

MEDICAL BENEFITS OF MEDICINAL MUSHROOMS

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ABSTRACT

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

1. INTRODUCTION

Historically, the larger fungi, the mushrooms, have had a long and successful medicinal use especially in traditional Chinese clinical medicine for many forms of human illness with particular emphasis on immune disorders [1, 2, 3]. Chinese Pharmacopeias document the use of well over 100 species of mushrooms by practitioners of TCM for a wide range of ailments [4, 5]. Many of these mushroom-derived medicinal products are now produced by major Japanese, Chinese and Korean pharmaceutical companies. Increasingly, many of these products are being used worldwide by holistically-oriented physicians, chiropractors, herbalists and naturopathic physicians in a clinical environment. To date, Western medicine has made little use of such products in part due to their complex structure, lack of acceptable pharmaceutical purity and inconsistent methods of production.

In 2000 Cancer Research Campaign (now called Cancer Research UK) commissioned a Report [8] recently published to examine and collate the current scientific and medical literature pertaining to the efficacy and safety of these compounds with special emphasis on cancer treatments [8]. This report specifically made no recommendations but rather aimed to present a holistic coverage of an immensely complex scientific and medical area covering the historical evolutionary methods of large-scale production, clinical analyses of the medicinal compounds, interaction with the animal and human immune system, current status in cancer research and clinical practice and, above all, a full examination of the overall safety data.

Mushrooms are not a taxonomic group but do include well over 12,000 species which have macroscopic fruit-bodies, the mushrooms, which are large enough to be seen by the naked eye. Mushrooms are increasingly being evaluated in the West for their nutritional value and acceptability as well as their pharmacological properties. Increasingly, many are being viewed nutritionally as functional foods as well as a source of physiologically-beneficial and non-invasive medicines, while others are distinctly non-edible but considered purely as a source of medicinally-beneficial compounds. Some of the more recently isolated and identified compounds originating from the medicinal mushrooms have shown promising immunomodulatory, antitumour, cardiovascular, antiviral, antibacterial, antiparasitic, hepatoprotective and antidiabetic properties [1, 2, 6, 7]. Modern scientific studies of the medicinal mushrooms have expanded exponentially during the last two decades primarily in Japan, Korea and China but also in the USA and scientific explanations of how these

compounds function in the animal and human systems are increasingly appearing in peer-reviewed scientific and medical journals.

While the Report [8] concentrated on the immunomodular and anti-cancer activities of certain medicinal mushrooms, emphasis was also given to other significant medical properties such as blood-pressure lowering, cholesterol lowering, liver protective, antifibrotic, anti-inflammatory, anti-diabetic and other anti-microbial activities. These aspects of the Report are now presented in this review paper with permission of Cancer Research UK, the major cancer research body in the United Kingdom. Other aspects of the Report have been published or are in press [9, 10, 11].

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 (LDL) 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) [12]. 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 [1, 13].

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 [14].

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 hypocholesterolemia [15]. The genus *Pleurotus* of the medicinal mushrooms has several species that produce mevinolin [16]. *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. saeva* and in the surface fermentation broth of *P. sapidus* [17].

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 HDL, reduced production of VLDL and LDL cholesterol, reduced cholesterol absorption and reduced HMG-CoA reductase activity in the liver [18]. Limited clinical trials with 15-20 g dried *Pleurotus* supplement in the daily diet over a one-month period reduced hypercholesterolemia in many but not all patients. It has been suggested that *Pleurotus* mushrooms could be recommended as a natural cholesterol lowering substance within the human diet [3]. Somewhat similar results have been achieved with *Grifola frondosa* and *Auricularia auricula* [19].

Antilipemic effects of polysaccharides from *Tremella fuciformis* and *T. aurantia* have been shown to lower plasma cholesterol levels [20, 21], while an antihypercholesterolemic agent has been produced from fruit bodies and mycelium of *T. aurantia* [22].

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 [23]. 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 [24]. It has been suggested that high dosages of eritadenine 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 [25]. 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 [1].

Nucleic acids from *L. edodes* also have significant platelet agglutinating inhibitory effects (antithrombotic activity). PSK also decreases LDL cholesterol in hyperlipidemia patients.

A recent review of literature by Francia *et al.* [26] 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 [27]. 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.* [26]. Many of these extracts have long been used in traditional Chinese medicine for treating various cardiovascular disorders [1].

Table 1. Effects of macrofungi on lipids and cholesterol [Seven fungi had an effect on lipids in general and cholesterol in particular][26]

1.	Six species reduced total cholesterol level <i>Auricularia auricula – judae</i> <i>Cordyceps sinensis</i> : the activity could be due to a polysaccharide, the CS- F30, composed of galactose, glucose and mannose. <i>Ganoderma lucidum</i> <i>Grifola frondosa</i> <i>Pleurotus ostreatus</i> <i>Tremella fuciformis</i>
2.	Two species reduced the 'bad cholesterol' level <i>Auricularia auricula – judae</i> <i>Tremella fuciformis</i>
3.	Three species reduced the triglyceride level <i>Cordyceps sinensis</i> <i>Grifola frondosa</i> <i>Lentinus edodes</i>
4.	<i>Agaricus campestris</i> : demonstrated no hypocholesterolemic activity.

Table 2. Macrofungi reducing blood platelet binding [Six species reduced platelet binding (in vitro)] [26]

<p><i>Auricularia auricula-judae</i> <i>Calyprella</i> sp: the active compound is the 5-hydroxy-3-vinyl-2 (5H) – furanone. <i>Ganoderma lucidum</i>: the binding activity is due to adenosine. <i>Kuehneromyces</i> sp: the active compound is kuehneromycine B. <i>Neolentinus adhaereus</i>: the active compound is 2-methoxy-5-methyl-1,4 benzoquinone. <i>Panus</i> sp: the activity is due to two compounds, panudial and nematolon.</p>
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Table 3. Macrofungi with an arterial blood pressure lowering effect [Three fungal species reduced the arterial pressure] [26]

<p><i>Ganoderma lucidum</i> <i>Grifola frondosa</i> <i>Tricholoma mongolicum</i>: the decrease of arterial pressure attributable to a lectin.</p>

Table 4. Macrofungi reducing glycemia [Six species appeared to decrease glycemia] [26]

1.	<p>Four species were active in insulin-dependent-diabetes. <i>Agaricus bisporus</i> <i>Agrocybe aegerita</i>: 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. <i>Cordyceps sinensis</i>: could be due to the CS-F30, a polysaccharide composed of galactose, glucose and mannose. <i>Tremella aurantia</i>: the active compound is the TAP (<i>Tremella</i> acidic polysaccharide).</p>
2.	<p>One species was active in non-insulin-dependent-diabetes. <i>Grifola frondosa</i>: this mushroom is able to diminish glycemia but also insulemia and the blood level of triglycerides.</p>
3.	<p>One species showed an activity only in non-diabetic animals. <i>Coprinus comatus</i>.</p>

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 [3]. Extracts of several medicinal mushrooms, including *Tremella aurantia*, '*Cordyceps sinensis*', *Ganoderma lucidum* and *Auricularia auricula-judae* have been shown to lower blood glucose [29, 30, 31]. 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 [32, 33]. Such results strongly suggest that these mushrooms have potential preventive and therapeutic action in diabetes mellitus (types 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. Several mushroom polysaccharides have shown antiviral activity against ectromelia virus and cytomegalovirus infections [34]. 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 japonicum*, *Sch. mansoni*; (e) exhibited activity against *Mycobacterium tuberculosis* bacilli resistant to antituberculosis drugs, *Bacillus subtilis*, *Staphylococcus aureus*, *Micrococcus luteus*, *Candida albicans* and *Saccharomyces cerevisiae*; (f) increased host resistance to infections with potentially lethal *Listeria monocytogenes* (for original references see Wasser and Weis [2]).

LEM and a new lignan-rich compound JLS-18 derived from LEM block the release of infectious *Herpes simplex* virus in animals 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 [35].

Sulfated Schizophyllan polysaccharide displayed strong anti-HIV activity while the anti-tumour effect was reduced or lost [36]. Schizophyllan has also been reported to enhance protection against *Staphylococcus* sp. infection [37].

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 [38, 39]. Interestingly, *G. frondosa*, D-fraction together with dimethyl sulfoxide (DMSO) has also shown success in treating AIDS associated Kaposi sarcoma [40].

PSK has been shown to induce potent antimicrobial activity against *Escherichia coli*, *Listeria monocytogenes* and *Candida* [41, 42].

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 [43]. 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 [44].

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 displayed a high broad spectrum antibiotic activity [45].

Researchers have shown that a water extract of *L. edodes* demonstrated growth-enhancing effects on colon-inhabiting beneficial lactic acid bacteria, *Lactobacillus brevis* and *Bifidobacterium brevis*. 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 [46].

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.

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) [47]. Three separate multicentre (including Harvard Medical 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 [48]. In a second study, patients given β -glucan had 1.4 infections per patient vs. 3.4 infections in the placebo group [49]. In a further study involving 1,249 patients the β -glucan-treated patients showed a statistically significant (39 %) reduction in serious infections and death compared with placebo. 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 [51]. There is also growing evidence to show that production of ROS at the site of inflammation can contribute to tissue damage [52]. Interventions against ROS could exert beneficial effects on inflammation and shock. Several mushroom species have been studied for anti-inflammatory and antioxidant activities [53] and patents have been established for these usages [54].

Extracts of *G. lucidum* can apparently remove the hyperoxide radical believed to be a main factor in the human ageing process [55] and the ageing mouse model [56]. 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.

A *Ganoderma lucidum* polysaccharide GLB7 decreased the production of oxygen free radicals and antagonised the respiratory burst induced by PMA in murine peritoneal macrophages [58]. 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 [59]. PSK further

repressed the mimetic activity of superoxide dismutase (SOD) and promoted oxidative stress relief for cancer-bearing hosts [60]. PSK also gave protection to macrophages from lipoperoxide accumulation and foam cell formation created by oxidatively modified low-density lipoprotein [61]. This protection is believed to be due to the induction of gene expression of antioxidative enzymes. PSP shows similar scavenging effects on superoxide and hydroxyl radicals [62]. Significant superoxide and hydroxyl radical scavenging activities have been demonstrated for several mushroom antitumour polysaccharides [55].

Hepatoprotective effects

Fruit-bodies of *Ganoderma lucidum* have long been a major factor in folk medicine for the treatment of chronic hepatitis [28]. 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. Another hepatoprotective compound, ganosporic acid A, was isolated from the ether-soluble fraction of the spores of *G. lucidum* [64]. The wide spectrum of medical efficacies of *Ganoderma lucidum*, including hepatoprotective activities, is shown in Table 5.

A polysaccharide fraction from *L. edodes* showed liver protective action in animals together with improved liver function and an enhanced production of antibodies to hepatitis B [66]. Lentinan and LEM have given favourable results in treating chronic persistent hepatitis and viral hepatitis B patients. Extracts of *G. lucidum* have shown good results in treating hepatitis, particularly in cases without severe liver impairment [67]. A clinical study with lyophilised extract of *G. lucidum* showed highly beneficial results on quality of life with patients suffering from active hepatitis B [68].

There have been other interesting medical reports relating to marked improvement in patients suffering from cirrhosis of the liver and chronic hepatitis B with extracts from *Dendropolyporus umbellatus* [69], *Schizophyllum commune* [70], *Trametes versicolor* [71]. PSP may, thus, be useful in the wider context of the treatment of hepatitis [72].

This paper 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 outside cancer and immunotherapy.

Table 5. Medical efficacies of *Ganoderma lucidum* [65][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
	3 β , 5 α -Dihydroxy-6 β -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	Ganoderic acids T, V, W, X, Y, Z
	3 β -Hydroxy-26-oxo-5 α -lanosta-8,24-dien-11-one
	Ergosta-7,22=diene-3 β , 3 α ,9 α -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-5 α ,8 α -ergosta-6,22E=dien-3 β -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

^aFPT : farnesyl protein transferase

^bPLA₂: phospholipase A₂

^cDNA pol: DNA polymerase

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