CHAPTER 8 ADDITIONAL MEDICINAL PROPERTIES

Synopsis

Extracts from many medicinal mushrooms have long been used for a wide range of ailments in traditional Chinese medicine. Modern scientific and medical studies are increasingly supporting many of these health claims. The main areas of medical studies include blood pressure-lowering, cholesterol lowering, liver protective, antifibrotic, anti-inflammatory, anti-diabetic and anti-microbial activites.

While the role of medicinal mushrooms in immunomodular and anti-cancer activities represents the dominating theme of this report, it is important to recognise that many of these mushrooms also show other quite significant medical properties, such as blood pressure- lowering, cholesterol lowering, liver protective, antifibrotic, anti-inflammatory, anti-diabetic, anti-viral and other anti-microbial activities (Ooi and Liu, 1999; Ooi; 2000, Wasser and Weis, 1999a, b, Hobbs, 1995; Gunde-Cimerman, 1999). Only a brief resume will be given here of the extensive additional medical properties of certain medicinal mushrooms which have been supported by recent scientific and medical studies.

Cardiovascular and hypercholesterolemia effects

A highly significant cause of death in most developed countries is coronary artery disease. The main risk factors are hypercholesterolemia and dyslipoproteinemia, disturbance in blood platelet binding, high blood pressure and diabetes. Increased blood levels of total cholesterol, low density lipoprotein (LDO) and very low density lipoprotein (VLDL) cholesterol as well as lowered levels of high density lipoprotein (HDL) cholesterol have been identified as major risk factors in the development of coronary artery disease (CAD)(Alberts *et al*., 1989). As much as 2/3rd of total body cholesterol in most individuals is of endogenous origin. Clinical

intervention studies have clearly demonstrated the therapeutic importance of correcting hypercholesterolemia.

The initial steps in the prevention and treatment of CAD and hypercholesterolemia is the modification of the nutritional regime with a diet low in fats and saturated fatty acids and rich in crude fibres. Mushrooms in general, and *Pleurotus, Lentinus* and *Grifola* in particular, because of their high fibre content, sterols, proteins, microelements and a low calorific value, are *almost ideal for diets designed to prevent cardiovascular diseases* as first suggested by Traditional Chinese Medicine (Breene, 1990; Hobbs, 1995).

When diet control is not successful the next step is drug therapy. Early attempts to identify inhibitors of cholesterol synthesis resulted in the development of inhibitors that could affect stages in the biosynthetic pathway for cholesterol formation. A major rate-limiting step in the pathway is at the level of the microsomal enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase; mevalonate $NADP^+$ oxidoreductase [CoA acylating] EC 1.1.1.34). HMG-CoA reductase occurs early in the biosynthetic pathway and is among the first committed steps to cholesterol formation that catalyses the reductions of HMG-CoA into mevalonate (Rodwell *et al*., 1976).

Mevinolin (lovastatin) produced commercially from the filamentous fungus *Aspergillus terreus* was the first specific inhibitor of HMG-CoA reductase to receive approval for the treatment of hypocholesteremia (Alberts *et al*., 1980). The genus *Pleurotus* of the medicinal mushrooms has several species that produce mevinolin (Gunde-Cimerman and Cimerman, 1995). *P. ostreatus* has been shown to produce the highest amount of lovastatin in the fruit-body, especially in the lamellae or gills.

Mevinolin has been detected in submerged fermentation broth of *P. saca* and in the surface fermentation broth of *P. sapidus* (Gunde-Cimerman *et al*., 1993).

The addition of 4% dried *Pleurotus* to a high cholesterol diet effectively reduced cholesterol accumulation in the serum and liver of experimental rats redistributing cholesterol in favour of HLDL, reduced production of VLDL and LDL cholesterol, reduced cholesterol absorption and reduced HMG-CoA reductase activity in the liver (Bobek *et al*., 1991). Limited clinical trials with 15-20g dried *Pleurotus* supplement in the daily diet over a one-month period reduced hypercholesterolemia in many but not all patients (Bobek *et al*., 1998). It has been suggested that *Pleurotus* mushrooms could be recommended as a natural cholesterol lowering substance within the human diet (Gunde-Cimerman, 1999). Somewhat similar results have been achieved with *Grifola frondosa* and *Auricularia auricula* (Ryong and Tertov, 1989).

Antilipemic effects of polysaccharides from *Tremella fuciformis* and *T. aurantia* have been shown to lower plasma cholesterol levels (Sheng and Chen, 1989; Kiho *et al*., 2000), while an antihypercholesterolemic agent has been produced from fruit bodies and mycelium of *T. aurantai* (Koichi and Takahiro, 1999).

It has long been recognised that eritadenine, a compound extracted from *Lentinus edodes* is able to lower blood serum cholesterol (BSC). Eritadenine reduces BSC in mice not by inhibition of cholesterol biosynthesis but by the acceleration of the excretion of ingested cholesterol and its metabolic decomposition (Susuki and Oshima, 1974). Various studies have shown that *Lentinus* mushrooms can lower both blood pressure and free cholesterol in plasma, as well as accelerate accumulation of lipids in the liver, by removing them from circulation (Kabir and Kumura, 1989). It has been suggested that high dosages of eritadenime may impair

the secretion of very low-density lipoprotein cholesterol and in a similar manner to soybean protein, eritadenine lowers cholesterol by decreasing the ratio of phosphatidylcholine (PC) to phosphatidylethanolamine (PE) in liver microsomes (Sugiyama and Yamakawa, 1996). Several small studies with *Lentinus* extracts in Japan have shown positive decreases in serum cholesterol in young women and people older than 60 years of age (Hobbs, 1995).

Nucleic acids from *L. edodes* also have significant platelet agglutinating inhibitory effects (antithrombotic activity) (Hokama and Hokama, 1981). PSK also causes decreases in LDL cholesterol in hyperlipidemia patients (Tsukagoshi 1984).

A recent review of literature by Francia *et al*. (1999) has collated how different fungal activities can reduce the effects of risk factors for cardiovascular diseases in experimental animals. Of the 17 species of macrofungi examined, including some well recognised medicinal mushrooms, 16 showed at least one of the following activities, i.e. ability to reduce hypercholesterolemia or to treat dyslipoproteinemia; possibility to decrease arterial hypertension or hyperglycemia, and the ability to cure disturbances in platelet aggregation (Tables 1-4). However, water extracts of fruitbodies of *L. edodes* have been shown to lessen the effectiveness of blood platelets in the process of coagulation and consequently those who bleed easily and who take anticoagulants should exert caution when chronically consuming extracts of *L. edodes* in therapeutic amounts or water-soluble fractions such as LEM (Yang and Jong, 1989). Nevertheless, the exact mechanisms of action remains to be elucidated before considering an eventual human treatment application for prevention or cure of cardiovascular diseases. This review contains an extensive list of relevant references.

References for Tables 1-4 can be found in Francia *et al*. (1999). Many of these extracts have long been used in traditional Chinese medicine for treating various cardiovascular disorders (Hobbs, 1995; Willard, 1990).

Table 1 Effects of macrofungi on lipids and cholesterol

[Seven fungi had an effect on lipids in general and cholesterol in particular]

1. Six species reduced total cholesterol level
   Auricularia auricula – judae
   Cordyceps sinensis: the activity could be due to a polysaccharide, the CS-F30, composed of galactose, glucose and mannose.
   Ganoderma lucidum
   Grifola frondosa
   Pleurotus ostreatus
   Tremella fuciformis

2. Two species reduced the 'bad cholesterol' level
   Auricularia auricula – judae
   Tremella fuciformis

3. Three species reduced the triglyceride level
   Cordyceps sinensis
   Grifola frondosa
   Lentinus edodes

4. *Agaricus campestris*: demonstrated no hypocholesterolemic activity.

Table 2 Macrofungi reducing blood platelet binding

[Six species reduced platelet binding (*in vitro*]

Auricularia auricula-judae
Calyptella sp: the active compound is the 5-hydroxy-3-vinyl-2 (5H) – furanone.
Ganoderma lucidum: the binding activity is due to adenosine.
Kuehneromyces sp: the active compound is kuehneromycine B.
Neolentinus adhaereus: the active compound is 2-methoxy-5-methyl-1,4 benzoquinone.
Panus sp: the activity is due to two compounds, panudial and nematolon.

Table 3 Macrofungi with an arterial blood pressure lowering effect

[Three fungal species reduced the arterial pressure]

Ganoderma lucidum *Grifola frondosa* *Tricholoma mongolicum*: the decrease of arterial pressure attributable to a lectin.

Table 4 Macrofungi reducing glycemia

[Six species appeared to decrease glycemia]

1	Four species were active in insulin-dependent-diabetes. *Agaricus bisporus* *Agrocybe aegerita*: the glycemia lowering was due to two polysaccharides: AG-HN1, a polysaccharide of high molecular weight composed of glucose and AG-HN2, a polysaccharide of low molecular weight composed of fructose, galactose, glucose and mannose. *Cordyceps sinensis*: could be due to the CS-F30, a polysaccharide composed of galactose, glucose and mannose. *Tremella aurantia*: the active compound is the TAP (*Tremella* acidic Polysaccharide).
2.	One species was active in non-insulin-dependent-diabetes. *Grifola frondosa*: this mushroom is able to diminish glycemia but also insulemia and the blood level of triglycerides.
3.	One species showed an activity only in non-diabetic animals. *Coprinus comatus*.

Due to their high content of fibre and proteins and low fat content, extracts of edible mushrooms have been considered to be ideal foods for dietetic prevention of hyperglycemia (Gunde-Cimerman, 1999). Extracts of several medicinal mushrooms, including *Tremella aurantia, 'Cordyceps sinensis', Ganoderma lucidum* and *Auricularia auricula-judae* have been shown to lower blood glucose (Kiho *et al*., 1995; Yan *et al*., 1998; Hikimo *et al*., 1989). The blood glucose and triglyceride (TG) lowering effects of water soluble extracts from *Lentinus edodes, Pleurotus ostreatus* and *Phellinus linteus* in the streptozotocin-induced diabetic model have been clearly

demonstrated (Kim *et al*., 1997, Kim *et al*., 2001). Such results strongly suggest that these mushrooms have potential preventive and therapeutic action in diabetes mellitus (type I and II).

Antimicrobial effects

Antimicrobial drugs have long been used for prophylactic and therapeutic purposes. Unfortunately the recent increase in the occurrences of drug-resistant bacterial strains is creating serious treatment problems. Consequently, the antimicrobial activity of various antitumour polysaccharides from medicinal mushrooms are being re-evaluated in terms of their clinical efficacy. Such compounds would be expected to function by mobilising the body's humoral immunity to ward off viral, bacterial, fungal and protozoal infections resistant to current antibiotics.

Many cancer and AIDS patients die of opportunistic infections because of immunosuppression (Table 5). Several mushroom polysaccharides have shown antiviral activity against ectromelia virus and cytomegalovirus infections (Jong and Donovich, 1990). Lentinan from *L. edodes* when used in conjunction with azidothymidine (AZT) suppressed the surface expression of HIV on T-cells more than AZT did alone. Lentinan and sulphated lentinan exhibited a potent anti-HIV activity resulting in inhibition of viral replication and cell fusion.

Lentinan has also shown: (a) antiviral activity in mice against VSV (vesicular stomatis virus), encephalitis virus, Abelson virus, an adenovirus type 12; (b) stimulated non-specific resistance against respiratory viral infection in mice; (c) conferred complete protection against an LD75 challenge dose of virulent mouse influenza A/SW15; (d) increased resistance to the protozoal parasites *Schistosoma japanicum*, *Sch. mansoni;* (e) exhibited activity against *Mycobacterium tuberculosis*

bacilli resistant to antituberculosis drugs, *Bacillus subtilis*, *Staphylococcus aureus, Micrococcus lenteus, Candida albicans* and *Saccharomyces cerevisiae*; (f) increased host resistance to infections with potentially lethal *Listeria monocytogenes* (for original references see Wasser and Weis, 1999a).

LEM and a new lignan-rich compound JLS-18 derived from LEM block the release of infectious *Herpes simplex* virus in animals (Sarkar, 1993) and it has been suggested because of its high activity that JLS-18 could be of value in the treatment of hepatitis B and AIDS patients (Yamamoto, 1997).

Sulfated Schizophyllan polysaccharide displayed strong anti-HIV activity while the anti-tumour effect was reduced or lost (Ito and Sugawara, 1990). Schizophyllan has also been reported to enhance protection against *Staphylococcus* sp. infection (Matsuyama *et al*., 1992).

The Japanese National Institute of Health and the US National Cancer Institute have both stated that sulfated *Grifola frondosa* extract are able to prevent as much as 97% HIV infected T-helper lymphocytes from being destroyed *in vitro*. This is important because measuring the T-helper cell count makes it possible to trace the progress of HIV to full blown AIDS (Ishikawa, 1991; US National Cancer Institute, 1992). Interestingly, *G. frondosa*, D-fraction together with dimethyl sulfoxide (DMSO) has also shown success in treating AIDS associated Kaposi sarcoma (Zhuang and Mizuno, 1999).

PSK has been shown to induce potent antimicrobial activity against *Escherichia coli*, *Listeria monocytogenes* and *Candida* (Tsukagoshi, 1984; Sakagami and Takeda, 1993).

In recent years Basidiomycetes and other higher fungi including some recognised as medicinal mushrooms have been re-investigated as sources of novel

antibiotics – mainly as a result of the increasing difficulty and cost of isolating novel bioactive compounds from the Actinomycetales such as *Streptomyces*.

Difficulties such as slow growth rate in fermenters of Basidiomycetes and the low yield of products derived from them compared with the Actinomycetes are now far outweighed by the opportunity of finding new antibiotics with novel structures types as well as compounds with new modes of action (Brizuela and Garcia, 1998). The fact that the Basidiomycetes have been insufficiently investigated coupled with the broad range of structural types of antibiotics which are produced by these organisms, suggests that they may well be a source of new and useful bioactive compounds (Anke, 1989).

A recent extensive examination of over 200 species of Basidiomycetes in Spain demonstrated that almost 50% had significant direct antibiotic activity against a range of test organisms. It was interesting to note that the bracket polypore *Piptoporus betulinus* carried by the historic Iceman (Chapter 2) displayed a high broad spectrum antibiotic activity! (Suay and Arenal, 2000).

Researchers have shown that a water extract of *L. edodes* demonstrated growth-enhancing effects on colon-inhabitating beneficial lactic acid bacteria, *Lactobacillus brevis* and *Bifidobacteria breve*. The effective factor in the extract is considered to be the disaccharide sugar, trehalose. The authors suggest that the *L. edodes* extracts can improve the beneficial intestinal flora of the gut and reduce the harmful effects of certain bacterial enzymes such as β-glucosidase, β-glucuronidase and tryptophanase as well as reducing colon cancer formation (Bae, 1997).

Clearly, the antimicrobial potential of extracts of several types of medicinal mushrooms and indeed other Basidiomycetes not yet exploited must warrant further examination. The proven immuno-modulatory effects of many of these mushroom

species will be of significance especially when such infections occur in individuals where the immune system is not functioning well such as young children, the elderly and with patients enduring major anaesthetic and surgical procedures.

Table 5 Spectrum of mycoses and mycetes related to AIDS (Wasser *and Weis*, 1999a)

Mycoses	Causative organisms/saprophytes	Main target issues	Incidence %
Dermatophytoses	Anthropophillic dermatophytes: *Trichophyton rubum, Epidermophyton floccosum*, and others	Skin and appendages	80-90
Candidoses	*Candida albicans, C. tropicalis, C. parapsilosis, C. guiliermondii, C. krusci,* and other species	Oral cavity; skin; vagina; oesophagus	70-90 25-30 20-25
Torulopsidoses	*Torulopsis glabrata, T. candida*	Intestinal tract; Parasitic; Saprobic Systemic, mainly brain	 1-2 70-90 <1
Trichosporosis	*Trichosporon cutaneum*		
Cryptococcosis Histoplasmosis	*Cryptococcus neoformans*	Brain (lungs, skin)	5-7

A series of studies has recently been carried out with a PGG-glucan on patients undergoing high-risk major abdominal and thoracic surgery or high-risk gastrointestinal surgery. PGG-glucan is a highly purified proprietary β-(1-3)-glucan with β-1,6 branches (poly 1-6 glucotriosyl-β 1-3 glucopyranose glucan) (Onderdonk *et al*., 1992). Three separate multicentre (including Harvard Medicial School), randomised, placebo-controlled, double-blind clinical trials were carried out. In the initial study patients receiving high doses of β-glucan (2.0 mg/kg) exhibited significantly fewer postoperative infections complications when compared with placebo (Babineau *et al*., 1994a). In a second study, patients given β-glucan had 1.4 infections per patient vs. 3.4 infections in the placebo group (Babineau *et al*., 1994b). In a further study involving 1,249 patients the βb-glucan-treated patients showed a

statistically significant (39%) reduction in serious infections and death compared with placebo (Dellinger *et al*., 1999). However, this final study was terminated before anticipated completion because of an increased incidence of adverse effects in patients receiving PGG-glucan. Since β-(1-3) glucans exhibit considerable structural diversity such trials should be repeated with β-(1-3) glucans derived from the medicinal mushrooms which have demonstrated no adverse human side-effects. With the increasing concern of hospital-derived postoperative microbial infections together with antibiotic resistance, such studies must warrant serious consideration, and further expansion with mushroom-derived β-glucans must be considered because of their proven antimicrobial effects.

Antioxidant , anti-inflammatory, free radical scavenging activities and the ageing process

A wide variety of pathological damage, such as DNA, carcinogenesis and cellular degeneration, related to the ageing process and ageing itself can be caused by reactive oxygen species (ROS) produced by sunlight, ultraviolet and ionising radiation, chemical reactions and metabolic processes. Furthermore, there is a vast accumulation of studies that implicate oxygen derived free radicals such as superoxide, hydroxyl radicals and high energy oxidants such as peroxy nitrite as mediators of inflammation, shock and ischemia/reperfusion injury (Cuzzocrea *et al*., 2001). There is also growing evidence to show that production of ROS at the site of inflammation can contribute to tissue damage (Salvimini *et al*., 1996). Interventions against ROS could exert beneficial effects on inflammation and shock (Halliwell and Parihar, 1984). Several mushroom species have been studied for anti-inflammatory and antioxidant activities (Ukai *et al*., 1983) and patents have been established for these usages (Xiu, 1996).

Extracts of *G. lucidum* can apparently remove the hyperoxide radical believed to be a main factor in the human ageing process (Liu *et al*., 1997), and the ageing mouse model (Pan *et al*., 1999). In a clinical trial with 30 elderly people *Ganoderma lucidum* extract (GLE) was given oral 1.5 g 3 times daily for 30 days. Interleukin-2 and interferon (IFN) production by peripheral mononuclear cells (PBMC) and NK cell activity *in vitro* were respectively measured. Production of IL-2 and IFN were significantly increased after GLE treatment. Such results could suggest that GLE is a possible treatment to raise the cellular immunological activity in ageing people (Tao and Feng, 1991; Tao, 1993).

A *Ganoderma lucidum* polysaccharide GLB7 decreased the production of oxygen free radicals and antagonised the respiratory burst induced by PMA in murine peritoneal macrophages (Li and Lei, 2000). Such observations could imply that the polysaccharide-induced inhibition of oxygen free radicals in murine peritoneal macrophages play an important role in the anti-ageing effect of *Ganoderma* extracts.

PSK in a cell-free system consisting of hypoxanthine-xanthine oxidase rapidly quenched the superoxide radical, a property not shared by Schizophyllan (Sakagami and Aoko, 1991). PSK further repressed the mimetic activity of superoxide dismutase (SOD) and promoted oxidative stress relief for cancer-bearing hosts (Kobayashi and Kariya, 1994). PSK also gave protection to macrophages from lipoperoxide accumulation and foam cell formation created by oxidatively modified low-density lipoprotein (Yuan and Meiz, 1996). This protection is believed to be due to the induction of gene expression of antioxidative enzymes (Chen and Zhou,1997). PSP shows similar scavenging effects on superoxide and hydroxyl radicals (Hu and Chen, 1992). Significant superoxide and hydroxyl radical scavenging activities have

been demonstrated for several mushroom antitumour polysaccharides (Liu *et al*., 1997).

Hepatoprotective effects

Fruit-bodies of *Ganoderma lucidum* have long been a major factor in folk medicine for the treatment of chronic hepatitis (Willard, 1990). Ganoderic acids R and S were isolated from cultured mycelia and shown to have strong antihepatotoxic activity in galactosamine-induced cytotoxic tests with primary cultured rat hepatocytes (Hirotani and Ito, 1986). Another hepatoprotective compound, ganosporeric acid A, was isolated from the ether-soluble fraction of the spores of *G. lucidum* (Chen and Yu, 1991). The wide spectrum of medical efficacies of *Ganoderma lucidum*, including hepatoprotective activities, is shown in Table 6.

A polysaccharide fraction from *L. edodes* showed liver protective action in animals together with improved liver function and an enhance production of antibodies to hepatitis B (Mizuno, 1995). Lentinan and LEM have given favourable results in treating chronic persistent hepatitis and viral hepatitis B patients (Zhu, 1985; Amagase, 1987). Extracts of *G. lucidum* have shown good results in treating hepatitis, particularly in cases without severe liver impairment (Yan, 1987). A clinical study with lyophilised extract of *G. lucidum* showed highly beneficial results on quality of life with patients suffering from active hepatitis B (Soo, 1994).

There have been other interesting medical reports relating to marked improvement with patients suffering from cirrhosis of the liver and chronic hepatitis B with extracts from *Dendropolyprus umbellatus* (Bensky and Barolet, 1990), *Schizophyllan commune* (Kakuma, 1991), *Trametes versicolor* (Zhou, 1989), and *Poria cocos* (Guo, 1984). PSP may, thus, be useful in the wider context of the treatment of hepatitis (Yeung, 1995).

Table 6 Medical efficacies of *Ganoderma lucidum* (Kim and Kim, 1999)[see for relevant references].

Efficacy	Compound
Anti-HIV activity	Ganoderic acid α Ganoderic acid β Ganoderic acids B, C1, H Ganoderiols A, B, F Ganodermanondiol Ganodermanontriol Ganolucidic acid A Lucidumol B 3β, 5α-Dihydroxy-6β-methoxyergosta-7-diene
Antihypertension (ACE inhibitor)	Ganoderic acids B, D, F, H, K, S, Y Ganoderol B
Bitterness	Ganoderic acids A, C1, J Lucidenic acids A, D1 Lucidone A, C
Cytotoxicity	Ganonderic acids T, V, W, X, Y, Z 3β-Hydroxy-26-oxo-5α-lanosta-8,24-dien-11-one Ergosta-7,22=diene-3β, 3α,9α-triol
Enzyme inhibitor	
FPT inhibition[a]	Ganoderic acids A and C
PLA-2-inhibition[b]	Ganoderic acid T
DNA pol. β inhibition[c]	5,8-Epidoxy-5α,8α-ergosta-6, 22E=dien-3β-ol
Hepatoprotective	Ganoderic acids R, S Ganosporeric acid A
Histamine release inhibition	Cyclooctasulfur Ganoderic acids C and D
Hypocholesterolemic	Ganoderic acid Mf Ganodermic acid B Ganodermic acid T-O
Platelet aggregate inhibition	Ganodermic acid S

[a]FPT : farnesyl protein transferase
[b]PLA_2: phospholipase A_2
[c]DNA pol: DNA polymerase

This Chapter has only been a brief overview of the many other aspects of medical usage of the medicinal mushrooms which are being pursued worldwide. It, hopefully, shows the direction of medical research into these compounds and their undoubted value and significance in areas outwith cancer and immunotherapy.

References

Alberts, A.W., Chen, J., Kuron, V. and Hunt, J. 1980. Mevinolin, a highly potent competitive inhibitor of hydroxymethylglutaryl-co-enzyme A reductase and cholesterol-lowering agent. *Proceedings of the National Academy of Science* **77**, 3957-3961.

Alberts, A.W., MacDonald, J.S., Till, A.E. and Tobert, J.A. 1989. Lovastatin. *Cardiovascular Drug Reviews* **7**, 89-109.

Amagase, H. 1987. Treatment of hepatitis B patients with *Lentinus edodes* mycelium. *Proceedings of the XII International Congress of Gastroenterology*, Lisbon, p. 197.

Anke, T. 1989. Basidiomycetes: a source of new bioactive secondary metabolites. *Progress in Industrial Microbiology* **27**, 51-66.

Babineau, T.J. *et al*. 1994a. A phase II muti-centre double-blind randomised placebo-controlled study of three dosages of an immunomodulator (PGG-glucan) in high-risk surgical patients. *Archives of Surgery* **129**, 1204-1210.

Babineau, T.J. *et al*. 1994b. Randomised phase I/II trial of a macrophage-specific immunomodulator (PGG-glucan) in high-risk surgical patients. *Annals of Surgery* **220**, 601-609.

Bae, E-A., Kim, D-H. and Han, M.J. 1997. Effect of *Lentinus edodes* on the growth of intestinal lactic acid bacteria. *Archives Pharmaceutical Research* **20**, 443-447.

Bensky, D. and Barolet, R. 1990. *Chinese herbal medicine: formulas and strategies*. Easte and Peers, Seattle, WA.

Bobek, P., Ozdin, L. and Galbavy, S. 1998. Dose and time dependent hypocholesterolemic effect of oyster mushroom (*Pleurotus ostreatus*) in rats. *Nutrition* **14**, 282-286.

Bobek, P., Ginter, E., Jurcovicova, M., Ozdin, L. and Mekinova, D. 1991. Cholesterol lowering effect of the mushroom *Pleurotus ostreatus* in hereditary hypercholesterolemic rats. *Annuals of Nutrition and Metabolism* 35, 191-195.

Breene, W.M. 1990. Nutritional and medicinal value of speciality mushrooms. *Journal of Food Protection* **53**, 883-894.

Brizuela, M.A. and Garcia, L. 1998. Basidiomicetos: nueva fuente de metabolitos secundarios. *Rev Iberoam Mic.* **15**, 69-74.

Chen, R.Y. and Yu, D.Q. 1991. Studies on the triterpenoid constituents of the spores from *Ganoderma lucidum*. *Yao Hsueh Hsueh Pao (Acta Pharmaceut Simica)* **26**, 267-273.

Chen, Y. and Zhou, M. 1997. Damage to macrophages by tetrabutyl hydroperoxide and the protective actions of the protein-bound polysaccharide Krestin. *Medical Science Research* **25**, 606-609.

Cuzzocrea, S., Riley, D.P., Caputi, A.P. and Salvemini, D. 2001. Antioxidant therapy: a new pharmacological approach in shock, inflammation and ischemia/reperfusion injury. *Pharmacology Reviews* 53, 135-139.

Dellinger, E.P. *et al*. 1999. Effect of PGG-glucan on the rate of serious postoperative infection or death observed after high-risk gastrointestinal operation. Betafactin Gastrointestinal Study. *Archives of Surgery* **13**, 977-983.

Francia, C., Rapior, S., Courtecuisse, R. and Siroux, Y. 1999. Current research findings on the effects of selected mushrooms on cardiovascular diseases. *International Journal of Medicinal Mushrooms* **1**, 169-172.

Gunde-Cimerman, N. 1999. Medicinal value of the genus *Pleurotus* (Fr.) P. Karst. (Agaricales S.R., Basidiomycetes). *International Journal of Medicinal Mushrooms* **1**, 69-80.

Gunde-Cimerman, N. and Cimerman, A. 1995. *Pleurotus* fruiting-bodies contain the inhibitor of 3-hydroxy-3-methylglutaryl-Coenzyme A reductase-lovastatin. *Experimental Mycology* **19**, 1-6.

Gunde-Cimerman, N., Plemenitas, A. and Cimerman, A. 1993. *Pleurotus* fungi produce mevinolin, an inhibitor of HMG CoA reductase. *FEMS Microbiology Letters* 113, 333-338.

Guo, D. 1984. Preliminary observation on carboxymethyl *Poria cocos* polysaccharide (CMPLP) in treating chronic viral hepatitis. *Journal of Traditional Chinese Medicine* **4**, 282-285.

Halliwell, B. and Parihar, J.M.C. 1984. Lipid peroxidation, oxygen radicals, cell damage and antioxidant therapy. *Lancet* 1396-1397.

Hikimo, H., Ishiyama, M., Suzuki, Y. and Konno, C. 1989. Mechanisms of hypoglycaemic activity of ganoderan B: a glycan of *Ganoderma lucidum* fruitbodies. *Planta Medica* **55**, 423-428.

Hirotani, M. and Ito, C. 1986. Ganoderic acids T, S and R, new triterpenoids from the cultured mycelia of *Ganoderma lucidum*. *Chemical Pharmaceutical Bulletin* **34**, 2282-2285.

Hobbs, C. 1995. *Medicinal Mushrooms: An exploration of Traditional, Healing and Culture*. Santa Cruz, CA., Botanica Press.

Hokama, Y. and Hokama, J.L. 1981. *In vitro* inhibition of platelet aggregation with low Dalton compounds from aqueous dialysates of edible fungi. *Research Communications in Chemistry, Pathology and Pharmacology* 31, 17-180.

Hu, T.X. and Chen, J.W. 1992 Effects of polysaccharide-peptide of *Coriolus* and polysaccharide of *Ganoderma* on scavenging active oxygen species. *Acta Biochimica Biophysica Simca* **24**, 465-470.

Ishikawa, K. January 23, 1991. Anti-HIV activity in cytopathic effects of proteoglucan extracted from maitake mushroom. *National Institute of Health* (Japan).

Ito, W. and Sugawara, I. 1990. Immunopharmacological study of sulfated schizophyllan (SPG). 1. Its action as a mitogen and anti-HIV agent. *International Journal of Immunopharmacology* **12**, 225-233.

Jong, S.C. and Donovick, R. 1990. Antitumour and antiviral substances from fungi. *Advances in Applied Microbiology* **34**, 183-262.

Kabir, Y. and Kimura, S. 1989. Dietary mushrooms reduce blood pressure in spontaneously hypertensive rats. *Journal of Nutritional Science and Vitaminology* **35**, 91-94.

Kakuma, S. 1991. Effect of schizophyllan, a polysaccharide, on interferon gamma antibody production and lymphocyte proliferation specific for hepatitis B virus antigen in patients with chronic hepatitis B. *International Journal Immunopharmacology* **13**, 969-975.

Kiho, T., Morimoto, H., Sakushima, M., Usui, S. and Ukai, S. 1995. Polysaccharides in fungi. XXXV. Anti-diabetic activity of an acidic polysaccharide from the fruiting bodies of *Tremella aurantia. Biological and Pharmaceutical Bulletin* **18**, 1627-1629.

Kiho, T., Merimoto, H., Kobayashi, T., Usiu, S., Ukai, S., Aizawa, K. and Inakuma, T. 2000. Effect of polysaccharide (TAP) from the fruiting bodies of *Tremella aurantia* on glucose metabolism in mouse liver. *Bioscience, Biotechnology and Biochemistry* 64, 417-419.

Kim, H.W. and Kim, B.K. 1999. Biomedical triterpenoids of *Ganoderma lucidum* (Curt.:Fr.) P. Karst. (Aphylopharomycetideae). *International Journal of Medicinal Mushrooms* **1**, 121-138.

Kim, M.W., Park, M.H. and Kim, G.H. 1997. Effects of mushroom protein-bound polysaccharides on the blood glucose levels and energy metabolism in streptozotocin-induced diabetic rats. *Journal of Korean Nutrition* **30**, 743-750.

Kim, O-H, Yang, B-K., Hur, N-I., Das, S., Yun, J-W., Choi, Y-S. and Song, C-H. 2001. Hypoglycemic effects of mycelia produced from submerged culture of *Phellinus linteus* (Berk. Et Curt) Teng (A phyllopharomycetideae) in streptozotocin-induced diabetic rats. *International Journal of Medicinal Mushrooms* **3**, 21-26.

Kobayashi, H. and Kariya, K. 1994. Suppressive effects on cancer cell proliferation of the enhancement of superoxide dismutase (SOD) activity associated with the protein-bound polysaccharide of *Coriolus versicolor* Quel. *Cancer Biotherapy* **9**, 171-178.

Koichi, A. and Takahiro, I. 1999. Antihypercholesterolemic agent, hypocholesterolemic agent and agent for preventing and treating arteriosclerosis. JP Patent No. 11193244 published 21.07.1999.

Li, M. and Lei, L.S. 2000. Effect of *Ganoderma lucidum* polysaccharides on oxygen-free radicals in murine peritoneal macrophages. *Zhongguo Yadikxue Yu Dulixue Zazhi – Chinese Journal of Pharmacology and Toxicology* **14**, 65-68.

Liu, F., Ooi, V.E.C. and Chang, S.T. 1997. Free radical scavenging activities of mushroom polysaccharide extracts. *Life Sciences* **64**, 1005-1011.

Matsuyama, H., Mangindaan, R.E.P. and Yano, T. 1992. Protective effect of schizophyllan and scleroglucan against *Streptococcus* sp. infection in yellow tail (*Seriola quinqueradiata*). *Aquaculture* **101**, 97-203.

Mizuno, T. 1995. Bioactive biomolecules of mushrooms: food function and medicinal effect of mushroom fungi. *Food Reviews International* **11**, 7-21.

Onderdonk, A.B., Cisneros, R.L., Huakson, P.L. and Ostroff, G.R. 1992. Anti-infective effect of poly β 1-6 glucotriosyl-β-103-glucopyranose glucan *in vivo*. *Immunology* **60**, 1642-1647.

Ooi, V.E.C. 2000. Medicinally important fungi. In: *Science and Cultivation of Edible Fungi*. Van Griensven (ed). Pp. 41-51. 2000 Balkema, Rotterdam.

Ooi, V.E.C. and Liu, F. (1999). A review of pharmacological activities of mushroom polysaccharides. *International Journal of Medicinal Mushrooms* **1**, 195-206.

Pan, J.H. *et al*. 1998. Preventative effects of *Ganoderma lucidum* on the radical injury induced by adriamycin. *Pharmacological Clinical Chinese Materia Medicine* **14**, 27-28.

Todwell, V.W., Nordstrom, J.L. and Mitschelen, J.J. 1976. Regulatin of HMG-CoA reductase. *Advances in Lipid Research* **14**, 1-74.

Ryong, L.H. and Tertov, V.V.1989. Antiatherogenic and antiatherosclerotic effects of mushroom extracts revealed in human aorta intima cell culture. *Drug Development Research* **17**, 109-117.

Sakagami, H. and Takeda, M. 1993. Diverse biological activity of PSK (Krestin), a protein bound polysaccharide from *Coriolus versicolor*. In *Mushroom Biology and Mushroom products*. Chang, S.T., Buswell, J.A. and Chiu, S.W. eds. Chinese University Press, Hong Kong, 237-245.

Sakagami, H. and Aoki, T. 1991. Induction of immunopotentiation activity by a protein-bound polysaccharide, PSK (Review). *Anticancer Research* **11**, 993-1000.

Salvimini, D., Wang, Z.Q., Bourdon, D.M., Ster, M.K., Currie, M.C. and Manning, P.T. 1996. Evidence of peroxinitrite involvement in the carrageenan induced rat paw oedema. *European Journal of Pharmacology* 303, 217.

Sarkar, S. 1993. Antiviral effect of the extract of culture medium of *Lentinus edodes* on the replication of the herpes simplex virus type 1. *Antiviral Research* **20**, 293-303.

Sheng, J.H. and Chen, Q.H. 1989. Antilipemic effect of polysaccharides from A*uricularia aurantia, Tremella fuciformis* and *T. fuciformis* spores. *Journal of China Pharmaceutical University* 20, 344-347.

Soo, T.S. 1994. The therapeutic value of *Ganoderma lucidum*. *8th International Mycological Congress (IMC5) Abstracts*, Vancouver, B.C., p. 95.

Suay, I. and Arenal, F. 2000. Screening of Basidiomycetes for antimicrobial activities. *Antonie van Leeuwenhoek* **78**, 129-139.

Sugiyama, K. and Yamakawa, A. 1996. Dietary eritadenine-induced alteration of molecular species composition of phospholipids in rats. *Lipds* **31**, 399-404.

Susuki, S. and Ohshima, S. 1974. Influence of shiitake *Lentinus edodes* on human serum cholesterol. *Annual Report of National Institute of Nutrition* **25**, 89-94.

Tao, E.X. 1993. The effect of *Ganoderma lucidum* on the cellular immunological functions in the elderly. *Chinese Journal of Geriatrics* **12**, 298-310.

Tao, S. and Feng, K.A. 1991. Influence of *Ganoderma lucidum* on platelet aggregation of 15 healthy volunteers and 33 senile or presenile patients. *Acta University Medical Tong Ji*. **20**, 186-188.

Tsukagoshi, S. 1984. Krestin (PSK). *Cancer Treatment Reviews* **11**, 131-155.

Ukai, S., Kohi, T., Hara, C., Kuruma, I. and Tanaker, Y. 1983. Polysaccharides in fungi: XIV. Antiinflammatory effect of the polysaccharides from the fruit bodies of several fungi. *Journal of Pharmacology Dynamics* 6, 983-990.

U.S. National Cancer Institute. January 17, 1992. *In vitro* anti-HIV drug screening results, development therapeutics program.

Wasser, S.P. and Weis, A.L. 1999a. Medicinal properties of substances occurring in higher Basidiomycete mushrooms: current perspective. *International Journal of Medicinal Mushrooms* **1**, 31-62.

Wasser, S.P. and Weis, A.L. 1999b. Therapeutic effects of substances occurring in higher Basidiomycete mushrooms: a modern perspective. *Critical Review of Immunology* **19**, 65-96.

Willard, T. 1990. *Reishi Mushroom: Herb of Spiritual Potency and Medical Wonder*. Sylvan Press, Washington.

Xiu, R.J. 1996. Accelerated wound healing. US Patent No. 5547672 published 20.01.1996.

Yan, R. 1987. Treatment of chronic hepatitis B with Wulingdan pill. *Journal of Fourth Military Medical College* **8**, 380-383.

Yeung, J.H.K. 1995. Effect of polysaccharide peptide (PSP) on *in vivo* sulphation and glucuronidation of paracetamol in the rat. *European Journal of Drug Metabolism and Pharmacokinetics* **20**, 287-292.

Yuan, C. and Meiz, Z. 1996. PSK protects macrophages from lipoperoxide accumulation and foam cell formation caused by oxidatively modified low density lipoprotein. *Atherosclerosis* **124**, 171-181.

Yuan, Z., Hei, P.M., Cui, J.H. and Takeuchi, H. 1998. Hypoglycemic effect of water soluble polysaccharide from *Auricularia auricula-judae* Quel on genetic diabetic KK-Ay mice. *Bioscience, Biotechnology and Biochemistry* **62**, 1898-1903.

Yamamoto, Y. 1977. Immunopotentiating activity of the water-soluble lignin rich fractions prepared from LEM, the extract of the solid culture medium of *Lentinus edodes* mycelia. *Bioscience, Biotechnology and biochemistry* **61**, 1909-1912.

Yang, Q.Y. and Jong, S.C. 1989. Medicinal mushrooms in China. *Mushroom Science* (Part 1), 631-643.

Zhou, H.1989. Antihepatitis and antimutation effect of polysaccharides from *Tremella fuciformis* and *Auricularia auricula*. *Zhongguo Yoaoke Duxue Xuebao* **20**, 51-53.

Zhu, X. 1985. Treatment of chronic viral hepatitis B and HBSAG carriers with polysaccharides of *Lentinus edodes*. *Jiangxi Zhongyiyao* **5**, 20-25.

Zhuang, C. and Mizuno, T. 1999. Biological responses from *Grifola frondosa* (Dick.: Fr.) S.F. Gray – Maitake (Aphyllophoromycetideae). *International Journal of Medicinal Mushrooms* **1**, 317-324.