concentrated mixture of aglycone isoflavones was produced due to the hydrolytic cleavage of the sugar moiety from the isoflavone via *G. lucidum*-derived β-glycosidase. The potential utility of GCP as a prostate cancer chemopreventative agent was analyzed in vitro and in vivo. GCP was reported to significantly suppress LNCaP and PC-3 cell growth, which was associated with apoptosis in LNCaP cells but not in PC-3 cells. GCP induced p27 and p53 (LNCaP only) protein expression within 6 h and suppressed phosphorylated Akt in both cell lines. The 2% GCP-supplemented diet significantly slowed LNCaP tumor growth, increasing apoptosis and decreasing proliferation over 4 wk (110). Zaidman et al. (95,139) measured 3 parameters that indicate induction of apoptosis in LNCaP cells: PARP cleavage, caspase-3 activity, and annexin V-FITC staining of externalized PS membranes. *G. lucidum* extracts induce apoptosis in LNCaP cell line by triggering the caspase cascade through the extrinsic or death receptor mediated pathway that includes the “initiator” caspase, caspase-8 and the “effector” caspase, caspase-3.

The ability of *G. lucidum* extracts and compounds to induce apoptosis was also demonstrated in several cell lines such as human leukemia, lymphoma, and multiple myeloma (112), human breast cancer MCF-7 (87), human prostate cancer PC-3 (86), human hepatoma HuH-7 (113), and human colonic carcinoma HT-29 (114) cell lines. One report showed that a mixture of extracts from *G. lucidum* and the herb *Duchesnea chrysanthaa* induces apoptosis in human leukemia HL-60 cells (115). However, in some of these cell lines, it was found that *G. lucidum* extracts induce apoptosis through the intrinsic or mitochondrial pathway (87,113,115).

In a series of experiments, Sliva et al. (116,117) and Jiang et al. (85) showed that *G. lucidum* extracts inhibit Akt/NF-κB signaling in prostate cancer PC-3 and breast cancer MDA-MB-231 cells, resulting in the inhibition of proliferation, apoptosis induction, and decreased motility.

**Ganoderma Lucidum Induces Cell Cycle Arrest in Prostate Cancer Cells**

Mammalian cell growth and proliferation are mediated via cell cycle progression (119). In each cell division cycle, chromosomes are replicated once (DNA synthesis or S-phase) and segregated to create two genetically identical daughter cells (mitosis or M-phase). These events are spaced by intervals of growth and reorganization (gap phases G1 and G2). Progression through the G1 phase of the cell division cycle is a rate-limiting step in mammalian cell proliferation and is governed by numerous mitogenic pathways until the restriction point is passed. CDK4 and CDK6 complexed with cyclin D1 are responsible for cell cycle progression through the G1 phase (120), and the CDK2/cyclin E complex functions in the progression of the cell from the late G1 to the early S-phase (121). These complexes lead to the phosphorylation of retinoblastoma gene product, a tumor suppressor gene active in controlling the G1 phase (122). Hyperphosphorylated pRB leads to its release from the E2F family of transcription factors and induces expression of a number of genes required for S-phase transition (123).

DNA content (as an indicator of cell proliferation) analysis showed that *G. lucidum* fungal extracts blocked LNCaP cell cycle at the transition from the G1 to the S phase (95,139). These results are in accordance with several recent reports showing G1 phase arrest in a variety of cancer cell types caused by the treatment of chemotherapeutic agents (85–88,124). Cell cycle arrest at the G1 phase was reported to be mediated through the downregulation of cyclin D1 (85,87). In addition, other
reports have demonstrated a G2 phase arrest caused by *G. lucidum* fungal extracts that is mediated by the downregulation of cyclin B (86,97,118). These data imply the existence of two separate chemical moieties that regulate cyclin D1 and cyclin B and consequently cause cell cycle arrest at G1 and G2, respectively.

Defects in cell cycle are one of the most common features of cancer cells. In prostate cancer, 16–68% of the cases reveal a loss of p27kip1 protein or low-grade expression (125). The function of the p27kip1 protein is regulated mainly by posttranslational, ubiquitin-mediated, proteosomal proteolysis (126). The tumor suppressor gene p21 was also reported missing in several solid tumors. For example, in prostate cancer PC-3, DU 145, and LNCaP cell lines, p21 was expressed at low or undetectable levels (127). On the other hand, overexpression of cyclin D1 has been documented in a number of human cancers. However, evidence suggests that this event in prostate cancer is quite rare (128). A common polymorphism in the cyclin D1 gene is associated with the production of an alternate transcript of cyclin D1 termed cyclin D1b. It was found that this variant actually stimulates cell-cycle progression in AR-dependent LNCaP cells but had no effect on AR-independent PC-3 cells (129).

Additional studies by Lu et al. (118) and Hu et al. (87) reported that the extract of *G. lucidum* inhibited cell proliferation in vitro and induced G1 cell cycle in prostate and breast cancer cell lines including MCF7. Later, Zaidman et al. (95,139) has reported that *G. lucidum* downregulated cyclin D1 expression leading to dephosphorylation of pRb and growth arrest of LNCaP prostate cancer cell line. Interestingly, cyclin D1 is controlled by the Akt and NF-κB pathways (130), which are constitutively active in LNCaP cells and can be inhibited by *G. lucidum*.

**Ganoderma Lucidum Inhibits Angiogenesis in Prostate Cancer**

Angiogenesis is a physiological process involving the growth of new blood vessels from preexisting vessels. It is a normal process in growth and development as well as in wound healing. However, this is also a fundamental step in the transition of tumors from a dormant state to a malignant state. Tumors induce angiogenesis by secreting various growth factors such as VEGF and bFGF that induce capillary growth into the tumor and allow it to grow by supplying nutrients and oxygen and removing waste products. Moreover, the new vessels allow tumor cells to escape into the circulation and lodge in other organs (tumor metastases) (135, 136).

*G. lucidum* extract was reported to inhibit early events in angiogenesis, capillary morphogenesis of the human aortic endothelial cells (137). The anti-angiogenic effect of *G. lucidum* was mediated by the inhibition of constitutively active AP-1 in prostate cancer cells, resulting in the downregulation of the secretion of VEGF and TGF-β1 from PC-3 cells. Inhibition of AP-1 activity was mediated by the inhibition of Erk 1/2 phosphorylation and Akt kinases activity in PC-3 cells (137).

**Ganoderma Lucidum Interferes With Androgen Receptor Function**

LNCaP cell lines are considered as a laboratory model for hormone-responsive prostate cancer. These cells are sensitive to androgen and contain high levels of mutated androgen receptor, a T877A mutation (ACT → GCT, Thr → Ala) in the LBD (138). This mutation renders LNCaP cells sensitive not only to androgen but also to antiandrogens, estrogens, and progestins. In contrast, the androgen insensitive cell lines DU 145 and PC-3 do not express the androgen receptor. DHT is an androgen receptor ligand generated from testosterone by the activity of 5α-reductase. Thus, 5α reductase inhibitors might have activity against prostate diseases including benign prostatic hyperplasia (BPH) and prostate cancer. Fujita et al. (140) examined the inhibitory effects of methanol extracts of 19 medicinal mushrooms on 5α-reductase activity including *Ganoderma lucidum*. The extract of *Ganoderma lucidum* showed the strongest 5α reductase inhibitory activity, and it significantly inhibited testosterone-induced growth of the ventral prostate in castrated rats (140).

Zaidman et al. (95,139) have reported that the treatment of LNCaP cell lines with *G. lucidum* organic extract resulted in a concentration-dependent inhibition of androgen receptor transcriptional activity, a concentration-dependent decrease of androgen receptor-regulated PSA, abrogation of nuclear translocation, and DNA binding activity of the androgen receptor (95,139). Furthermore, an active fraction was isolated from *G. lucidum* that competes with Dihydrotestosterone for receptor binding and consequently interferes selectively with androgen receptor function but not with the glucocorticoid receptor (GR) (95,139). The authors suggested that interference with androgen receptor function might be explained by the ability of *G. lucidum* to stimulate the assembly of a transcriptionally inactive androgen receptor on DNA as suggested by some other antiandrogen compounds (141) possibly through the inhibition of the interaction with coactivators and/or the enhancement of the interaction with corepressors (61).

Liu et al. (62) isolated Ganoderol B from *G. lucidum* fruiting body extract with 5α-reductase inhibitory activity, which suppressed the regrowth of the ventral prostate induced by testosterone in rats. In addition, Ganoderol B reduced androgen receptor levels in treated animals. The downregulation of androgen receptor signaling by Ganoderol B provided an important mechanism for its antiandrogenic activity. The important implication of this study was that Ganoderol B intervention strategy could be helpful in controlling the morbidity of prostate cancer. It was suggested that Ganoderol B might be useful in prostate cancer therapy through the inhibition of androgen synthesis and the function and level of its receptor (142).
Ganoderma Lucidum Interferes With Prostate Cancer Invasion: The PI3K/Akt/NF-κB Pathway Connection

To invade and metastasize, cancer cells must effectively degrade extracellular matrix (ECM) components. Plasminogen activation has been implicated as one of the mechanisms of ECM degradation. Mammalian cells contain two types of plasminogen activators, the urokinase type (uPA) and the tissue type (tPA), of which uPA is primarily involved in ECM degradation and consequently in tumor invasion (69,99,100). The uPA system consists of the serine proteases uPA and plasmin, their serpin inhibitors PAI-1, PAI-2, and α2AP, as well as an uPA cell surface receptor, uPAR (63). uPA is synthesized and released by cells as an inactive, single-chain, proenzyme: pro-uPA. It binds to an uPAR on the cell surface (63,64), which has an accelerating and positioning function for both the uPA and plasmin activation (64,65). Pro-uPA is cleaved to an active, two-chain protease form by plasmin (66). uPA has restricted substrate specificity, the main function of which is cleaving plasminogen to plasmin (65), which degrades several ECM components and also activates many promatrix metalloproteases (65,67). The plasminogen activation system is controlled specifically by their serpin inhibitors PAI-1, PAI-2, and α2AP, of which PAI-1 plays a more important role in cancer invasion, and α2AP is the main inhibitor of plasmin (68,100). However, during cancer invasion and metastasis, this degradation system goes out of control, allowing cancer cells to cross the normal tissue boundaries. Both the uPA secretion and the presence of receptor bound uPA at the cell surface characterize prostate cancer having an invasive phenotype (70), increased metastatic potential, and poor survival.

The expression of uPA is regulated by the transcription factors NF-κB and AP-1. The NF-κB is a dimeric transcription factor belonging to the Rel/NF-κB family of transcription factors (56–60). The major activator of NF-κB is known as the IkB kinase complex (IKK) (58). *G. lucidum* extract inhibited the constitutively active transcription factors, NF-κB and AP-1, which resulted in the inhibition of the expression of uPA and its receptor uPAR. *G. lucidum* also suppressed cell adhesion and cell migration of highly invasive prostate and breast cancer cells, suggesting its potency in blocking tumor invasiveness (71). Furthermore, Jiang et al. (85) reported that *Ganoderma lucidum* downregulated the expression of NF-κB-regulated uPA and uPAR receptor (uPAR), as well as levels of the antiapoptotic genes, Bcl-2 and Bcl-xl, accompanied by increased expression of the proapoptotic Bax protein, resulting in the enhancement of the ratio of Bax/Bcl-2 and Bax/Bcl-xl. Other reports showed that suppressing NF-κB activity by *G. lucidum* spore and fruit body extracts is mediated by the inhibition of the prosurvival factor Akt in MDA-MB-231 cells (98,116,117).

**Clinical Activity of Ganoderma lucidum**

*Ganoderma lucidum* shows a very promising effect on prostate cancer in different preclinical systems. An herbal mix-
different herbs used that resulted in the enhanced clinical efficacy of *Ganoderma lucidum* extract.

Ghafar et al. (111) reported the case of a patient with biopsy proven prostate cancer showing clinical and pathologic evidence of regression following administration of GCP, a concentrated soybean isoflavones fermented with *G. lucidum* mycelia, named genisteen combined polysaccharide (GCP). The patient received GCP for 6 wk prior to radical prostatectomy. The patient’s PSA decreased from an initial value of 19.7 to 4.2 ng/ml after 44 days of low-dose GCP. No cancer was identified in the radical prostatectomy specimen and no side-effects were observed in this patient. This case also suggested that GCP, which had shown potent inhibitory effects against prostate cancer cell lines in vitro studies, may exhibit some potential activity in the treatment and prevention of prostate cancer.

**CONCLUSIONS**

*Ganoderma lucidum* is a popular medicinal mushroom that has been used as a home remedy in traditional Chinese medicine (TCM) for the prevention or treatment of a variety of diseases including cancer. Today, *G. lucidum* is recognized as a dietary supplement recommended in many countries as a cancer therapeutic. In addition, *G. lucidum* is considered by some investigators as a therapeutic biofactory that consists of diverse bioactive molecules mediating its biological functions. This raises the need to explore the full potential of this natural product and also to recognize its various active substances capable of combating a variety of diseases including cancer.

Preliminary clinical data based on a number of clinical trials that were conducted have shown promising efficacies of *G. lucidum* extracts or powders in cancer treatment as well as in other indications. Some of the clinical trials were not well designed and lacked appropriate controls. We believe that there is a need to explore the full potential of the dietary supplement of *G. lucidum* to assess its safety and efficacy in well-designed, double-blinded, randomized, placebo-controlled clinical trials using *G. lucidum* powders or extracts as stand-alone treatment or in combination with other treatments. To achieve this goal, standardization of *G. lucidum* is an important element. Because the composition and amount of biologically active substances depend on places of production, cultivation conditions, extraction procedures, and the strains of *G. lucidum*, standardization will help its acceptance as a natural product suitable for cancer treatment.

*Ganoderma lucidum* extracts exhibited anticancer activity in in vitro systems against a variety of cancer cells including leukemia, lymphoma, breast, prostate, liver, lung, and myeloma cell lines. The anticancer activity of *G. lucidum* includes the inhibition of proliferation, induction of apoptosis, induction of cell cycle arrest, inhibition of invasive behavior, and suppression tumor angiogenesis in many experimental systems including prostate cancer. Studies have aimed at elucidating the mechanism of action revealed that *G. lucidum* inhibits the function androgen receptor and interferes with the PI3K/Akt/NF-κB pathway. The reported activity of *G. lucidum* is mostly reported using crude extractions. Thus, isolating active fractions and moieties responsible for the reported activity is an obstacle that must be overcome to allow the structural elucidation of active moieties and to define the exact mechanism of action of such substances. Moreover, *G. lucidum* extracts that exhibited diverse pharmacologic functions were also shown to contain highly diverse pharmacological moieties (40–48, 91). Currently, more than 100 different moieties have been reported from *G. lucidum*. Thus, the immediate goal must be to identify the different chemical structures mediating the different pharmacological activities aimed at improving their potency, selectivity, bioavailability, as well as pharmacokinetics and pharmacodynamics parameters and explore their potential synergy with other pharmaceutical compounds available for combating different diseases including prostate cancer.

**REFERENCES**


MEDICINAL MUSHROOMS FOR PROSTATE CANCER THERAPY


