Mushroom Biology and Mushroom Products, Royse (ed.) © *1996 Penn State Univ. ISBN 1-883956-01-3*

Biomedical Research and the Application of Mushroom Nutriceuticals from *Ganoderma lucidum*

Alice W. Chen and Philip G. Miles
Rochester Area Mycological Association, 1730 Penfield Rd., Penfield, NY 14526, USA, and the Department of Biological Sciences, State University of New York at Buffalo, Buffalo, NY 14260

ABSTRACT: This paper focuses on the concept and mechanisms of how mushroom nutriceutical components from *G. lucidum* function, and why this fungus is important based on biomedical research and trials. Molecular structures of its major bioactive components and their functions will be covered as well as product evaluation. New developments and practical knowledge for *Ganoderma* consumers will be presented. The paper also considers growing and processing *G. lucidum* for bioactivity. The complete review will be published elsewhere.

1 INTRODUCTION

The love affair of Asians with Ling Zhi, the Chinese name for *Ganoderma lucidum* and related species, can be traced back over two thousand years. Recent reports, mostly on *G. lucidum* in Asia, but also in North America, France, Germany, Poland, and Russia, give credibility to some of the ancient claims of the biomedical benefits of this number one medicinal mushroom in China. A number of reviews have been written on the bioactive components in *G. lucidum*, their structures, functions and medicinal benefits (*e.g.* Dharmananda 1988, Willard 1990, Jong and Birmingham 1992, Hseu 1993, Shaio *et al.* 1994, Lindequist 1995).

A new class of compounds with nutritional and medicinal features, extractable from either the mycelium or the fruiting body of mushrooms, have been referred to as "mushroom nutriceuticals", a term coined by Chang and Buswell. *G. lucidum* is rich in mushroom nutriceutical components with potential therapeutic values.

2 BIOMEDICAL APPLICATIONS

Ganoderma lucidum has been used for a broad spectrum of health benefits from preventative measures and maintenance of health to the regulation or treatment of chronic as well as acute life threatening illness (Chang 1995). Some of the current biomedical applications of this mushroom are given in Table 1. The use of *Ganoderma* in Russian cosmonaut training is a dramatic example of its use to improve working capacity, particularly under stress, and for rapid restoration to normal physiology. The fungus is best known for its immuno-stimulatory effect in managing certain types of cancer in combination with conventional therapy and for its anti-HIV effect.

Table 1. Current biomedical applications of *Ganoderma lucidum*.

	Applications	Source
A.	Cosmonaut training in Russia	Alexeev and Kupin 1993
	1. Improving working capacity	
	2. Rapid recovery to normal physiology	
B.	Use with conventional therapy in cancer	
	1. Maintain leukocyte counts	Teow 1995, Chang 1994
	2. Enhance the immune system	Teow 1995
	3. Reduction of toxicity by chemotherapy & elimination of induced leukopenia (low blood leukocytes) by chemotherapy & radiation	Chen *et al.* 1995
	4. Accelerate post-surgery recovery	Kupin 1992, Hseu 1993
	5. Sedation, pain relief & reduce dependence on morphine in terminal cancer patients	Kupin 1992, Liu *et al.*1993
	6. Use during remission to prevent relapses	Chang, 1994
C.	Cardiovascular disorder including:	Lee and Rhee 1990, Liu *et al.* 1993, Teow 1995
	1. Coronary dilation & increase coronary circulation	
	2. Increase heart contraction frequency & amplitude	
	3. Blood pressure regulation with other medication	Teow 1993
	4. Anti-hyperlipidemia, hypoglycemia & anti-platelet aggregation (blood clots)	
	5. Relief of oxygen deprivation	Yang *et al.* 1995
D.	Immunomodulatory effects	Chang 1995
	1. Anti-cancer	
	2. Anti-viral (e.g., anti-HIV)	
	3. Anti-inflammatory	
	4. Improve autoimmune disorders	
	5. Inhibit histamine release in allergy & prevention of anaphylactic shock	
E.	Use during remission of cancer & hepatitis B & treatment	Chang 1993
F.	Increase oxygen utilization	Dharmananda 1988, Yang *et al.* 1995
	1. Relief of discomfort from high altitude stress, headaches, dizziness, nausea & insommnia	
	2. Relief from oxygen deprivation when coronary arteries are blocked by atheromas, spasms, or clots	
	3. Tolerance to hypobaric (low pressure) conditions	
G.	Other examples	
	1. Use in combination with other medication (see text)	
	2. Anti-aging: anti-oxidant as scavenger for free radicals	

2.1 *Effective dosage in humans*

The suggested *Ganoderma* dosage is based on traditional, empirical, and anecdotal references, as well as recent reports on a cell surface β-D-glucan receptor model on human white blood cells (Czop and Kay 1991). The receptor is specific for β-glucans with β-1,3 and/or β-1,6 linkages (Janusz *et al.* 1989, Chang 1995).

Ganoderma lucidum is known generally to be safe for longterm use. The LD 50 for a single intraperitoneal injection dose of *Ganoderma* extract in rodents was as high as 38g/kg (Chang and Butt 1986). The LD 50 of a water soluble polysaccharide fraction of *G. lucidum* in rodents was higher than 5g/kg (Kim *et al.* 1986). Since the toxic/lethal doses in rodents are quite high relative to conventional human dosages, they do not pose significant limitations for clinical dosages of *Ganoderma* (Chang 1995).

Precautions should be taken to stop temporarily the usage during surgery or with severe cuts to avoid excessive bleeding since *G. lucidum* is a blood vessel dilator and accelerates blood circulation (Andreacchi 1995). Use of *Ganoderma* should be temporarily reduced or stopped in case of an initial reaction of slight diarrhea or rash (Dharmananda 1988).

3 USE IN COMBINATION WITH OTHER MEDICATION

No apparent adverse reactions have been observed from the use of *G. lucidum* with other Western pharmaceuticals (Dharmananda 1988). A polysaccharide-enriched GL-P fraction from *G. lucidum* significantly inhibited fibrosarcoma growth in mice when it was used in combination with bleomycin (Lee *et al.* 1984). Likewise, a *Ganoderma* polysaccharide fraction, GLP(AI), greatly increased the life-span of tumor-implanted mice when it was administered intraperitoneally with cytotoxic antitumor drugs, such as: adriamycin, fluorouracil, thioguanine, methotrexate and cisplatin, or the synthetic immuno-modulator, Imexon, according to Lee *et al.* (1994).

Concurrent use of glutathione (a free radical scavenging amino acid) and *G. ludicum* extract was beneficial against hepatic necrosis and hepatitis in rats (Byun and Kim 1987). *Ganoderma lucidum* extract also increased the sleeping time induced by barbital and pentobarbital in clinical trials (Liu 1993). Reports indicated that *G. lucidum* elevated pain threshold and reduced dependence on morphine (Kupin 1992), as well as enhancing the functions of drugs for regulating blood pressures (Hseu 1993).

4 MOLECULAR STRUCTURES AND FUNCTIONS OF MAJOR BIOACTIVE COMPONENTS

A number of bioactive components have been isolated from *G. lucidum*. Polysaccharides and tripertenes are two major physiologically active constituents in the fungus (Dharmananda 1988). The molecular structures of major bioactive components are given in a number of publications (Mizuno 1991, Lindequist 1995). Table 2 gives an overall perspective on important bioactive nutriceutical components in *G. lucidum* and their functions.

Table 2. Major bioactive nutriceutical components in *G. lucidum* and their functions.

A.	Polysaccharides	
	1. ImmunomodulatoryMizuno, 1992, Anti cancer Anti HIV	Kim *et al.* 1993
	2. Hepato-protective/anti-hepatotoxic	Sohn *et al.* 1995
	3. Hypoglycemic	Hikino *et al.* 1985
	4. Anti-histamine release Prevent experimental asthma & contact dermatitis Improve oxygen utilization	Yang *et al.* 1995
	5. Anti-angiogenic	Cheng *et al.* 1986
	6. Radiation protective	Chu *et al.* 1988
B.	Triterpenes and related compounds	
	1. Cytotoxic tumors	Toth *et al.* 1983
	2. Anti-HIV	Luu 1995
	3. Anti-hyperlipidemic	Liu *et al.* 1988, Komoda *et al.* 1989
	4. Hypotensive	Morigawa *et al.* 1986
	5. Anti-platelet aggregation	Wang *et al.* 1991
	6. Hepatoprotective	Hirotani *et al.* 1986, Lin *et al.* 1991, Chen and Yu 1993
	7. Analgesic	Kubata *et al.* 1982, Koyama *et al.* 1993
	8. Cardioactive	Hattori 1995
	9. Immunomodulatory	Luu 1992, Lindequist 1995
C.	LZ-8 (MW 12,420 daltons, 110 amino acid residues)	Kino *et al.* 1989
	1. Anti-hypersensitivity	
	2. Anti-autoimmune diabetes	
	3. Anti-hepatitis B	
	4. Immunomodulatory	
D.	Adenosine and derivatives	Shimizu 1985, Kasahara and Hikino 1987
	1. 5'-deoxy-5'-methylsulfinyl adenosine Inhibition of platelet aggregation Analgesic	Kawagishi 1995
E.	Organic germanium (Ge-$CH_2CH_2COOH)2O_3$; GE 132 (carboxyethyl germanium sesquioxide)	
	1. Anti-tumor: hepatoma cells, bladder cancer	Sato and Iwaguchi 1979
	2. Anti Lewis-lung carcinoma	Kumano *et al* 1980, Quian and Zhang 1993
	3. Promote blood circulation/ O2 utilization	Liu *et al.* 1990
E.	Oleic acids & cyclooctasulphur	Tasako *et al.* 1988a, b
	1. Inhibition of histamine release	
F.	RNA	
	1. Anti-viral (encephalitis)	
	2. Immunomodulatory	Kandefer-Szerszen *et al.* 1979

4.1 *Ganoderma polysaccharides*

As fungal wall constituents (Bartnicki-Garcia 1968), bioactive polyglycans (polysaccharides), such as β-glucans in *G. lucidum*, are found in all parts of the mushroom, including the mycelium. Fungal polyglycans can also be secreted into the growth medium and become extracellular (Buck *et al.* 1968).

Bioactive polyglycans in *G. lucidum* include neutral polysaccharides (β-1-3, β-1-6 homo D-glucan), acidic glucan and polyglycan (Mizuno 1984, 1992), protein-bond heteroglucan (Mizuno 1992), arabinoxyoglucan, a highly branched heteroglucan (Miyazaki and Nishijima, 1981), a heteroglycan with β-1-4 core (Miyazaki and Nishijima 1982), and peptidoglycan: Ganoderan A, B, C (Hikino *et al.* 1986), in the fruiting body (Yang 1995), β-D glucan (Sone *et al.* 1985) and Lucidan, a protein-bond heteroglycan (Kim *et al.* 1993), as well as other polyglycans in the mycelium which have not been characterized.

How effective is the antitumor activity of β-D-glucans from *G. lucidum* compared to the commercially available β-D-glucans produced in Japan from shiitake and other mushrooms? It appears that *Ganoderma* polysaccharides are better absorbed orally. The experiments with *Lentinula* and *Coriolus* were carried out with injections of small amounts of polysaccharides. When the edible mushrooms, such as *Lentinula edodes* (shiitake), were fed to laboratory animals, tumor regression could be induced at a significant level only when they were supplemented as 20-30% of the diet. In contrast, 5% (w/w) powdered *G. lucidum* dry fruiting body as a diet supplement of rats in 5 weeks produced a significant retardation in the formation and growth of microadenomas in the colon (Stavinoha *et al.* 1993).

The basic structure of the major bioactive *Ganoderma* glucans, β-1-3, β-1-6 D-glucan is β-1-3 D-glucopyronan with 1-15 units of β-1-6 monoglucosyl side chains (Mizuno, 1991). Numerous reports show that high molecular weight β-1-3, β-1-6 D-glucans (MW 10^{4-6} daltons) exhibit antitumor activity. It seems that the higher the molecular weight, the higher the water solubility, and the more effective is the antitumor activity (Mizuno 1991). Antitumor activity is also linked to the frequency of polysaccharide branching which varies during different stages of mycelial growth.

Different extraction and purification processes yield a variety of bioactive glycans. Identification of large and highly complex bioactive *Ganoderma* polysaccharides, whose precise structures have not been elucidated, is an involved and expensive process. Not all polysaccharides are active in *G. applanatum* mycelium. Only one fraction contained a bioac-

tive water-soluble anti-tumor β-1-3 D-glucan, while the bulk of the glucan fraction consisted of β-glucans without any antitumor activity. Some water-insoluble polysaccharides in *Ganoderma* spp. known as diet fibers also have antitumor effects (Wang *et al.* 1993).

Growers of *Ganoderma* should be aware of the structural change of the bioactive polysaccharides in the mushroom during growth. The structure of a mycelial glucan from another fungus, *Claviceps fusiformis*, changes during incubation in submerged culture. Variation in branching in the extracellular β-1-3, β-1-6 D-glucan harvested at different times was observed. The yield of a glucan in the culture of *Sclerotium rolfsii* was increased by adding 2% (v/v) ethanol (Buck *et al.* 1968).

4.2 *Triterpenes*

Triterpenes are relatively simple molecules which are easy to isolate and quantify. They can be used as a measure of the quality of different *Ganoderma* samples (Dharmananda 1988, Stavinoha 1995). Twenty or so bioactive triterpenes have been isolated from *G. lucidum* although over one hundred with known chemical compositions and molecular configurations have been reported to occur in *G. lucidum*. There is some confusion over the designated names of *Ganoderma* triterpenoids, resulting from multiple use by different chemists. It is best to include in reports systematic IUC names which indicate chemical structures (Lindequist 1995).

Triterpenes are produced in the fruiting body. They can also be induced in the mycelial mat on solid medium (Nishitoba *et al.* 1987) or in the still liquid culture of late stationary phase at 6 weeks (Yeh *et al.* 1987). Little triterpene is formed in the mycelial pellets of liquid shaking culture (Su 1991). It is said that strains producing basidiocarps with a light yellow underside may contain a high amount of triterpenes in their caps. Such observation has been used to grade commercial *Ganoderma* fruiting bodies in Asia (Hseu 1993). Stavinoha (1991) found that the highest concentration of *Ganoderma* triterpenes is in the spore scrapings obtained from the underside of the mushroom in the 1-2 mm tube region (the hymenial layer). Only 18-58 mg of bioactive triterpenes were obtained from 1000 g of *G. tsugae* basidiocarps, while 4.5% (w/v) of crude EtOH extract was obtained from the sample (Su *et al.* 1993); thus, Stavinoha *et al.* (1993) use spore scrapings from the mushroom underside instead of the whole mushroom for extracting bioactive triterpenes.

The bitter taste of *G. lucidum* as a traditional Chinese medicine or tonic is attributed to highly oxygenated polar triterpenes (Lindequist 1995). Sugar is added to some of the *Ganoderma* products to mask this bitterness. Triterpenes as secondary metabolites are more strain specific in

G. lucidum (Nishitobe *et al.* 1986). High temperature and prolonged oxidation should be avoided during extraction to retain intact structures of these volatile compounds (Hseu 1993).

Traditionally, bioactive components are extracted from the fruiting body. More recently, the mycelium of *G. lucidum* has also been shown to contain bioactive constituents.

5 CONCEPT AND MECHANISMS BIOACTIVITY

Many bioactive components in *G. lucidum* are biological response modifiers which stimulate the host's own defense system (Chung 1993, Lindequist 1995) by evoking favorable immune responses. The cell surface is the *Ganoderma* bioactivity target site in terms of receptors and membrane alternation. In contrast to starch and a number of other naturally occurring polysaccharides, bioactive *Ganoderma* glycans are not degraded into their component sugars in animals or humans. Thus, such fungal polysaccharides are able to produce therapeutic effects. Starch, on the other hand, is decomposed enzymatically into its component sugar, glucose, and can be used as an energy source (Hseu 1993).

Of great interest is the recent discovery of β-D-glucan receptors on the surface of a number of white blood cells (leukocytes, monocytes, macrophages, NK cells, and other lymphocytes) in animals and humans (Czop and Kay 1991, Chang 1994). The broad stimulatory effects of *Ganoderma* β-glucans, via transduced cell surface receptors in the immune system, lead to the release of cytokines and lymphokines (cell mediators), such as: IL-1, IL-2, IL-4 (interleukins), interferon and TNF (tumor necrosis factor). Many immune parameters are improved, *e.g.*, increase of T-cell functions and antibody production. These mechanisms account for the antitumor, anti-inflammatory, and bacteriocidal effects (Chang 1994). Potential benefits and low toxicity make *Ganoderma* polysaccharides desirable for boosting the immune system of patients undergoing chemotherapy, radiation therapy or during recovery from major surgery (Chang 1994). Immunomodulatory effects of *Ganoderma* polysaccharides may also be useful in autoimmune disorders, AIDS and cancer prevention.

The mammalian cell surface is also the interactive site for triterpenes. Ganodermic acid S isolated from cultured mycelium can be inserted into the membrane of platelets. The morphologically altered membrane contributes to inhibition of platelet aggregation by the triterpene at a concentration of 20 μm or lower (Wang *et al.* 1991). Triterpenic derivatives, analogues of betulinic acids acting on the cell membrane, are able to disturb the entry of a virus into the cells (Mayaux *et al.* 1994). Cucurbitacin deriva-

tives (triterpenic derivatives similar to ganoderic acids) from a plant extract have been recently reported to produce anti-HIV activity (Konoshima *et al.* 1994). Luu (1995) showed that a fraction of *G. lucidum* extract, possibly containing ganoderic acids, was able to inhibit HIV-1 replication *in vitro*.

It is suggested that cyclo-octasulphur inactivates membrane-associated protein kinase C (Tasako *et al.* 1988a) while oleic acid, an unsaturated fatty acid, stabilizes the membrane (Tasako *et al.* 1988b).

6 DISCUSSION AND CONCLUSIONS

Of meaningful significance is the realization that many bioactive nutriceutical components in *G. lucidum* are biological response modifiers (BRM's). These physiologically active BRM's (polysaccharides, LZ-8, triterpenes/sterols and related compounds, and RNA) activate the immune systems of the hosts against some of the most devastating health problems, such as, cancer, AIDS and CFS (chronic fatigue syndrome).

Ling Zhi-8 is a newly discovered BRM from the mycelium of *G. lucidum* (Kino *et al.* 1989). Through the elegant work of many Japanese scientists, the small-molecule immuno-protein was shown to activate defense systems in promoting T-cell functions and cytokine production for a host of health benefits. Sequencing 110 amino acid residues in resolving its molecular structure (Tanaka *et al.* 1989) and the application of molecular biology in cloning the gene encoding the protein (Murasugi, *et al.* 1991) elevate *Ganoderma* research to a new level.

Most supporting evidence on the biomedical effect of *G. lucidum*, however, comes from research using animal models or cell cultures rather than large-scale, long-term, controlled human clinical studies. Despite such limitations, Dr. Raymond Chang, M.D. in New York endorses the use of *G. lucidum* (Chang 1995).

The antitumor effect of polysaccharides in *G. lucidum* is well documented. Antitumor triterpenes have also been found in the fungus. There are no substantial comparative studies on the relative effectiveness on tumors of polysaccharides extracted by hot water, and triterpenes extracted by an organic solvent. Studies by Maruyama *et al.* (1989) indicated that only the aqueous extract of *G. lucidum* showed antitumor effect against Sarcoma 180 tumor. The methanol extract had no effect.

Ganoderma nutriceutical components have shown potential antiviral effects on HIV (Kim *et al.* 1993, Luu 1995), hepatitis B (Kino *et al.* 1989), Epstein-Barr virus (Chairul *et al.* 1990), encephalitis (Kandefer-Szerszen *et al.* 1979), and possibly cold or flu (Willard 1990). These preliminary investigations should be further explored.

The reservation on the part of the Western medical professionals can be understood since: 1) *Ganoderma* efficacy in clinical use has not been adequately demonstrated, 2) some reports are on the effects of extracts, rather than purified compounds, 3) most studies on the biomedical benefits of *G. lucidum* were carried out in Asia, 4) products of *G. lucidum* are generally available in nutraceuticals (non-extract), nutriceuticals (crude extract), or a mixture of the two, and in the West, only pharmaceuticals of defined chemical preparations can be prescribed by a medical doctor. It is hoped that increased laboratory and clinical tests will be performed in the future.

The growing interest of investigators in the West has led to studies which have confirmed some of the Eastern findings on the biomedical benefits of *G. lucidum*. Stavinoha *et al.* (1995), following their findings on the anti-inflammatory efficacy of triterpenes isolated from the fruiting body of *G. lucidum* cultivated in the United States, are interested in developing an FDA approved anti-inflammatory triterpene-analogue which can be patented and used as a new, effective, and safe pharmaceutical. We noted also that Luu (1992) in France succeeded in synthesizing antitumor, water soluble products, the phosphodiesters of oxysterols, from similar lipophilic parent compounds in *G. lucidum*.

Ganoderma products vary widely in form and quality (Chen 1995). Product choice depends on the scientific information of the bioactive components found in the mushroom; how the product is made in relation to strain, growth stage, specific location of the mushroom used and processing; and identification of a reliable source. There is, however, a need for objective evaluation of *Ganoderma* products.

Although *Ganoderma* mycelium shows bioactivity, the fruiting body is a major source of high-molecular weight antitumor polysaccharides, such as β-1-3, β-1-6 D-glucans (Mizuno 1992). It is also the fruiting body which contains the high concentration of bioactive triterpenes in its spore scrapings from the underside tube region (Stavinoha *et al.* 1995). With electron microscopy, Mims and Seabury (1989) observed extensive hyphal distintegration and autolysis in association with tube formation in the basidiocarp of *G. lucidum*. A distinct zone of darkly stained mass was found between the context and trama (the hymnenial layer containing the tubes). It would be of great interest to find out if there is any correlation between these materials and bioactive triterpenoids in the fungus.

Bioactive mycelial polysaccharides differ from the ones isolated from the fruiting body in *Ganoderma* species (Mizuno 1992, Kim *et al.* 1993, Sohn 1995). Hirotani and Furuya (1986) also found that the triterpene acids of the differentiated fruiting body, such as ganoderic acids B and D, have the 3β-hydroxyl group, whereas the main triterpene com-

pounds in the cultured mycelium were 3 α-hydroxytriterpene acids. These two growth stages, the mycelium and the fruiting body, produce some similar types but different forms of bioactive components derived from different stages of primary (polyglycans) or secondary (triterpenes) fungal metabolites. Review suggests that for prevention and treatment of tumors and cancer, *Ganoderma* products containing a high concentration of anti-tumor polysaccharides should be the choice. For prevention of blocked arteries and stroke, on the other hand, products containing a high concentration of specific bioactive triterpenes, adenosine and perhaps polysaccharides (for improving oxygen utilization) should be the choice.

Ganoderma lucidum, a mushroom of biomedical importance, contains a number of bioactive components, many of them biological response modifiers which activate our immune systems for a multitude of defensive functions. These identified compounds of known molecular structures account for a range of reported beneficial biomedical effects, most notably in prevention of physiological disorders and diseases, which can contribute to anti-cancer and anti-HIV measures. There is a need for different forms of quality *Ganoderma* preparations (nutriceuticals and pharmaceuticals) based on the fact that different bioactive *Ganoderma* components have different or overlapping functions, and there is little, if any, information on the relative effectiveness of constituents with similar functions.

REFERENCES

Alexeev, V., and V. Kupin. 1993. *Ganoderma lucidum* administration in air-space medicine, 5th Intl. Symposium on *Ganoderma lucidum*, Seoul, Korea, 60-63.

Andreacchi, A. 1995. Characterization of AA 567, a coronary vasodilator and ca-channel antagonist produced by a basidomycete species YL 8006. Ph.D. Dissertation, University of Rochester, Dept. of Chemical Engineering, 1995.

Bartnicki-Garcia, S. 1968. Cell wall chemistry, morphogenesis, and taxonomy of fungi. Ann. Rev. Microbiol. 22:87.

Buck, K. W., A. W. Chen, A. G. Dickerson and E. B. Chain. 1968. Formation and structure of extracellular glucans produced by *Claviceps* species. J. Gen. Microbiol. 51: 337-352.

Byun, S. H. and I. H. Kim. 1987. Studies on the concurrent administration of *Ganoderma lucidum* extract and glutathione on the liver damage induced by carbon tetrachloride in rats. J. Pharm. Soc. Korea 31:133-139.

Chairul, Tokuyama T., M. Nishizawa, M. Shiro, H. Tokuda and Y. Hayashi. 1990. Malonate half-esters of homolanostanoid from an Asian *Ganoderma* fungus. Phytochemistry 29:923-928.

Chang, H. and P. Butt (Eds). 1986. Pharmacology and application of Chinese materia medica. World Scientific Publishing, Singapore, 642-653.

Chang, R. 1993. Limitations and potential applications of *Ganoderma* and related fungal polyglycans in clinical oncology, In: Mushroom biology and mushroom products, S.T. Chang *et al.* (eds), The Chinese University Press, Hong Kong, 96.

Chang, Raymond. 1994. *Ganoderma* polysaccharides: current concepts and applications. '94 International Symposium On *Ganoderma* Research ('94 ISGR). Chang, R., 1995. Effective Dose of *Ganoderma* in humans, Beijing, China, *Ganoderma*: systematics, phytopathology and pharmacology, proceedings of contributed symposium 59A, B, 5th International Mycological Congress (IMC5) Vancouver, 39-40.

Chang, S. T. 1995. *Ganoderma*—the leader in production and technology of mushroom nutriceuticals. Recent advances in *Ganoderma lucidum* research, Seoul, Korea: The Pharmaceutical Soc. of Korea, 43-52.

Chen, R. Y. and D. Q. Yu. 1993. Studies on the triterpenoid constituents of the spores from *Ganoderma lucidum* Karst, J. Chin. Pharm. Sci. 2:91-96.

Chen, W. C., D. M. Hau and S. S. Lee. 1995. Effects of *Ganoderma lucidum* and krestin on cellular immunocompetence in gamma-ray-irradiated mice. J. Chin. Med. 23:71-80.

Cheng, H. H., Y. C. Tung and T. C. Tung. 1986. The antitumor effect of cultivated *Ganoderma lucidum* extract. III. effect of *Ganoderma lucidum* extract on human T-cell subsets. J. Chinese Oncol. Soc. 1:1-10.

Chu, F. , H. Luo, G. Luo, S. Chen and Z. Liu. 1988. Protection of nucleated bone marrow cells of mice against the effect of radiation-induced micronucleus formation with polysaccharides extracted from zizhi (*Ganoderma*). Fushe Fanghu 8:16-20.

Czop, J. K. and J. Kay. 1991. Isolation and characterization of β-glucan receptors on human mononuclear phagocytes. J. Exp. Med. 173:1511-1520.

Dharmananda, S. 1988. *Medicinal mushrooms*. Bestways.

Hattori, M. 1995. A new monitoring system of cultured myocardial cell motion-effects of crude drug including the fruiting bodies of *Ganoderma lucidum* on the spontaneous beating of myocardial cells in culture. Recent advances in *Ganoderma lucidum* research, Seoul, Korea: The Pharmaceutical Soc. of Korea, Kim, B. K., I. H. Kim and Y. S. Kim (eds), 11-22.

Hikino, H., C. Konno, Y.Mirin and T. Hayashi. 1985. Antidiabetes drugs: isolation and hypoglycemic activity of ganoderan A and ganoderan B, glycans of *Ganoderma lucidum* fruit bodies. Planta Medica 51:339-340.

Hirotani, M. & T. Furuya. 1986. Ganoderic acid derivatives. Highly oxygenated lanostane-type triterpenoids, from *Ganoderma lucidum*. Phytochemistry 25:1189-1193.

Hirotani, M. C. Ino, T. Furuya & M. Shiro. 1986. Ganoderic acids T, S, and R, new triterpenoids from the cultured mycelia of *Ganoderma lucidum*. Chem. Pharm. Bull. 34:2282-2285.

Hseu, R. Y. 1993. An overview on *Ganoderma* mushrooms. Taichung, Taiwan: Wann Nian Publishing Co. p. 141 (in Chinese).

Janusz, M. J., K. F. Austen and J. K. Czop. 1989. Isolation of a yeast hepatoglucoside that inhibits monocyte phagocytosis of zymosan particles. J. Immunol. 142:959-965.

Jong, S. C. and J. M. Birmingham. 1992. Medicinal benefits of the mushroom *Ganoderma*. Adv. Appl. Microbiol. 37:101-134.

Kandefer-Szerszen, M., Z. Kawecki, and M. Guz. 1979. Fungal nucleic acids as interferon inducers. Acta Microbiol. Pol. 28:277-291.

Kasahara, Y., and H. Hikino. 1987. Validity of the Oriental medicines. Part 122. Central actions of adenosine, a nucleotide of *Ganoderma lucidum*. Phytother. Res. 1:173-176.

Kawagishi, H. 1995. Isolation of 5'-deoxy-5'-methylsulfinyladenosine as a platelet aggregation inhibitor from *Ganoderma lucidum*, recent advances in *Ganoderma lucidum* research, Kim, B. K., I. H. Kim and Y. S. Kim (eds) Seoul, Korea, 53-60.

Kim, M. J., H. W. Kim, Y. S. Lee, M. J. Shim, E. C. Choi and B. K. Kim. 1986. Studies on safety of *Ganoderma lucidum*. Kor. J. Mycol. 14: 49-59 (in Korean).

Kim, B. K., H. W. Kim and E. C. Choi. 1993. Anti-HIV activities of *Ganoderma lucidum*. 5th International Symposium on *Ganoderma lucidum*, Seoul, Korea, 67-69.

Kino, K. A. Yamashita , K. Yamaoka, J. Watanabe, S. Tanaka, K. Ko, K. Shimizu and H. Tsunoo. 1989. Isolation and characterization of a new immunomodulatory protein, Ling Zhi-8 (LZ-8), from *Ganoderma lucidum*. J. Biol. Chem. 264:472-478.

Komoda, Y., H. Nakamura, S. Ishihara, M. Uchida, H. Kohda and K. Yamasaki. 1985. Structures of new terpenoid? Constituents of *Ganoderma lucidum* (Fr.) Karst. (Polyporaceae). Chem. Pharm. Bull. 33:4829-4835.

Komoda, Y., M. Shimizu, Y. Sonoda and Y. Sato. 1989. Ganoderic acid and its derivatives as cholesterol synthesis inhibitors. Chem. Pharm. Bull. (Tokyo) 37:531-533.

Konoshima, T., Y. Kashiwada, M. Takasaki, M. Kozuka, I. Yasuda, M. Cosentino, and K. H. Lee, 1994. Cucurbitacin F derivatives, anti-HIV principles, from *Cowania Mexicana*. Bioorg. Med. Chem. Lett. 4:1323.

Koyama,K., K. Kinoshita, T. Imaigumi, M. Akiba, E. Negishi, K. Takahashi,A. Suzuki, K. Watanabe, S. Yano, S. Horie & Y. Naoji. 1993. Analgesic activity of triterpenoids and steroid isolated from mushrooms (*Ganoderma lucidum* and *Auricularia polytricha*). First Intl. Cong. on mushroom biology and mushroom products, Hong Kong, Chinese Univ. Press, 5:22-28.

Kubota, T. Y., Asaka, I. Miura and H. Mori. 1982. Structures of ganoderic acid A and B. Two lanostane type bitter triterpenes from *Ganderma lucidum* (Fr.) Karst. Helvetica Chimica Acta 65:611-619.

Kumano, N., Y. Nakai, T. Ishiwaka, S. Koinumarus, T. Kikumoto and K. Konno. 1980. Antitumor effect of organogermanium compound (Ge-132) in mouse tumors. Proc. 11th Int. Cong. Chemotherapy. Am. Soc. Microbiol. 1525-1527.

Kupin, V. 1992. A new biological response modifier—*Ganoderma lucidum*—and its application in oncology. 4th Intl. Sym. on *Ganoderma lucidum*. Seoul, Korea, 36-37.

Lee, S. S. , F. D. Chen, S. C. Chang, Y. H. Wei, I. Liu, C. F. Chen, R. D. Wei, K. Y. Chen and P. W. Han. 1984. *In vivo* antitumor effect of crude extracts from the mycelium of *Ganoderma lucidum*. J. Chinese Oncol. Soc. 5: 22-28.

Lee, S. Y. and H. M. Rhee. 1990. Cardiovascular effects of mycelium extract of *Ganoderma lucidum*: inhibition of sympathetic outflow as a mechanism of its hypotensive action. Chem. Pharm Bull. (Tokyo) 38:1359-64.

Lin, C. N., W. P. Tome and S. J. Won. 1991. Novel cytotoxic principles of Formosan *Ganoderma lucidum*. J. Nat. Prod. 54:998-1002.

Lindequist, U. 1995. Structure and biological activity of triterpenes, polysaccharides and other constituents of *Ganoderma lucidum*, in Recent advances in *Ganoderma lucidum* research, Kim, B. K., I. H. Kim and Y. S. Kim (eds.), Seoul, Korea: Pharmaceutical Society of Korea, 61-92.

Liu, K. C., S. F. Phounsavan, R. L. Huang, C. Liao, S. Y. Hsu and K. J. Wang. 1988. Pharmacological and liver functional studies on the mycelium of *Ganoderma lucidum*. Chinese Pharmaceut. J. 40:21-29.

Liu, B. Y., W. Liu and Y. Z. Kao. 1990. Ling Zhi. Beijing, China: Shueh Wan Publisher. (in Chinese).

Liu, W. K., V. E. C. Ooi, T. B. Ng, and S. T. Chang. 1993. Immunomodulatory activities of mushroom mycelial extracts in mushroom biology and mushroom products, Hong Kong: Chinese University Press, 285-291.

Luu, B. 1992. Chemistry and biology of oxysterols and oxytriterpenes. 4th International Symposium on *Ganoderma lucidum*. Seoul, Korea, 49-50.

Luu, B. 1995. Does *Ganoderma lucidum* contain anti-HIV agents? Occurence and antiviral activities of oxycholesterols and oxylanosterols, In: Recent advances in *Ganoderma lucidum* research, Kim, B.K., I. H. Kim and Y. S. Kim (eds.), Seoul, Korea: Pharmaceutical Society of Korea, 23-28.

Maruyama, H., K. Yamazaki, S. Murofushi, C. Kona, and T. Ikekwa. 1989. Antitumor activity of *Sarcodon asparatus* (Berk.) S. Ito and *Ganoderma lucidum* (Fr.) Karst. J. Pharmcobiodyn. 12:118-123.

Mayaux, J. F., A. Rousseau, R. Pauwels, T. Hue, Y. Henin, N. Dereu, M. Evers, F.Soler,C. Poujade, E. De Clerq and J. B. Le Pecq. 1994. Triterpene derivatives that block entry of human immunodeficiency virus type 1 into cells. Proc. Natl. Acad. Sci, USA 91:3564.

Mims, C. W. and F. Seabury. 1989. Ultrastructure of tube formation and basidiospore development in *Ganoderma lucidum*. Mycologia 81:754-764.

Miyazaki, T. and M. Nishijima. 1981. Studies on fungal polysaccharides-Part XXVII, Structural examination of a water soluble, antitumor polysaccharide of *Ganoderma lucidum*. Chem. Pharm. Bull. 29:3611-3616.

Miyazaki, T. and M. Nishijima. 1982. Studies on fungal polysaccharides-Part XXXII. Structural examination of alkali-extracted, water soluble heteroglycan of the fungus *Ganoderma lucidum*. Carbohydr. Res. 109:290-294.

Mizuno, T., N. Kato, A. Totsuka, K. Takenaka, K. Shinkai and M. Shimizu. 1984. Fractionation, structural features and antitumor activity of water-soluble polysaccharides from "Reishi", the fruit body of *Ganoderma lucidum*. Nippon Nogei Kagaku Kaishi 58:871-880.

Mizuno, T. 1991. Antitumor polysaccharides of polyporaceae fungi, *Ganoderma applanatum* and *Fomitopsis pinicola*. The 3rd Symposium on *Ganoderma lucidum*. Seoul, Korea, 25-31.

Mizuno, T. 1992. Comparative studies on the host-mediated antitumor polysaccharides isolated from the fruiting body and mycelium of three *Ganoderma* species fungi, *Ganoderma lucidum*, *G. tsugae* and *G. applanatum*. 4th International Symposium on *Ganoderma lucidum*, Seoul, Korea, 21-29.

Murasugi, A., S. Tanaka, N. Komiyama, N. Iwata, K. Kino, H. Tsunoo and S. Sakuma. 1991. Molecular cloning of a cDNA and a gene encoding an immunomodulatory protein, Ling Zhi-8, from a fungus, *Ganoderma lucidum*. J. Biol. Chem. 266:2486-2493.

Nishitoba, T., H. Sato, S. Shirasu and S. Sakamura. 1986. Evidence on the strain-specific terpenoid pattern of *Ganoderma lucidum*. Agric. Biol. Chem. 50:2151-2154.

Nishitoba, T., H. Sato, and S. Sakamura. 1987a. Triterpenoids from the fungus *Ganoderma lucidum*. Phytochemistry 26:1777-1784.

Nishitoba, T., H. Sato, S. Shirasu and S. Sakamura. 1987b. Novel triterpenoids from the mycelial mat at the previous stage of fruiting of *Ganoderma lucidum*. Agric. Biol. Chem. 51:619-622.

Quian, F., and S. Zhang. 1993. Studies on medicinal mushroom and germanium: Ge-132. First international conference on mushroom biology and mushroom products, Hong Kong: The Chinese University of Hong Kong. Aug. 23-26, 1993, Abst. p. 144.

Sato, H. and T. Iwaguchi. 1979. Antitumor activity of new novel organogermanium compound, Ge-132. Cancer Chemotherapy 6:79-83.

Shiao, M. S., R. L. Kuan, L. J. Lin and C. T.Wang. 1994. Natural products and biological activities of the Chinese medicinal fungus *Ganoderma lucidum*. In: Food phytochemicals for cancer prevention II. ACS Symposium Series. C. T. Ho *et al.* 547:342-354.

Shimizu, A., T. Yano, Y. Saito and Y. Inada. 1985. Isolation of an inhibitor of platelet aggregation from a fungus, *Ganoderma lucidum*. Chem. Pharm. Bull. 33:3012-3015.

Sohn, D. H. 1995. Antifibrotic effect of polysaccharides from *Ganoderma lucidum* in experimental hepatic cirrhosis model. In: Recent advances in *Ganoderma lucidum* research, Ed. by B.K. Kim, *et al.* Seoul, Korea: The Pharmacol. Soc. Korea, 29-41.

Sone, Y., R. Okuda, N. Ada, E. Kishida and A. Misaki. 1985. Structures and antitumor activities of the polysaccharides isolated from fruiting body and the growing culture of mycelium of *Ganoderma lucidum*. Agric. Biol. Chem. 49:2641-2653.

Stavinoha, W. B. , B. J. Slama, S. T. Weintraub and P. L. Mobley. 1991. The anti-inflammatory activity of *Ganoderma lucidum*. 3rd International Symposium on *Ganoderma lucidum*, Seoul, Korea, 9-15.

Stavinoha,W. B., N. Satanji and S. T. Weintraub. 1995. Study of the anti-inflammatory efficacy of *Ganoderma lucidum*. In: Recent advances in *Ganoderma lucidum* research, Ed. by B.K. Kim *et al.*, Seoul, Korea: The Pharmaceutical Society of Korea, 3-10.

Stanvinoha, W. B., W. E. Hardman and I. L. Cameron. 1993. Short-term dietary supplementation with *Ganoderma lucidum* slows development and growth of microadenomatous lesions in the colon of rats treated with the carginogen, 1,2-dimethylhydrazine. 5th International symposium on *Ganoderma lucidum*, Seoul, Korea, 12-17.

Stanvinoha,W. B., N. Satanji and S. T. Weintraub. 1995. Study of the anti-inflammatory efficacy of *Ganoderma lucidum*. In: Recent advances in *Ganoderma lucidum* research, Ed. by B.K. Kim *et al.*, Korea: The Pharmaceutical Society of Korea, 3-10.

Su, C. H. 1991. Taxonomy and physiologically active compounds of *Ganoderma*—a review, Bull. Taipei Med. Coll. 20:1-16.

Su, C. H., M. N. Lai and M. H. Chan. 1993. Hepato-protective triterpenoids from *Ganoderma tsugae* Murell. In: Mushroom biology and mushroom products, Eds. S.T. Chang *et al.*, Hong Kong: The Chinese University Press, 275-283.

Tanaka, S.K., K. Ko, K. K. Kino, K. K. Tsuchiya, A. Yamashite, A. Murasugi, S. Sakuma and H. Tsunoo. 1989. Complete amino acid sequence of an immunomodulatory protein, Ling Zhi-8 (L-Z8), an immunomodulator from a fungus *Ganoderma lucidum*, having similarity to immunoglobulin variable regions. J. Biol. Chem. 264:16372-16377.

Tasaka, K., M. Akagi, K. Miyoshi, M. Mio and T. Makino. 1988a. Anti-allergic constituents in the culture medium of *Ganoderma lucidum* (1) inhibitory effect of oleic acid on histamine release. Agents Actions 23:153-156.

Tasaka, K., M. Mio, K. Izushi, M. Akagi, and T. Makino. 1988b. Anti-allergic constituents in the culture medium of *Ganoderma lucidum* (2) The inhibitory effect of cyclooctasulfuron histamine release. Agents Actions 23:157-160.

Teow, S. S. 1995. The therapeutic value of *Ganoderma lucidum*. In: *Ganoderma*: systematics, phytopathology and pharmacology, P. K. Buchanan *et al.*, (eds.), Proceedings of Contributed Symposium 59 A. B., 5th International Mycological Congress, Vancouver, 105-114.

Toth, J. O., B. Luu and G. Ourisson. 1983. Ganoderic acids T-Z, cytotoxic triterpenes from *Ganoderma lucidum* (*polyporaceae*), Tetrahedron Letters 24:1081-1084.

Wang, C. N., J. C. Chen, M. S. Shiao and C. T. Wang. 1991. The inhibition of human platelets function by Ganodermic acid. S. Biochem. J. 277:189-197.

Wang, G., J. Zhang, T. Mizuno, C. Zhuang, H. Ito, H. Mayuzumi, H. Okamoto and J. Li. 1993. Antitumor active polysaccharides from *Ganoderma tsugae*. Biosci. Biotechnol. Biochem. 57:894-900.

Willard, T. 1990. Reishi mushroom: herb of spiritual potency and medical wonder, Issaquah, Washington, Sylvan Press.

Yang, Q. Y., J. N. Fang and X. T. Yang. 1995. The isolation and identification of two polysaccharides of *Ganoderma lucidum* (GL-A, GL-B) In: *Ganoderma*: systematics, phytopathology and pharmacology. P.K. Buchanan, R. S. Hseu and J. M. Monocalno (eds), Proceedings of Contributed Symposium 59, A, B, 5th International Mycological Congress, Vancouver, 95-99.

Yeh, S. F., K. C. Lee, and M. S. Shiao. 1987. Sterols, triterpenes and fatty acid patterns in *Ganoderma lucidum*. Proc. Natl. Sci. Counc., ROCCA 11:129-134.