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Chapter 9 Ganoderma lucidum (Lingzhi or Reishi)

A Medicinal Mushroom

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9.1 INTRODUCTION

Ganoderma lucidum, an oriental fungus (Figure 9.1), has a long history of use for promoting health and longevity in China, Japan, and other Asian countries. It is a large, dark mushroom with a glossy exterior and a woody texture. The Latin word *lucidus* means "shiny" or "brilliant" and refers to the varnished appearance of the surface of the mushroom. In China, *G. lucidum* is called lingzhi, whereas in Japan the name for the Ganodermataceae family is reishi or mannentake.

In Chinese, the name lingzhi represents a combination of spiritual potency and essence of immortality, and is regarded as the "herb of spiritual potency," symbolizing success, well-being, divine power, and longevity. Among cultivated mushrooms, *G. lucidum* is unique in that its pharmaceutical rather than nutritional value is paramount. A variety of commercial *G. lucidum* products are available in various forms, such as powders, dietary supplements, and tea. These are produced from different parts of the mushroom, including mycelia, spores, and fruit body. The specific applications and attributed health benefits of lingzhi include control of blood glucose levels, modulation of the immune system, hepatoprotection, bacteriostasis, and more. The various beliefs regarding the health benefits of *G. lucidum* (Figure 9.2) are based largely on anecdotal evidence, traditional use, and cultural mores. However, recent reports provide scientific support to some of the ancient claims of the health benefits of lingzhi.

9.2 HISTORY: LINGZHI AS A MEDICINAL MUSHROOM

Lingzhi has been recognized as a medicinal mushroom for over 2000 years, and its powerful effects have been documented in ancient scripts (Wasser 2005). The proliferation of *G. lucidum* images in art began in 1400 AD, and they are associated with Taoism (McMeekin 2005). However, *G. lucidum* images extended beyond religion and appeared in paintings, carvings, furniture, and even women's accessories (Wasser 2005). The first book wholly devoted to the description of herbs and their medicinal value was *Shen Nong Ben Cao Jing*, written in the Eastern Han dynasty of China (25-220 AD). This book is also known as "Classic of the Materia Medica" or "Shen-nong's Herbal Classics." It describes botanical, zoological, and mineral substances, and was composed in the second century under the pseudonym of Shen-nong ("the holy farmer"; Zhu, 1998). The book, which has been continually updated and extended, describes the beneficial effects of several mushrooms with a reference to the medicinal mushroom *G. lucidum* (Zhu, 1998; Upton 2000; Sanodiya et al. 2009). In the *Supplement to Classic of Materia Medica* (502-536 AD) and the *Ben Cao Gang Mu* by Li Shin-Zhen, which is considered to be the first pharmacopoeia in China (1590 AD; Ming dynasty), the mushroom was attributed with therapeutic properties, such as tonifying effects, enhancing vital energy, strengthening cardiac function, increasing memory, and antiaging effects. According to the *State Pharmacopoeia of the People's Republic of China* (2000), *G. lucidum* acts to replenish Qi, ease the mind, and relieve cough and asthma, and it is recommended for dizziness, insomnia, palpitation, and shortness of breath.

Wild lingzhi is rare, and in the years before it was cultivated, only the nobility could afford it. It was believed that the sacred fungus grew in the home of the immortals on the "three aisles of the blest" off the coast of China (McMeekin 2005). However, its reputation as a panacea may have been earned more by virtue of its irregular distribution, rarity, and use by the rich and privileged members of Chinese society than by its actual effects. Nevertheless, the *Ganoderma* species continue to be a popular traditional medicine in Asia and their use is growing throughout the world (Wachtel-Galor, Buswell et al. 2004; Lindequist, Niedermeyer, and Jülich 2005).

9.3 TAXONOMY

The family Ganodermataceae describes polypore basidiomycetous fungi having a double-walled basidiospore (Donk 1964). In all, 219 species within the family have been assigned to the genus *Ganoderma*, of which *G. lucidum* (W. Curt.: Fr.) P. Karsten is the species type (Moncalvo 2000). Basidiocarps of this genus have a laccate (shiny) surface that is associated with the presence of thickwalled pilocystidia embedded in an extracellular melanin matrix (Moncalvo 2000). *Ganoderma* species are found all over the world, and different characteristics, such as shape and color (red, black, blue/green, white, yellow, and purple) of the fruit body, host specificity, and geographical origin, are used to identify individual members of the species (Zhao and Zhang 1994; Woo et al. 1999; Upton 2000). Unfortunately, the morphological characteristics are subject to variation resulting from, for example, differences in cultivation in different geographical locations under different climatic conditions and the natural genetic development (e.g., mutation, recombination) of individual species. Consequently, the use of macroscopic characteristics has resulted in a large number of synonyms and a confused, overlapping, and unclear taxonomy for this mushroom. Some taxonomists also consider macromorphological features to be of limited value in the identification of *Ganoderma* species due to its high phenotypic plasticity (Ryvarden 1994; Zhao and Zhang 1994). More reliable morphological characteristics for *Ganoderma* species are thought to include spore shape and size, context color and consistency, and the microanatomy of the pilear crust. Chlamydospore production and shape, enzymatic studies and, to a lesser extent, the range and optima of growth temperatures have also been used for differentiating morphologically similar species (Gottlieb, Saidman, and Wright 1998; Moncalvo 2000; Saltarelli et al. 2009). Biochemical, genetic, and molecular approaches have also been used in *Ganoderma* species taxonomy. Molecular-based methodologies adopted for identifying *Ganoderma* species include recombinant (rDNA) sequencing (Moncalvo et al. 1995; Gottlieb, Ferref, and Wright 2000), random amplified polymorphic DNA-PCR (RAPD; PCR stands for polymerase chain reaction), internal transcribed spacer (ITS) sequences (Hseu et al. 1996), sequence-related amplified polymorphism (SRAP; Sun et al. 2006), enterobacterial repetitive intergenic consensus (ERIC) elements, and amplified fragment length polymorphism (AFLP; Zheng et al. 2009). Other approaches to the problem of *G. lucidum* taxonomy include nondestructive nearinfrared (NIR) methods combined with chemometrics (Chen et al. 2008), nuclear magnetic resonance (NMR)-based metabolomics (Wen et al. 2010), and high-performance liquid chromatography (HPLC) for generating chemical fingerprints (Su et al. 2001; Chen et al. 2008; Shi, Zhang et al. 2008; Chen et al. 2010).

9.4 CULTIVATION, GLOBAL USE, AND MANUFACTURE OF PRODUCTS

Owing to its irregular distribution in the wild and to an increasing demand for *G. lucidum* as a medicinal herb, attempts were made to cultivate the mushroom (Chang and Buswell 2008). Different members of the *Ganoderma* genus need different conditions for growth and cultivation (Mayzumi, Okamoto, and Mizuno 1997). Moreover, different types are favored in different geographical regions. For example, in South China, black *G. lucidum* is popular, whereas red *G. lucidum* is preferred in Japan. *G. lucidum* thrives under hot and humid conditions, and many wild varieties are found in the subtropical regions of the Orient. Since the early 1970s, cultivation of *G. lucidum* has become a major source of the mushroom. Artificial cultivation of *G. lucidum* has been achieved using substrates such as grain, sawdust, wood logs (Chang and Buswell 1999; Wasser 2005; Boh et al. 2007), and cork residues (Riu, Roig, and Sancho 1997).

Since it takes several months to culture the fruiting body of *G. lucidum*, mycelia-based and culture broth-based products have assumed greater importance due to demands for increased quality control and year-round production (Sanodiya et al. 2009). The processes and different growth parameters (e.g., temperature, pH) involved in submerged mycelial culture can easily be standardized under controlled conditions, and purification and other downstream processing of active components such as polysaccharides released into the culture medium usually involve relatively simple procedures. Different culture conditions and medium compositions have also been reported to strongly influence mycelial growth and the production of biopolymers (e.g., polysaccharides) that are extruded from the cell (exopolysaccharides [EPSs]; Mayzumi, Okamoto, and Mizuno 1997; Chang and Buswell 1999; Habijanic and Berovic 2000; Fang and Zhong 2002; Boh et al. 2007; Sanodiya et al. 2009). For example, Yang and Liau (1998) reported that polysaccharide production by fermenter-grown mycelia of *G. lucidum* was optimum at 30°C–35°C and a pH of 4–4.5, and the addition of supplements such as fatty acids was found to accelerate mycelial growth and the production of bioactive components. In a submerged culture of *G. lucidum*, the optimum pH for cell growth has been shown to be lower than that for EPS formation. A two-stage pH-control strategy, developed to maximize mycelial biomass and EPS production, revealed that culture pH had a significant effect on EPS yield, chemical composition and molecular weight, and mycelial morphology (Kim, Park, and Yun 2006). The productive mycelial morphological form for EPS production was a dispersed pellet (controlled pH shift from 3.0 to 6.0) rather than a compact pellet with a dense core (pH maintained at 4.5) or a featherlike pellet (controlled pH shift from 6.0 to 3.0). Three different polysaccharides were obtained under each pH condition, and their molecular weights and chemical compositions were significantly different (Kim, Park, and Yun 2006). More recently, a novel three-stage light irradiation strategy has been developed in submerged cultures of *G. lucidum* for the efficient production of polysaccharides and one of the triterpene components, ganoderic acid (Zhang and Tang 2008).

A decade ago, more than 90 brands of *G. lucidum* products were registered and marketed internationally (Lin 2000). Worldwide consumption is now estimated at several thousand tonnes, and the market is growing rapidly. Although there are no recently published data relating to the total world market value of ganoderma products, in 1995, the total estimated annual market value given by different commercial sources was US$1628 million (Chang and Buswell 1999). Numerous *G. lucidum* products, prepared from different parts of the mushroom, are currently available on the market (Chang and Buswell 2008). In manufacturing terms, the simplest type consists of intact fruiting bodies ground to powder and then processed to capsule or tablet form. Other "nonextracted" products are prepared from the following three sources: (1) dried and powdered mycelia harvested from submerged liquid cultures grown in fermentation tanks; (2) dried and powdered combinations of substrate, mycelia, and mushroom primordia, following inoculation and incubation of a semisolid medium with fungal mycelia; and (3) intact fungal spores or spores that have been broken by mechanical means or have had the spore walls removed. Although spore preparations have been researched and promoted vigorously in recent years, any added medicinal effects attributable to the removal or breakage of spore walls, which represents an additional and often costly step in the production process, are still controversial. Other products are prepared with materials (e.g., polysaccharides, triterpenes) extracted, usually with hot water or ethanol, from fruiting bodies or mycelia harvested from submerged liquid cultures and then evaporated to dryness and tabulated/encapsulated either separately or integrated together in designated proportions. The adoption of supercritical fluid CO_2 extraction technologies has enlarged the spectrum of extracted substances due to the low temperature required during processing. Several other products have been prepared as binary, ternary or more complex mixtures of powdered ganoderma and other mushrooms (e.g., *Lentinula edodes, Agaricus brasiliensis, Grifola frondosa, Pleurotus* spp., and *Flammulina velutipes*) and even with other medicinal herbs (e.g., spirulina powder or flower pollen grains).

9.5 MAJOR BIOACTIVE COMPONENTS

Most mushrooms are composed of around 90% water by weight. The remaining 10% consists of 10–40% protein, 2–8% fat, 3–28% carbohydrate, 3–32% fiber, 8–10% ash, and some vitamins and minerals, with potassium, calcium, phosphorus, magnesium, selenium, iron, zinc, and copper accounting for most of the mineral content (Borchers et al. 1999). In a study of the nonvolatile components of *G. lucidum*, it was found that the mushroom contains 1.8% ash, 26–28% carbohydrate, 3–5% crude fat, 59% crude fiber, and 7–8% crude protein (Mau, Lin, and Chen 2001).

In addition to these, mushrooms contain a wide variety of bioactive molecules, such as terpenoids, steroids, phenols, nucleotides and their derivatives, glycoproteins, and polysaccharides. Mushroom proteins contain all the essential amino acids and are especially rich in lysine and leucine. The low total fat content and high proportion of polyunsaturated fatty acids relative to the total fatty acids of mushrooms are considered significant contributors to the health value of mushrooms (Chang and Buswell 1996; Borchers et al. 1999; Sanodiya et al. 2009).

Polysaccharides, peptidoglycans, and triterpenes are three major physiologically active constituents in *G. lucidum* (Boh et al. 2007; Zhou et al. 2007). However, the amount and percentage of each component can be very diverse in natural and commercial products, as exemplified by the data shown in Table 9.1. When 11 randomly selected samples of commercial lingzhi products purchased in Hong Kong shops were evaluated for the two major active components, triterpenes and polysaccharides, it was found that the triterpene content ranged from undetectable to 7.8% and the polysaccharide content varied from 1.1–5.8% (Chang and Buswell 2008). Such variations can occur for several reasons, including differences in the species or strains of mushroom used and differences in production methods.

9.5.1 Polysaccharides and Peptidoglycans

Fungi are remarkable for the variety of high-molecular-weight polysaccharide structures that they produce, and bioactive polyglycans are found in all parts of the mushroom. Polysaccharides represent structurally diverse biological macromolecules with wide-ranging physiochemical properties (Zhou et al. 2007). Various polysaccharides have been extracted from the fruit body, spores, and mycelia of lingzhi; they are produced by fungal mycelia cultured in fermenters and can differ in their sugar and peptide compositions and molecular weight (e.g., ganoderans A, B, and C). *G. lucidum* polysaccharides (GL-PSs) are reported to exhibit a broad range of bioactivities, including anti-inflammatory, hypoglycemic, antiulcer, antitumorigenic, and immunostimulating effects (Miyazaki and Nishijima 1981; Hikino et al. 1985; Tomoda et al. 1986; Bao et al. 2001; Wachtel-Galor, Buswell et al. 2004). Polysaccharides are

normally obtained from the mushroom by extraction with hot water followed by precipitation with ethanol or methanol, but they can also be extracted with water and alkali. Structural analyses of GL-PSs indicate that glucose is their major sugar component (Bao et al. 2001; Wang et al. 2002). However, GL-PSs are heteropolymers and can also contain xylose, mannose, galactose, and fucose in different conformations, including 1–3, 1–4, and 1–6-linked β and α-D (or L)-substitutions (Lee, Lee, and Lee 1999; Bao et al. 2002). Branching conformation and solubility characteristics are said to affect the antitumorigenic properties of these polysaccharides (Bao et al. 2001; Zhang, Zhang, and Chen 2001). The mushroom also consists of a matrix of the polysaccharide chitin, which is largely indigestible by the human body and is partly responsible for the physical hardness of the mushroom (Upton 2000). Numerous refined polysaccharide preparations extracted from *G. lucidum* are now marketed as over-the-counter treatment for chronic diseases, including cancer and liver disease (Gao et al. 2005).

Various bioactive peptidoglycans have also been isolated from *G. lucidum*, including *G. lucidum* proteoglycan (GLPG; with antiviral activity; Li, Liu and Zhao 2005), *G. lucidum* immunomodulating substance (GLIS; Ji et al. 2007), PGY (a water-soluble glycopeptide fractionated and purified from aqueous extracts of *G. lucidum* fruit bodies; Wu and Wang 2009), GL-PS peptide (GL-PP; Ho et al. 2007), and F3 (a fucose-containing glycoprotein fraction; Chien et al. 2004).

9.5.2 Triterpenes

Terpenes are a class of naturally occurring compounds whose carbon skeletons are composed of one or more isoprene C_5 units. Examples of terpenes are menthol (monoterpene) and β-carotene (tetraterpene). Many are alkenes, although some contain other functional groups, and many are cyclic. These compounds are widely distributed throughout the plant world and are found in prokaryotes as well as eukaryotes. Terpenes have also been found to have anti-inflammatory, antitumorigenic, and hypolipidemic activity. Terpenes in *Ginkgo biloba*, rosemary (*Rosemarinus officinalis*), and ginseng (*Panax ginseng*) are reported to contribute to the health-promoting effects of these herbs (Mahato and Sen 1997; Mashour, Lin, and Frishman 1998; Haralampidis, Trojanowska, and Osbourn 2002).

Triterpenes are a subclass of terpenes and have a basic skeleton of C_{30}. In general, triterpenoids have molecular weights ranging from 400 to 600 kDa and their chemical structure is complex and highly oxidized (Mahato and Sen 1997; Zhou et al. 2007). Many plant species synthesize triterpenes as part of their normal program of growth and development. Some plants contain large quantities of triterpenes in their latex and resins, and these are believed to contribute to disease resistance. Although hundreds of triterpenes have been isolated from various plants and terpenes as a class have been shown to have many potentially beneficial effects, there is only limited application of triterpenes as successful therapeutic agents to date. In general, very little is known about the enzymes and biochemical pathways involved in their biosynthesis.

In *G. lucidum*, the chemical structure of the triterpenes is based on lanostane, which is a metabolite of lanosterol, the biosynthesis of which is based on cyclization of squalene (Haralampidis, Trojanowska, and Osbourn 2002). Extraction of triterpenes is usually done by means of methanol, ethanol, acetone, chloroform, ether, or a mixture of these solvents. The extracts can be further purified by various separation methods, including normal and reverse-phase HPLC (Chen et al. 1999; Su et al. 2001). The first triterpenes isolated from *G. lucidum* are the ganoderic acids A and B, which were identified by Kubota et al. (1982). Since then, more than 100 triterpenes with known chemical compositions and molecular configurations have been reported to occur in *G. lucidum*. Among them, more than 50 were found to be new and unique to this fungus. The vast majority are ganoderic and lucidenic acids, but other triterpenes such as ganoderals, ganoderiols, and ganodermic acids have also been identified (Nishitoba et al. 1984; Sato et al. 1986; Budavari 1989; Gonzalez et al. 1999; Ma et al. 2002; Akihisa et al. 2007; Zhou et al. 2007; Jiang et al. 2008; Chen et al. 2010). Examples of triterpenes are shown in Figure 9.3.

G. lucidum is clearly rich in triterpenes, and it is this class of compounds that gives the herb its bitter taste and, it is believed, confers on it various health benefits, such as lipid-lowering and antioxidant effects. However, the triterpene content is different in different parts and growing stages of the mushroom. The profile of the different triterpenes in *G. lucidum* can be used to distinguish this medicinal fungus from other taxonomically related species, and can serve as supporting evidence for classification. The triterpene content can also be used as a measure of quality of different ganoderma samples (Chen et al. 1999; Su et al. 2001)

9.5.3 Other Components

Elemental analysis of log-cultivated fruit bodies of *G. lucidum* revealed phosphorus, silica, sulfur, potassium, calcium, and magnesium to be their main mineral components. Iron, sodium, zinc, copper, manganese, and strontium were also detected in lower amounts, as were the heavy metals lead, cadmium, and mercury (Chen et al. 1998). Freeze-dried fruit bodies of unidentified *Ganoderma* spp. collected from the wild were reported to have a mineral content of 10.2%, with potassium, calcium, and magnesium as the major components (Chiu et al. 2000). Significantly, no cadmium or mercury was detected in these samples. *G. lucidum* can also contain up to 72 μg/g dry weight of selenium (Se; Falandysz 2008) and can biotransform 20–30% of inorganic selenium present in the growth substrate into selenium-containing proteins (Du et al. 2008).

Some attention has been given to the germanium content of *Ganoderma* spp. Germanium was fifth highest in terms of concentration (489 μg/g) among the minerals detected in *G. lucidum* fruit bodies collected from the wild (Chiu et al. 2000). This mineral is also present in the order of parts per billion in many plant-based foods, including ginseng, aloe, and garlic (Mino et al. 1980). Although germanium is not an essential element, at low doses, it has been credited with immunopotentiating, antitumor, antioxidant, and antimutagenic activities (Kolesnikova, Tuzova, and Kozlov 1997). However, although the germanium content of *G. lucidum* has been used to promote *G. lucidum*-based products, there is no firm evidence linking this element with the specific health benefits associated with the mushroom.

G. lucidum contains some other compounds that may contribute to its reported medicinal effect, such as proteins and lectins. The protein content of dried *G. lucidum* was found to be around 7–8%, which is lower than that of many other mushrooms (Chang and Buswell 1996; Mau, Lin, and Chen 2001). Bioactive proteins are reported to contribute to the medicinal properties of *G. lucidum*, including LZ-8, an immunosuppressive protein purified from the mycelia (Van Der Hem et al. 1995); a peptide preparation (GLP) exhibiting hepatoprotective and antioxidant activities (Sun, He, and Xie 2004; Shi, Sun et al. 2008); and a 15-kDa antifungal protein, ganodermin, which is isolated from *G. lucidum* fruiting bodies (Wang and Ng. 2006).

The carbohydrate and crude fiber content of the dried mushroom was examined and found to be 26–28% and 59%, respectively (Mau, Lin, and Chen 2001). Lectins were also isolated from the fruit body and mycelium of the mushroom (Kawagishi et al. 1997), including a novel 114-kDa hexameric lectin, which was revealed to be a glycoprotein having 9.3% neutral sugar and showing hemagglutinating activity on pronase-treated human erythrocytes (Thakur et al. 2007). Lectins (from the Latin word *legere*, which means to pick up, choose) are nonenzymatic proteins or glycoproteins that bind carbohydrates. Many species of animals, plants, and microorganisms

produce lectins, and they exhibit a wide range of functions. In animals, for example, lectins are involved in a variety of cellular processes and the functioning of the immune system (Wang, Ng, and Ooi 1998).

Other compounds that have been isolated from *G. lucidum* include enzymes such as metalloprotease, which delays clotting time; ergosterol (provitamin D_2); nucleosides; and nucleotides (adenosine and guanosine; Wasser 2005; Paterson 2006). Kim and Nho (2004) also described the isolation and physicochemical properties of a highly specific and effective reversible inhibitor of α-glucosidase, SKG-3, from *G. lucidum* fruit bodies. Furthermore, *G. lucidum* spores were reported to contain a mixture of several long-chain fatty acids that may contribute to the antitumor activity of the mushroom (Fukuzawa et al. 2008).

9.6 THERAPEUTIC APPLICATIONS

The combination of benefit without toxicity represents the desired end result in the development of effective therapeutic interventions. *G. lucidum* has been used for hundreds of years as a health promotion and treatment strategy; there are now many published studies that are based on animal and cellculture models and on in vitro assessment of the health effects of *G. lucidum*, and there are also some reports of human trials in the field. However, there is no cohesive body of research, and the objective evaluation of this traditional therapy in terms of human health remains to be clearly established. In Sections 9.6.1 through 9.6.6, studies on the properties of *G. lucidum* in relation to cancer (which has attracted the most interest), viral and bacterial infection, diabetes, and liver injury are discussed.

9.6.1 Cancer

G. lucidum is a popular supplement taken by healthy individual to boost the immune system and by cancer patients along with conventional therapies. In this section, the scientific studies of *G. lucidum* on its anticancer properties are summerized.

9.6.1.1 Introduction

Cancer is a worldwide leading cause of death, and despite comprehensive advances in the early diagnosis of the disease and chemotherapy, it remains a major clinical challenge (WHO 2008). As part of searching for new chemopreventive and chemotherapeutic agents, hundreds of plant species, including mushrooms, have been evaluated. This has resulted in the isolation of thousands of bioactive molecules that were shown to have antitumor activity from numerous mushroom species, including *Ganoderma* species (Wasser and Weis 1999; Borchers et al. 2008). In *G. lucidum*, a large number of chemical compounds can be extracted from the fruiting body, mycelia, or spores. Many polysaccharides and triterpenes, the two major groups of components in the mushroom, exhibit chemopreventive and/or tumoricidal effects, as proved by numerous studies from in vitro experiments and animal and human in vivo studies (Yuen and Gohel 2005; Zaidman et al. 2005). Tumorimplanted animal models have shown inhibitory effects on angiogenesis and metastasis. However, evidence from well-designed human trials is still scarce.

9.6.1.2 In Vitro Anticancer Activities

Tomasi et al. (2004) tested 58 basidiomycetes mushrooms, of which *G. lucidum* was shown to be the most effective in killing cancer cells. *G. lucidum* induced cell-cycle arrest and apoptosis in various human and rodent tumor cells, including murine lymphocytic leukemia L1210 and Lewis lung carcinoma (LLC; Min et al. 2000; Tomasi et al. 2004), mouse reticulocyte sarcoma L-II (Liu et al. 2002), murine sarcoma Meth-A (Min et al. 2000; Gao, Min et al. 2002) and S180 (Gao, Min et al. 2002; Liu et al. 2002), human leukemia HL-60 (Muller et al. 2006; Kim et al. 2007; Fukuzawa et al. 2008; Liu et al. 2009) and U937, K562, Blin-1, Nalm-6, RPMI8226 (Muller et al. 2006; Shang et al. 2009), human hepatoma PLC/PRF/5, KB (Lin et al. 2003), HepG2 (Liu et al. 2009; Weng et al. 2009), Hep3B (Chung et al. 2001), Huh-7 (Lin et al. 2003; Li, Chan et al. 2005), human liver tumor SMMC7721 (Tang et al. 2006), human breast cancer MDA-MB-123 (Jiang et al. 2008; Liu et al. 2009; Zhao et al. 2010), MCF-7 (Jiang, Slivova, and Sliva 2006; Liu et al. 2009; Shang et al. 2009), T-47D (Gao, Min et al. 2002) and MT-1 (Wu et al. 2006; Xie et al. 2009), human prostate cancer PC-3 (Jiang et al. 2004; Evans et al. 2009), human cervix uteri tumor Hela (Liu et al. 2002; Tang et al. 2006; Shang et al. 2009), human ovarian cancer SKOV4 (Shang et al. 2009), human colonic cancer HT-29 (Hong et al. 2004) and SW480 (Xie et al. 2006), human lung carcinoma PG (Cao and Lin 2006; Cao, Lin, and Wang 2007) and 95-D (Tang et al. 2006), human small-cell lung carcinoma NCI-H69 and multidrug-resistant strain VPA (Sadava et al. 2009), lowgrade bladder cancer MTC-11 (Lu et al. 2004), and human uroepithelial HUC-PC (Yuen, Gohel, and Au 2008) cells.

Through the regulation of expression of different signals, tumor cells were arrested by *G. lucidum* at different points of cell cycle, for example, breast at G0/G1 phase; lung at G1 phase; liver at G1/G2 phase; and bladder, prostate, and leukemia at G2 phase. A selenium-enriched extract of *G. lucidum* mycelia was shown to induce G1/S phase arrest in human erythroid chronic myeloid leukemia K562 cells (Shang et al. 2009). Another extract induced G0/G1 phase arrest in estrogen-dependent breast MCF-7 cells through the downregulation of estrogen-α receptor and serine/threonine-specific protein kinase Akt/nuclear factor κB (NF-κB) signaling (Jiang, Slivova, and Sliva 2006). In various human cancer cell lines, extracts of *G. lucidum* were shown to suppress the progression of the G1 phase in cell cycle, and apoptosis was confirmed by using terminal deoxynucleotidyl transferase dUTP nick and labeling (TUNEL) assay (Liu et al. 2009). Many of these activities were accompanied by apoptosis. Cao and Lin (2006) demonstrated that a fraction of GL-PP decreased the antiapoptotic protein Bcl-2 expression and increased the proapoptotic protein Bax expression in human umbilical cord vascular endothelial cells (HUVECs). A triterpene-rich extract from *G. lucidum* induced progressive apoptosis in the premalignant HUC-PC cell line by increasing the early apoptosis marker annexin-V within 3 hours. Half the cells stained positive for 7-amino-actinomycin D (indicating late apoptosis) after 8 hours. All cells were dead at 24 hours, and this was associated with the downregulation of telomerase (Yuen, Gohel, and Au 2008). Similar apoptotic activities were also demonstrated in other human cancer cells (Fukuzawa et al. 2008). An ethanol extract of *G. lucidum* decreased cyclooxygenase 2 (COX)-2 enzyme expression and increased nitric oxide synthesis in colon HT-29 cells (Hong et al. 2004). In lung 95-D tumor cells, the pure compound ganoderic acid T caused mitochondrial dysfunction, which resulted from the upregulation of proapoptotic p53 and Bax expression (Tang et al. 2006). Moreover, the use of a combination of *G. lucidum* and *Duschesnea* extracts upregulated cytochrome *c* and Bax translocation to trigger caspase-3 apoptosis in leukemia HL-60 cells (Kim et al. 2007). Activation of caspases-7 and -9 by *G. lucidum* has been demonstrated in breast MCF-7 and lung H69-SCLC cancer cells, respectively (Hu et al. 2002; Sadava et al. 2009). In hepatoma HepG2 cells, a lucidenic acid–rich *G. lucidum* extract was shown to suppress phosphorylation of ERK1/2 and Akt signaling, which downregulated their downstream NF-κB and proto-oncoproteins (c-Jun and c-Fos) activities, favoring apoptosis (Weng et al. 2009).

A tumor mass requires a continuous nutrient supply via new blood vessels formed by the process of angiogenesis. Invasive cancer cells spread to distant sites through blood and lymphoid vessels. Therefore, agents that inhibit angiogenesis inhibit tumor growth and spread. The potential antiangiogenic activities of *G. lucidum* have been demonstrated in ex vivo chick embryo chorioallantoic membrane (CAM) assay (Cao and Lin 2004; Song et al. 2004). Polysaccharide peptide and ethanol extract from *G. lucidum* has been

proved to decrease microvessels around a microfiber filter disc containing an embryo with intact yolks. Using a prostate cancer cell line, two angiogenic factors, known as vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β1, were suppressed by *G. lucidum* through inhibition of the ras/extracellular signal–regulated kinase (Erk1/2) and Akt signaling pathways (Johnston 2005; Stanley et al. 2005). Similar effects were also observed in a human lung cancer cell lines under hypoxic conditions after exposure to a high dose of GL-PP (Cao and Lin 2006).

Cell adhesion, invasion, and migration are the key factors in determining the aggressiveness of cancer; hence, control of cell motility is effective in avoiding cancer metastasis. A polysaccharide extract of *G. lucidum* mycelia inhibited the formation of oncogenic ras-induced transformed foci in an R6 embryo fibroblast cell line (Hsiao et al. 2004). Spores and the fruiting body of *G. lucidum* were shown to inhibit the regulatory proteins phosphatidylinositol and NF-κB in highly invasive breast and prostate cancer cells (Sliva et al. 2002). Cell adhesion, invasion, and colony formation of breast cancer cells were significantly inhibited on exposure to *G. lucidum* extracts (Sliva 2004). In addition, Lu et al. (2004) demonstrated that water and ethanol extracts of *G. lucidum* modulated the F/G-actin ratio, which, in turn, reduced the formation of stress fiber and focal adhesion complexes of bladder cancer cells, suggesting the actin remodeling was associated with the inhibition of carcinogen-induced cell migration. Inhibition of mitogen-induced invasion of HepG2 cells was demonstrated in a study by using Matrigel-coated filter inserts assay (Weng et al. 2009).

9.6.1.3 Animal Studies

Rodent studies of possible antitumorigenic effects of *G. lucidum* can be traced back to the early 1980s. Ten days of intraperitoneal (i.p.) injections of a polysaccharide fraction (GL-1) from the fruit body was reported to inhibit (by 95–98%) the growth of transplanted sarcoma 180 tumor cells in mice (Miyazaki and Nishijima 1981). A complex of polysaccharides and protein from the mushroom was also found to show significant antitumor activity in a similar study conducted by Kim et al. (1980). An inhibition rate of 88% was reported, and there was complete regression of tumor in a third of the test animals. In a study conducted by Hyun, Choi, and Kim (1990), which used a similar protocol but used various extracted polysaccharides, inhibition rates of 52–81% were found. A hot water extract (2 mg/mouse) given i.p. for 3 days resulted in an average 74% inhibition of tumor growth in mice, with 3 out of 10 animals showing complete regression, and an oral administration (daily for 5 weeks) showed 45–63% inhibition (Ohno et al. 1998). Similar inhibitory effects were shown with implanted sarcoma 180 cells after polysaccharide was given orally to mice (Zhang and Lin 1999). A pure β-(1→3) glucan was tested in parallel with crude *G. lucidum* extracts, which resulted in 90% inhibition of tumor growth (Ohno et al. 1998). A dry powder preparation of the antlered form of *G. lucidum* (known as deerhorn lingzhi due to its appearance) was shown to inhibit tumor growth and elongate the life span in both allogeneic sarcoma-180-bearing ddY mice and synergenic MM-46 mammary tumor–bearing C3H/He mice (Nonaka et al. 2006).

G. lucidum is a major component of many traditional botanical formulations, such as TBS-101, which was demonstrated to inhibit tumor growth and invasion in PC-3-implanted mice (Evans et al. 2009). Yun (1999) reported that 9 weeks of oral administration of mycelial extract significantly inhibited lung adenoma formation in mice. Oral administration of triterpenoid fractions for 18 consecutive days inhibited Martigel-induced angiogenesis, which significantly reduced tumor weight and the number of tumor cell colonies that had metastasized to the liver in female C57BL/6J strain mice with intrasplenic implantation of Lewis lung cancer cells (Kimura, Taniguchi, and Baba 2002; Wang et al. 2007). In male ICR-nu/nu nude mice injected with hepatoma HepG2 cells, daily oral administration of lucidenic acid–rich extract for 68 days (800 mg/kg dosage) decreased both the number and size of tumors by up to 99%, and also the number of metastatic tumors occurring in liver and lung (Weng et al. 2009). An aqueous extract (administered i.p. at 10, 20, and 40 mg/mouse) of the fruit body significantly increased the life span of mice implanted with Lewis lung carcinoma cells. However, no dose-response effect was seen (Furusawa et al. 1992). An additive effect was seen when *G. lucidum* was given in combination with cytotoxic antineoplastic drugs, and there was a suggestion of a possible synergistic effect with cisplatin (Furusawa et al. 1992). In another study, *G. lucidum* was found to also prolong the life span of tumor-transplanted mice by inhibiting metastasis to the lung (Lee et al. 1995). When given 1 week prior to the administration of a carcinogenic agent, a hot water extract of the mycelium/growth medium complex decreased the development of aberrant crypt foci (ACF) and precancerous lesions in the colon (Lu et al. 2001; Lu et al. 2003). No toxicity or side effects were seen in the rats when the extract was administered for 3 months. When tested with mouse colon tumor–implanted chambers, a polysaccharide mixture containing isoflavone aglycons from cultured *G. lucidum* mycelia was found to inhibit angiogenesis in vivo (Miura et al. 2002).

The chemopreventive activities of the mushroom on prostate cancer were demonstrated by a triterpenoid-rich extract of *G. lucidum* that suppressed the ventral prostate growth induced by testosterone (Liu et al. 2007a). Ganoderol B was identified as the active principle that was able to bind to an androgen receptor and inhibit 5α-reductase, suppressing androgen-induced LNCaP cell growth and downregulating the prostate-specific antigen (Liu et al. 2007b).

9.6.1.4 Human Studies

In humans, whether the antitumor effect of lingzhi is a direct one or is mediated via effects on the immune system is a key question to address. *G. lucidum* is one of the eight components of an herbal mixture called "prostate cancer-hope" (known as PC-SEPS), which has been used as an alternative in the treatment of androgen-dependent and -independent prostate cancer (Gao and Zhou 2009). However, only a few clinical trials have used *G. lucidum* as a single agent on cancer patients (Gao, Zhou et al. 2002; Gao, Zhou et al. 2003; Gao, Sai et al. 2003). Two randomized, controlled trials have been conducted using a GL-PS-rich extract (a patented over-the-counter product, Ganopoly; Gao et al. 2003; Gao and Sai et al. 2003). Gao, Zhou et al. (2003) recruited 134 patients with advanced cancers of different sites and supplemented them with *G. lucidum* capsules at a dosage of 1800 mg/ day for 12 weeks. Cellular immunity in 80% of these patients was significantly enhanced in terms of elevated plasma interleukin (IL)-2, IL-6, and interferon γ (IFN-γ) levels and natural killer (NK) cell activity. In another study, the same protocol was followed with 68 lung cancer patients (Gao, Sai et al. 2003) in whom immune parameters including total T cells, NK cells, and CD4/CD8 ratio were significantly enhanced in the *G. lucidum-treated* group. In addition, quality of life in terms of Karnofsky score was improved in about 65% of these patients (Gao, Sai et al. 2003). Ganopoly was also demonstrated to enhance mitogenic activity and NK cells in patients with advanced cancer in a before-and-after comparison study (Gao, Min et al. 2002). These results provide some evidence that the antitumor effects of *G. lucidum* are mediated via effects on the immune system. However, it must be noted that all studies were conducted by the same research group and that other direct antitumor effects of *G. lucidum* have not yet been studied on humans in vivo.

9.6.2 Immunomodulation

Agents that enhance the functioning of the host immune system could be expected to enhance health in terms of improved resistance and, thus, removal of malignant or premalignant cells. Many *G. lucidum* products on the market are labeled or promoted as immunomodulating agents.

There is considerable evidence to support the immunostimulating activities of *G. lucidum* via induction of cytokines and enhancement of immunological effector (Wang et al. 1997; Zhu and Lin 2006). Different components from *G. lucidum* were proved to enhance the proliferation and maturation of T and B lymphocytes, splenic mononuclear cells, NK cells, and dendritic cells in culture in vitro and in animal studies in vivo (Bao et al. 2001; Cao and Lin 2002; Zhu, Chen, and Lin 2007; Ma et al. 2008). In normal BALB/c mice, a polysaccharide-rich extract of *G. lucidum* promoted the proliferation of splenocytes and enhanced the activities of macrophages and NK cells, which resulted in the increase of IL-6 and IFN-γ (Chang et al. 2009). Although a commercial *G. lucidum* extract did not stimulate proliferation of lymphocytes, it activated the gene expression of IL-1β, IL-6, IL-10, and tumor necrosis factor (TNF)-α (Mao et al. 1999). A polysaccharide fraction (F3) was shown to enhance both adaptive and innate immunities by triggering the production of cytokines IL-1, IL-6, IL-12, IFN-γ, TNF-α, and colony stimulating factors (CSFs) from mouse splenocytes (Chen et al. 2004). It was reported also that TNF-α and IL-6 production were stimulated in human and murine macrophages by *G. lucidum* mycelia (Kuo et al. 2006). This effect might be due to increased synthesis of nitric oxide (NO) induced by β-D-glucan (Ohno et al. 1998). These polysaccharides were also found to be highly suppressive to tumor cell proliferation in vivo while enhancing the host's immune response (Ooi and Liu 2000).

Wang et al. (1997) found that a polysaccharide-enriched fraction from *G. lucidum* activated cultured macrophages and T lymphocytes in vitro, which led to an increase of IL-1β, TNF-α, and IL-6 in the culture medium. In another study (Zhang and Lin 1999), incubation of macrophages and T lymphocytes with a polysaccharide resulted in an increase in TNF-α and INF-γ levels in the culture medium. This "conditioned" culture medium was found to inhibit cell growth and induce apoptosis in sarcoma 180 and HL-60 cells (Zhang and Lin 1999). Furthermore, serum-incorporated treatment with a polysaccharide peptide fraction from *G. lucidum* markedly inhibited the proliferation of human lung carcinoma (PG) cells, whereas the pure fraction by itself did not induce similar effects (Cao and Lin 2004). In addition to polysaccharides, a lanostane triterpenoid, ganoderic acid Me, inhibited tumor growth and metastasis of Lewis lung carcinoma in "T helper 1 responder" C57BL/6 mice by enhancing immune function in terms of IL-2 and IFN-γ expression and NK cell activity (Wang et al. 2007). Zhu and Lin (2006) used cytokine-induced killer (CIK) cells to investigate the interaction between GL-PSs and cytokines, which mediated cell proliferation and antitumor activity. The cytotoxicity of CIK cells was correlated well with the expression of perforin and granzyme B induced by IL-2 and anti-CD3. Results indicated that GL-PSs enhance IL-2 and TNF-α production as well as protein and messenger ribonucleic acid (mRNA) expression of granzyme B and perforin in CIK cells culture, and thus decrease the doses of IL-2 and anti-CD3 without affecting the killing effects on NK-resistant mouse P815 mastocytoma cells and NK-sensitive mouse YAC-1 lymphoma cells (Zhu and Lin 2006).

9.6.3 Lingzhi as an Antioxidant

Consumption of antioxidant-rich plants may help prevent cancer and other chronic diseases (Collins 2005; Benzie and Wachtel-Galor 2009). Antioxidants protect cellular components from oxidative damage, which is likely to decrease risk of mutations and carcinogenesis and also protect immune cells, allowing them to maintain immune surveillance and response. Various components of *G. lucidum*, in particular polysaccharides and triterpenoids, show antioxidant activity in vitro (Lee et al. 2001; Mau, Lin, and Chen 2002; Shi et al. 2002; Wachtel-Galor, Choi, and Benzie 2005; Yuen and Gohel 2008; Saltarelli et al. 2009; Wu and Wang 2009). As shown in Figure 9.4, antioxidants from lingzhi were found to be absorbed quickly after ingestion, resulting in an increase in the plasma total antioxidant activity of human subjects (Figure 9.4; Wachtel-Galor, Szeto et al. 2004).

Ooi and Liu (2000) reported that protein-bound polysaccharide (PBP) and polysaccharide peptide were able to mimic the endogenous antioxidant superoxide dismutase (SOD) in cancer-bearing animals in vivo. These polysaccharides were also reported to protect the immune cells from oxidative damage (Ooi and Lui 2000). The protective effects of *G. lucidum* on DNA strand scission induced by a metal-catalyzed Fenton reaction, ultraviolet irradiation, and hydroxyl radical attack were shown in agarose gel electrophoresis in vitro (Lee et al. 2001). Hot water extracts of *G. lucidum* significantly protected Raji cells from hydrogen peroxide (H_2O_2)-induced DNA damage (Shi et al. 2002). Hot water extracts protected human lymphocyte DNA only at low (<.001% w/v) concentrations, and caused H_2O_2-mediated damage at higher concentrations (>.01% w/v) (Wachtel-Galor, Choi, and Benzie 2005). Two antioxidant-enriched extracts from *G. lucidum* acted oppositely in premalignant HUC-PC cells under carcinogenic attack (Yuen and Gohel 2008). The aqueous extract protected cellular DNA from oxidative damage, whereas the ethanolic extract damaged cellular DNA, with increased H_2O_2 production and significant cell-killing effects observed. The results suggested that different effects of *G. lucidum* could be exhibited by different extractable components in bladder chemoprevention. Methanol extracts of *G. lucidum* were reported to prevent kidney damage (induced by the anticancer drug cisplatin) through restoration of the renal antioxidant defense system (Sheena, Ajith, and Janardhanan 2003). In contrast, a fraction of ganoderma triterpenes (GTS) was found to enhance the intracellular reactive oxygen species (ROS)-producing effect of doxorubicin (DOX) in Hela cells, leading to more DNA damage and apoptosis, whereas such synergism was inhibited by a ROS scavenger (Yue et al. 2008). In an animal study (diabetic rats), nonenzymic and enzymic antioxidants levels increased and lipid peroxidation levels decreased with *G. lucidum* treatment (Jia et al. 2009). However, a direct link has not been established between the antioxidant properties of *G. lucidum* and its immunomodulatory and anticancer effects, and whether lingzhi acts as an antioxidant or pro-oxidant may depend on concentration and environment.

9.6.4 Viral and Bacterial Infections

The goal of research in the treatment of viral and bacterial infections is the discovery of agents that specifically inhibit viral and bacterial multiplication without affecting normal cells. The undesired side effects of antibiotics and antivirals and the appearance of resistant and mutant strains make the development of new agents an urgent requirement. This has led researchers to investigate the antibacterial and antiviral activity of medicinal plants and fungi (Wasser and Weis 1999; Zhong and Xiao 2009). Isolation of various water- and methanol-soluble, high-molecular-weight PBPs from *G. lucidum* showed inhibitory effects on herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), and vesicular stomatitis virus (VSV) New Jersey strain in a tissue culture system. Using the plaque reduction method, a significant inhibitory effect was seen at doses that showed no cytotoxicity (Eo et al. 1999; Oh et al. 2000). In addition, there was a marked synergistic effect when PBP from *G. lucidum* was used in tissue culture in conjunction with antiherpetic agents, acyclovir or vidarabine, and with IFN-α (Kim et al. 2000; Oh et al. 2000). Similar results were shown in HSV-1 and HSV-2 with a GLPG isolated from the mycelia of *G. lucidum* (Liu et al. 2004; Li, Liu, and Zhao 2005). The cells were treated before, during, and after infection, and viral titer in the supernatant of cell culture 48 hours postinfection was determined. The antiviral effects of the GLPG were more remarkable before viral treatment than after treatment. Although the mechanism was not defined, the authors concluded that GLPG inhibits viral replication by interfering with early events of viral adsorption (Li, Liu, and Zhao 2005).

Some triterpenes from *G. lucidum* have also been reported to have an inhibitory effect against human immunodeficiency virus (HIV)-1 protease activity, with IC_{50} values ranging from 20 to more than 1000 μM; however, not all of the examined triterpenes showed anti-HIV activity (El-Mekkawy et al. 1998; Min et al. 1998). In another study, a ganoderic acid isolated from *G. lucidum* showed inhibitory

effects on the replication of hepatitis B virus (HBV) in HepG2215 cells (HepG2- HBV-producing cell line) over 8 days. Production of HBV surface antigen (HBsAg) and HBV e antigen (HBeAg) were, respectively, 20% and 44% of controls without ganoderic acid treatment (Li and Wang 2006).

Some small studies in human patients have also reported beneficial effects of lingzhi intake. A dried hot water extract of *G. lucidum* taken orally (equivalent to 36 or 72 g of dried mushroom per day) was used as the sole treatment for postherpetic (varicella zoster virus) neuralgia in 4 elderly patients. This treatment was reported to dramatically decrease pain and promote the healing of lesions, without any toxicity even at very high doses (Hijikata and Yamada 1998). In another study, a mixture of *G. lucidum* with other herbs improved recovery time in patients with herpes genitalis ($n = 15$) and herpes labiallis ($n = 13$; Hijikata, Yamada, and Yasuhara 2007).

For evaluating the antibacterial effects of the mushroom, several in vitro and in vivo animal studies using *G. lucidum* were performed. Mice injected with *G. lucidum* extract (2 mg/mouse) 1 day prior to injection with *Escherichia coli* showed markedly improved survival rates (>80% compared to 33% in controls; Ohno et al. 1998). In an in vitro study that used the disk assay (Keypour et al. 2008), a chloroform extract of *G. lucidum* was investigated for its antibacterial effect on gram-positive bacteria (*Bacillus subtilis, Staphylococcus aureus, Enterococcus faecalis*) and gram-negative bacteria (*E. coli, Pseudomonas aeruginosa)*. Results showed that the extract had growth-inhibitory effects on two of the gram-positive bacteria with a minimal inhibitory concentration (MIC) of 8 mg/mL for *S. aureus* and *B. subtilis*. In another in vitro study, the direct antimicrobial effect of a *G. lucidum* water extract was examined against 15 species of bacteria alone and in combination with 4 kinds of antibiotics (Yoon et al. 1994). *G. lucidum* was found to be more effective than antibiotics against *E. coli, Micrococcus luteus, S. aureus, B. cereus, Proteus vulgaris*, and *Salmonella typhi*, but less effective against other species tested. The antimicrobial combination of *G. lucidum* with four commonly used antibiotics (Yoon et al. 1994) resulted in an additive or synergistic effect in most, but not all, instances, with apparent antagonism against cefazolin and ampicillin effects on *P. vulgaris*.

To date, the antimicrobial components of the tested crude extracts have not been identified, although antimicrobial polysaccharides have been identified in other fungi and plant terpenes have been reported to have antimicrobial activity (Wasser and Weis 1999; Zhong and Xiao 2009). In addition, the bioavailability of putative antimicrobial components of *G. lucidum* has not been established. Nonetheless, *G. lucidum* offers a potentially effective therapy. There is also the implication that combination therapy may be more safe and cost effective, as lower amounts of cytotoxic antiviral and antibacterial drugs could be used with a concomitant decrease in the risk of side effects. However, this needs further investigation in terms of in vitro studies and well-designed clinical trials.

9.6.5 Diabetes Mellitus

Components of *G. lucidum* have been proved to have a hypoglycemic effect in animals. The administration of ganoderans A and B (dose of 100 mg/kg), two polysaccharides isolated from fruit-body water extracts, by i.p. injection to normal and alloxan-induced diabetic mice significantly decreased (by up to 50%) the plasma glucose concentrations, and the hypoglycemic effect was still evident after 24 hours (Hikino et al. 1985). Using a mouse model, ganoderan B was also reported to increase plasma insulin, decrease hepatic glycogen content, and modulate the activity of glucose-metabolizing enzymes in the liver (Hikino et al. 1989). The same group reported that a third polysaccharide (ganoderan C) isolated from *G. lucidum* also showed significant hypoglycemic effects in mice, and that ganoderan B increased plasma insulin levels in both normal and glucose-loaded mice (Hikino et al. 1989; Tomoda et al. 1986).

In a more recent study, oral administration of *G. lucidum* hot water extract (0.03 and 0.3 g/kg BW) for 4 weeks was found to lower the serum glucose levels in obese/diabetic (+db/+db) mice, with effects seen after the first week of treatment (Seto et al. 2009). However, the glucose levels were still higher in these animals than in the control animals, and insulin levels were not altered. The extract markedly reduced levels of phosphoenol-pyruvate carboxykinase (PEPCK), which are usually high in obese/diabetic mice. The suggested mechanism, according to the authors, is that of lowering the serum glucose levels through suppression of the hepatic PEPCK gene expression. In another study (Jia et al. 2009), a polysaccharides-rich extract showed beneficial effects in streptozotocin-induced diabetic rats. The diabetic rats were treated with *G. lucidum* for 30 days. Following the treatment, serum insulin levels increased (compared with the nontreated diabetic group) and glucose levels decreased in a dose-dependent way. Treatment with streptozotocin also elevated levels of lipid peroxidation markers (thiobarbituric acid reactive substances [TBARS]), lipid hydroperoxides, and conjugated dienes); decreased levels of nonenzymic antioxidants (vitamin C, reduced glutathione [GSH] vitamin E); and decreased activities of the antioxidant enzymes, SOD, catalase, and glutathione peroxidase (Gpx). Following treatment with GL-PSs, levels of nonenzymic and enzymic antioxidants increased and lipid peroxidation levels decreased. Therefore, in addition to its glycemic modulation, treatment with *G. lucidum* helped to decrease oxidative stress (Jia et al. 2009).

In one study reported in the literature, 71 adult patients with confirmed type 2 diabetes mellitus (DM) were supplemented with Ganopoly (polysaccharide fractions extracted from *G. lucidum)*. The patients received either Ganopoly or placebo orally at 1800 mg, three times daily for 12 weeks. Glycosylated hemoglobin ($HbA1_C$) and plasma glucose decreased significantly after 12 weeks, indicating a hypoglycemic effect of the extract (Gao, Lan et al. 2004). Overall, the data from different studies suggest that *G. lucidum* intake helps in modulating blood glucose levels. However, the studies were performed mostly in animals. More support from well-planned human clinical studies is needed with and without combination with conventional medicines.

9.6.6 Liver and Gastric Injury

Hot water and water–ether extracts of the fruit body of *G. lucidum* were found to have a potent hepatoprotective effect on liver injury induced by carbon tetrachloride (CCl_4) given orally and intraperitoneally to rats (Lin et al. 1995; Kim et al. 1999). The measured markers for liver injury included aspartate and alanine transaminases (AST and ALT) and lactate dehydrogenase (LDH). One active compound of the extract was separated and identified as ganoderenic acid A. This was found to have a potent inhibitory effect on β-glucuronidase, and the authors suggest that this inhibitory effect may have mediated the hepatoprotection seen when this isolated compound was given (Kim et al. 1999). Protection was also reported in a study in which a hot water extract of *G. lucidum* was given orally to mice 30 minutes before administration of ethanol. The extract was found to have an inhibitory effect against the formation of malondialdehyde (MDA), a degradation product of lipid peroxides, in mouse liver and renal homogenate, with evidence of a dose response seen (Shieh et al. 2001). The MDA effect was also reported by Shi et al. (2008) when the extract was given orally to mice (at 60, 120, and 180 mg/kg/day) for 2 weeks prior to treatment with D-galactosamine, which induced hepatic injury. In addition, pretreatment with *G. lucidum* maintained normal values of AST, ALT, SOD, and GSH (Shi et al. 2008). Alcohol and CCl_4 toxicity is associated with increased oxidative stress and free-radical-associated injury. Therefore, hepatoprotection may also be mediated by the radical-scavenging properties of *G. lucidum*. Lin et al. (1995) reported that hot water extracts of *G. lucidum* showed significant radical-scavenging activity against both superoxide and hydroxyl radicals.

Further, *G. lucidum* methanolic extract was reported to show hepatic protection. The extract was given orally to rats (500 mg/kg/day)

for 30 days before hepatic damage was caused by benzo(a) pyrene (Lakshmi et al. 2006). The extract prevented the increase of serum AST, ALT, and alkaline phosphatase (ALP) activities that result from benzo(a)pyrene challenge, and enhanced the levels of GSH, SOD, GpX, CAT, and glutathione S-transferase (GST). Protection of liver injury induced by CCl_4 was also observed in mice treated with ganoderic acid (from *G. lucidum*) at 10 mg and 30 mg/kg/day given by intravenous injection for 7 days (Li and Wang 2006). The medium in which *G. lucidum* was grown was also proved to have liver-protective effects in an animal study of CCl_4- induced liver damage (Liu et al. 1998). Oral administration of the medium in which *G. lucidum* mycelia were grown (but not the mycelia alone) had marked beneficial effects, as assessed by lower serum AST and ALT activities at 96 hours postinjury. No decrease was seen in the actual damage caused, as transaminase activities at 24 hours were not different from levels in control animals, implying that the mycelium medium may have promoted recovery in some way. The release of a hepatoprotective component from *G. lucidum* mycelium was also reported by Song et al. (1998). In this study, an extracellular peptidoglycan (a polysaccharide/amino acid complex named WK-003) produced during mycelium fermentation was administered orally to rats for 4 days prior to CCl_4 intoxication. The increase in serum ALT levels was significantly decreased (by 70%; $P < .01$) at 24 hours postinjury compared with untreated, intoxicated rats. The AST levels decreased by 27%; however, this was not statistically significant. These studies of a possible mycelial product with hepatoprotective activity being extruded into the culture medium are of interest because the mycelia of *G. lucidum* are much easier and less costly to cultivate than the fruit body.

Polysaccharides extracted from *G. lucidum* and given orally to rats for 28 days were found to ameliorate cirrhosis induced by biliary ligation (Park et al. 1997). In addition, collagen (measured by hydroxyproline) content in the rat liver was lowered and improved liver morphology was found in comparison with control animals. The treatment significantly decreased ligation-induced increases in serum biochemical markers of liver damage (AST, ALT, ALP, and total bilirubin). Similar results were noticed in a study conducted by Wu, Fang, and Lin (2010) in which a decrease in hepatic hydroxyproline content and an improved liver histology were found in mice. In this study, liver fibrosis was induced by the administration of thioacetamide (TAA) for 12 weeks, which was followed by 4 weeks of treatment with *G. lucidum* extract (0.5 and 1.0 g/kg/day, per oral administration). The RT-QPCR analysis showed the extract treatment decreased mRNA expression of collagen (α1), smooth muscle α actin, and the enzymes metalloproteinase-1 and metalloproteinase-13. In addition, the TAA-induced decrease in total collagenase activity was reversed by the extract treatment, indicating that *G. lucidum* protection against injury may be related to the enhancement of collagenase activity.

Apart from its effects on chemical-induced liver injury, the effects of lingzhi on gastric injury have also been investigated. Gastric ulcers were induced in rats by acetic acid (Gao, Tang et al. 2004), and treatment with GL-PS fractions of 0.5 and 1.0 g/kg for 14 days significantly accelerated the ulcer healing by 40% and 56%, respectively. Treatment with 1.0 g/kg extract significantly restored mucus and prostaglandin levels compared with the control group.

9.7 CONCLUDING REMARKS

G. lucidum is a well-known Asian herbal remedy with a long and impressive range of applications. Global consumption of *G. lucidum* is high, and a large, increasing series of patented and commercially available products that incorporate *G. lucidum* as an active ingredient are available as food supplements. These include extracts and isolated constituents in various formulations, which are marketed all over the world in the form of capsules, creams, hair tonics, and syrups.

With its growing popularity, many studies on *G. lucidum* composition, cultivation, and reputed effects are being carried out, and there are data that support its positive health benefits, including anticancer effects; blood glucose regulation; antioxidant, antibacterial, and antiviral effects; and protection against liver and gastric injury. However, most studies have been performed on animals or in cell-culture models. Human experimental studies have often been small, and the results are not always supportive of the in vitro findings. Now, the great wealth of chemical data and anecdotal evidence on the effects of *G. lucidum* needs to be complemented by reliable experimental and clinical data from well-designed human trials in order to clearly establish if the reported health-related effects are valid and significant. Many challenges are encountered due to a range of factors from dosage to production quality. Strategies for enhancing quality control procedures to define and standardize *G. lucidum* preparations are needed to determine mechanisms of action and to help characterize the active component(s) of this putative medicinal mushroom.

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Figures

FIGURE 9.1

(See color insert.) The lingzhi mushroom (*Ganoderma lucidum*). (Courtesy of North American Reishi/Nammex.)

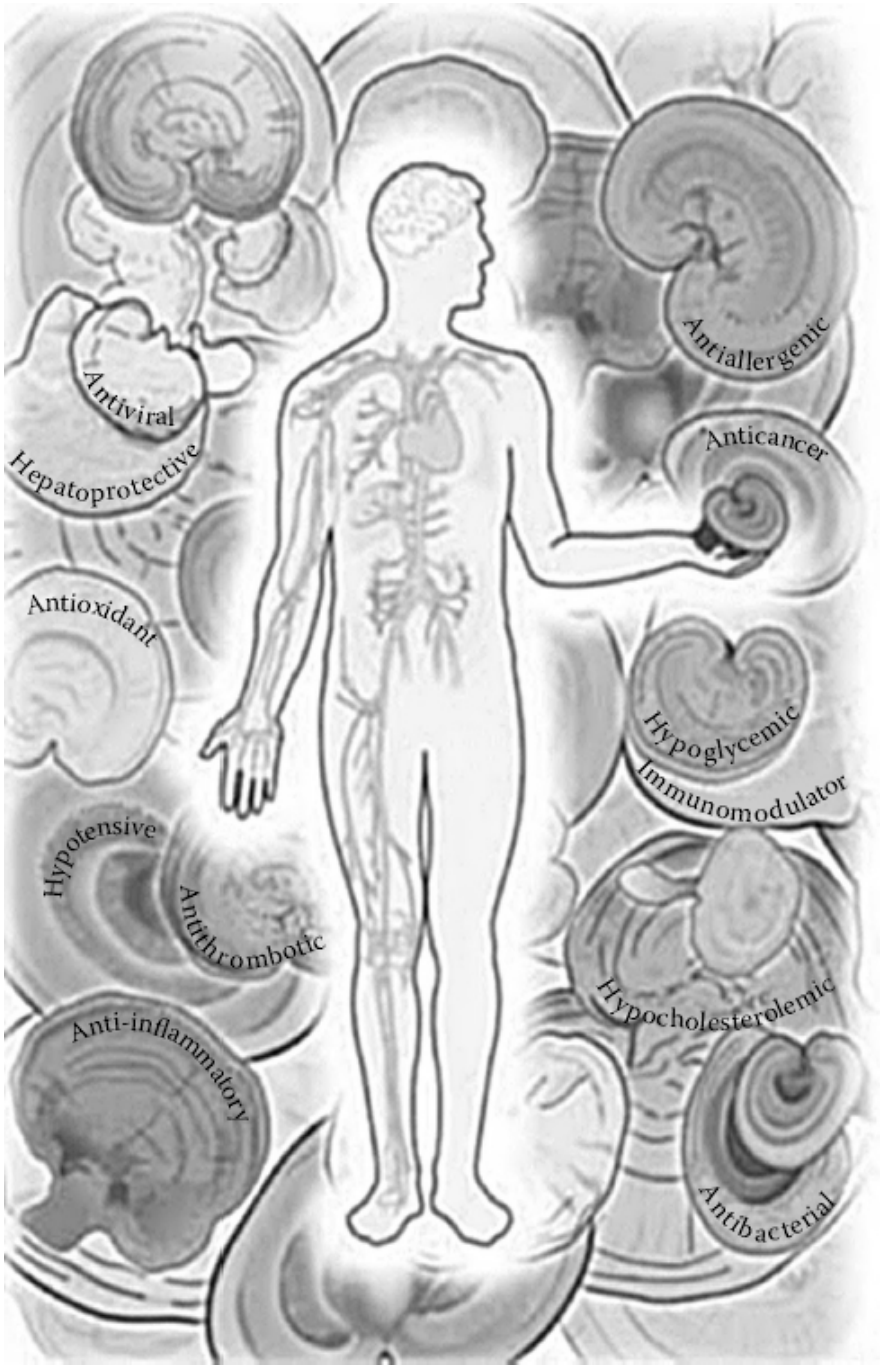
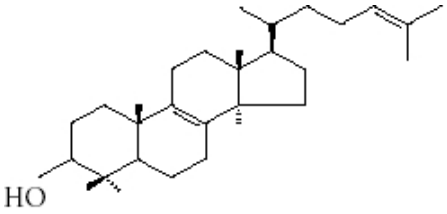
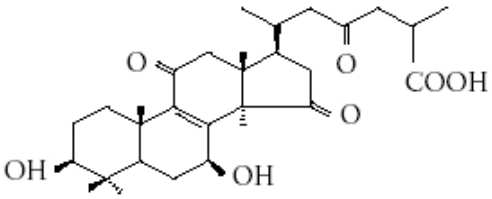


FIGURE 9.2

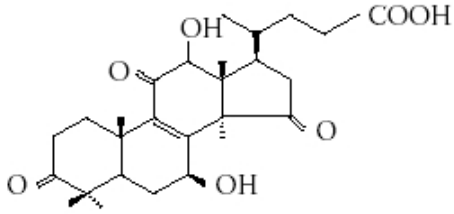
Postulated health benefits of lingzhi (*Ganoderma lucidum*).



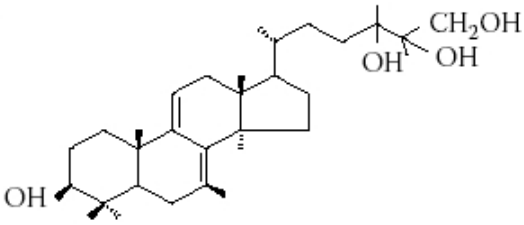
Lanosterol



Ganoderic acid B



Lucidenic acid B



Ganoderiol A

FIGURE 9.3

Chemical structure of lanosterol and three of the many triterpenes isolated from *Ganoderma lucidum*. (From Kubota, T., Y. Asaka, I. Miura, and H. Mori. 1982. *Helv Chim Acta* 65:611–9; Nishitoba, T., H. Sato, T. Kasai, H. Kawagishi, and S. Sakamura. 1984. *Agric Biol Chem* 48:2905–7; Sato, H., T. Nishitoba, S. Shirasu, K. Oda, and S. Sakamura. 1986. *Agric Biol Chem* 50:2887–90; Budavari, S. 1989. *The Merck Index*. 11 ed, 845. New Jersey: Merck & Co., INC. With permission.)

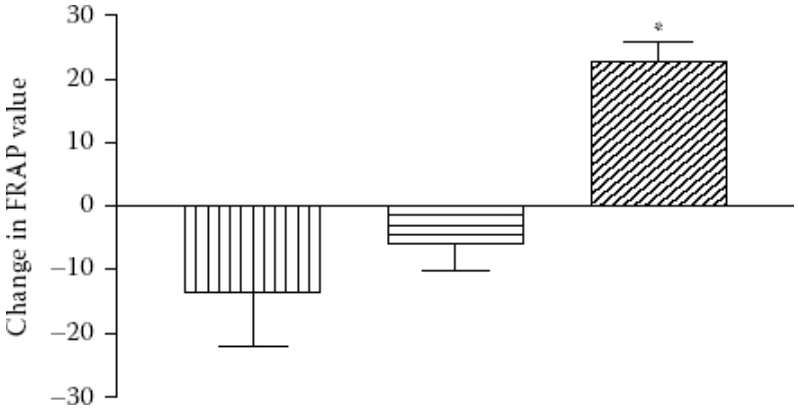


FIGURE 9.4

Mean +SEM (standard errors of the mean) change in plasma total antioxidant power (as the ferric reducing ability of plasma [FRAP] value) at 90 minutes postingestion of placebo (vertical lines), 1.1 g of *G. lucidum* extract (horizontal lines), and 3.3 g of *G. lucidum* extract (diagonal lines) in a human intervention trial ($n = 10$). A significant ($^*p < .05$) increase in plasma FRAP was seen after *G. lucidum* administration compared with placebo intake, indicating an absorption of antioxidant compounds into plasma. (From Wachtel-Galor, S., Y. T. Szeto, B. Tomlinson, and I. F. Benzie. F. 2004. *Int J Food Sci Nutr* 1:75-83. With permission.)

Tables

TABLE 9.1 Comparison of Triterpene and Polysaccharide Contents of 11 Commercial Lingzhi (*G. lucidum*) Products currently available on the Market

Nature of Product	Triterpenes (%)	Polysaccharide (%)
A (fruit body extract)	1.36	4.48
B (fruit body extract)	2.36	5.32
C (fruit body extract)	1.88	15.70
D (fruit body extract)	1.06	10.97
E (fruit body extract)	0.44	7.51
F (fruit body extract)	1.78	6.18
G (fruit body extract)	1.44	13.30
H (fruit body extract)	0.50	15.80
I (fruit body extract)	7.82	7.66
J (fruit body powder)	0.46	1.10
K (mycelium powder)	Undetectable	12.78

Source: Chang, S. T., and J. A. Buswell. 2008. Safety, quality control and regulational aspects relating to mushroom nutriceuticals. *Proc. 6th Intl.* Conf. *Mushroom Biology and Mushroom Products*, 188–95. Krefeld, Germany: GAMU Gmbh. With permission.

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