2nd edition
Updated and expanded

Medicinal Mushrooms

A Clinical Guide

by Martin Powell

mycology press

Medicinal Mushrooms

A Clinical Guide

2nd Edition

Martin Powell

mycology press

Contents

Introduction

Understanding Mushroom Products

Fruiting Body/Conk/Sclerotium
Extracts
Spores
Mycelium
Mycelial Biomass
Combination Products

Prescribing Medicinal Mushrooms

Side effects
Candidiasis or other fungal conditions
With conventional treatment
With other nutritional supplements
While pregnant or breastfeeding

Medicinal Mushrooms

Agaricus subrufescens Agaricus brasiliensis Agaricus blazei
Antrodia camphorata/Antrodia cinnamomea
Armillaria mellea (Honey Mushroom)
Auricularia auricula/Auricularia polytricha (Wood Ear)
Coprinus comatus (Lawyer's Wig / Shaggy Inkcap)
Cordyceps species
Flammulina velutipes (Enokitake)
Ganoderma lucidum (Reishi)
Grifola frondosa (Maitake)
Hericium erinaceus (Lion's Mane)

Inonotus obliquus (Chaga)
Lentinula edodes (Shiitake)
Phellinus linteus (Mesima)
Pleurotus ostreatus (Oyster Mushroom)
Polyporus umbellatus/*Grifola umbellata*
Poria cocos
Sparassis crispa (Cauliflower Mushroom)
Trametes versicolor/*Coriolus versicolor* (Turkey Tail)
Tremella fuciformis (Snow Fungus)

Medicinal Mushrooms in Cancer Therapy

Medicinal Mushrooms and Chemotherapy
Medicinal Mushrooms and Radiotherapy
Medicinal Mushrooms and Surgery
Cancer Prevention
- Bladder Cancer
- Brain Cancer
- Breast Cancer
- Cervical Cancer
- Colorectal Cancer
- Endometrial Cancer
- Gastric Cancer
- Leukaemia
- Liver Cancer
- Lung Cancer
- Lymphoma
- Ovarian Cancer
- Pancreatic Cancer
- Prostate Cancer

Medicinal Mushrooms for Other Conditions

Appendix, Glossary, Index and Additional Resources

Preface

The use of medicinal mushrooms is one of the most exciting areas of natural health, offering significant therapeutic benefit, supported by a long history of traditional use and increasing scientific evidence. However, many questions remain to be addressed if it is to fulfil its potential[1].

In particular the lack of standardisation of mushroom products and lack of comparative clinical research remain significant obstacles to more widespread use.

Given the fact that research has to be paid for, it is perhaps inevitable that most is designed to show the widest range of activity, and therefore sales opportunities, for individual mushroom products, rather than provide the information that clinicians need to decide:

- Which is the best mushroom or combination of mushrooms for my patient?
- What is the best form to give it in - extract or whole mushroom - mycelia or fruiting body?
- What dosage is therapeutically effective?

This book sets out to address these questions and it is my hope that it will assist practitioners and patients alike by providing at least partial answers.

The variable quality of much of the available information, together with the lack of standardisation among mushroom products and the extensive overlap of functionality between different mushrooms, means that there will inevitably be room for differences of opinion regarding the answers to the above questions.

As well as suggesting answers, I have therefore given an overview of the research so that readers can evaluate it for themselves and draw their own conclusions.

In putting the book together I have tried at all times to maximise its usability. A Quick Reference section is included at the beginning with brief summaries of individual mushrooms' main therapeutic application(s) and active constituents, and of the mushroom(s) commonly used for specific conditions, with suggested dosage formats.

In addition to the quick reference section, the book is divided into four parts:

- Introduction to medicinal mushrooms and mushroom products
- Individual monographs on the therapeutic potential of the major medicinal mushrooms
- Discussion of the use of medicinal mushrooms in cancer treatment
- Survey of the clinical application of medicinal mushrooms for other clinical conditions

There is also an appendix on the energetics of mushrooms in traditional Chinese medicine (TCM) for those practitioners trained in this approach.

Additional Comments on the Second Edition

Although it is only four years since the first edition was published, those four years have seen considerable advances in our understanding of medicinal mushrooms and their therapeutic value making a second edition timely.

As well as updating the information contained in the book in the light of recent research and expanding areas where feedback has indicated that a more detailed treatment was required I have included discussion of the use of mushrooms in several new conditions. I have also added two additional mushrooms and expanded the sections on others to more fully reflect their clinical use.

Acknowledgements

Despite my training as a TCM practitioner, my early attitude to mushrooms was very much shaped by my parents' warning on walks in the forest: 'Don't touch the mushrooms' and I would like to thank Michael Hsieh of Double Crane Enterprises, Taiwan for first introducing me to the therapeutic possibilities of mushrooms and starting me down the road to embracing them.

Many people have helped in the preparation of this book but I would especially like to thank my wife and family for their patient support and tolerance during its preparation, Gao Yufeng for her help with Chinese translation, Professor Godfrey Chan of The University of Hong Kong for his generous permission to use the images on pages 14 and 15, Well Shine Biotechnology (*Antrodia camphorata*), Umberto Pascali (*Armillariamellea*), Gerhard Schuster (*Polyporus umbellatus*) and Dr Frankie Chan (*Phellinus linteus*) for permission to use their mushroom images and Peter Deadman of the Journal of Chinese Medicine and Jo Dunbar for their suggestions on making the text more accessible.

Lastly I would like to thank the many practitioners who encouraged me in my efforts and to whom this book is dedicated.

A Note on Mushroom Names

Mushroom nomenclature is a complex area with alternative names in use for some medicinal mushrooms and others open to possible future review[1]. Although some mushrooms are more commonly referred to by alternative names (ie. Reishi for *Ganoderma lucidum*), I have decided for the sake of consistency to use the Latin name of each species.

Where alternative Latin names are in use for a given mushroom I have opted for the name used in the International Journal of Medicinal Mushrooms, except in the case of *Agaricus subrufescens* where this name is now considered correct in preference to the earlier names *Agaricus brasiliensis* and *Agaricus blazei*, and have noted alternative names where appropriate.

Martin Powell, Eastbourne September 2014

Disclaimer

This book is intended for use by qualified healthcare practitioners. The information it contains is presented for educational use only and is not meant to be used, nor should it be used, to diagnose or treat any medical condition. Anyone who is experiencing any symptoms, has been diagnosed with or suspects they may have a medical condition should contact a medical doctor or other appropriately qualified health professional. The reader should not assume that because an adverse reaction or interaction is not mentioned in this book the use of any given medicinal mushroom is always safe. If you suspect you could be experiencing an adverse reaction from a mushroom or a combination of mushroom(s) and drugs, you should immediately consult an appropriately qualified health professional. Likewise, you should always inform your healthcare provider of any supplements you may be taking. Both the author and publisher accept neither liability nor responsibility to any person with respect to loss, injury or damage caused, or alleged to be caused, directly or indirectly by the information contained in this book.

Quick Reference – Mushrooms

As well as indicating the key areas of clinical use for each mushroom I have suggested preferable dosage form(s) as consideration of this area is important for maximising clinical efficacy. Further discussion of dosage forms can be found in Understanding Mushroom Products (pages 29-31).

Agaricus subrufescens

Cancer, hepatitis –Polysaccharide extract (cancer), mycelial biomass or extract / mycelial biomass combination

Antrodia camphorata

Liver disorders

Fruiting-body or mycelium

Armillaria mellea

Neurological disorders

Mycelium

Auricularia auricula/Auricularia polytricha

Cardiovascular health
Polysaccharide extract

Coprinus comatus

Cancer
Polysaccharide extract

Cordyceps species

Lung/Liver/Kidney support, infertility/sexual function, diabetes, energy – Mycelial biomass

Flammulina velutipes

Cancer prevention, allergies, viral infections
Fruiting body

Ganoderma lucidum

Cancer, allergies, insomnia
Aqueous extract/ethanolic extract

Grifola frondosa

Cancer, PCOS – Polysaccharide extract or polysaccharide extract/fruiting body combination

Hericium erinaceus

Dementia, Alzheimer's disease, MRSA, anxiety
Fruiting body or mycelial biomass

Inonotus obliquus

Cancer, viral infections, psoriasis
Aqueous extract/ethanolic extract

Lentinula edodes

Cancer, cholesterol control – Polysaccharide extract (cancer) or fruiting body (cholesterol control)

Phellinus linteus

Cancer, autoimmune disorders
Polysaccharide extract

Pleurotus ostreatus

Cholesterol control

Fruiting body or mycelial biomass

Polyporus umbellatus / Grifola umbellata

Cancer, hepatitis, fluid retention – Polysaccharide extract (cancer/hepatitis) or sclerotium (fluid retention)

Poria cocos

Fluid retention

Sclerotium

Sparassis crispa

Skin repair, cancer, stroke prevention

Fruiting body

Trametes versicolor/Coriolus versicolor

Cancer, CFS/ME, HIV – Polysaccharide extract (cancer), mycelial biomass or extract/mycelial biomass combination

Tremella fuciformis

Cardiovascular/neurological support, radiation exposure

Polysaccharide extract

Quick Reference – Conditions

This is not an exhaustive list of every mushroom that can be used for every condition, or of every dosage form that may be beneficial, but rather of which mushrooms and which dosage forms are most relevant for each condition. A fuller discussion of each condition is included in the last section, or in some cases under the mushroom entry itself.

Ps - For several conditions the beneficial effect of medicinal mushrooms is largely due to the ability of **mushroom polysaccharides** (beta-glucans/proteoglycans etc.) to modulate and increase the cytotoxic efficacy of our immune response. In these cases the fact that one mushroom or one dosage form shows efficacy does not mean that other mushrooms would not be at least as effective, or that dosage forms with higher concentrations of polysaccharides would not be more effective.

Without clear evidence for superior activity of a single mushroom it can be beneficial, given the increased immunological activity of multi-mushroom formulae, to use combinations of polysaccharide extracts from several mushrooms (see combination products, page 28).

Allergic Rhinitis (Hayfever)

- *Ganoderma lucidum* - extract (triterpene-rich) - 1-3g/day

Alzheimer's Disease

- *Hericium erinaceus* - fruiting body or mycelial biomass - 3-5g/day
- *Ganoderma lucidum* - extract - 1-3g/day

Anti-ageing

- *Ganoderma lucidum* - spores - 1-3g/day
- *Ophiocordyceps sinensis* - mycelial biomass - 1-3g/day
- *Sparassis crispa* - fruiting body - 1-3g/day
- *Tremella fuciformis* - polysaccharide extract - 1-3g/day

Asthma

- *Ophiocordyceps sinensis* - mycelial biomass - 3g/day
- *Ganoderma lucidum* - extract (triterpene-rich) - 1-3g/day

Benign Prostatic Hyperplasia (BPH)

- *Ganoderma lucidum* - extract (triterpene-rich) - 1-3g/day
- *Coprinus comatus* - extract - 2-3g/day

Cancer

All medicinal mushrooms show anti-cancer properties with large scale clinical trials of *Trametes versicolor* and *Lentinula edodes*, and on a smaller scale, *Grifola frondosa*, *Ganoderma lucidum* and *Agaricus subrufescens*. All clinical trials have used polysaccharide extracts. There is some evidence that combinations of mushrooms may have higher activity.

- Polysaccharide extracts - 3-6g/day
- *Ganoderma lucidum* - triterpene-rich extract - 2-5g/day or spore oil - 0.5-1.0g/day
- *Inonotus obliquus* - aqueous/ethanolic extract - 2-5g/day
- *Cordyceps militaris* - extract (cordycepin-rich) - 2-5g/day

Candidiasis

- *Lentinula edodes* - mycelial biomass - 2-3g/day

- *Trametes versicolor* - mycelial biomass - 2-3g/day

Cardiovascular Health

- *Auricularia auricula/polytricha* - polysaccharide extract - 1-3g/day
- *Ganoderma lucidum* - extract - 1-3g/day
- *Tremella fuciformis* - polysaccharide extract - 1-3g/day

Chronic Fatigue Syndrome (CFS - ME)

- Polysaccharide extracts - 1-3g/day
- *Trametes versicolor* - mycelial biomass - 2-3g/day

Dementia

- *Hericium erinaceus* - fruiting body or mycelial biomass - 3-5g/day

Depression

- *Hericium erinaceus* - fruiting body or mycelial biomass - 3-5g/day

Diabetes

- *Ophiocordyceps sinensis* - mycelial biomass - 3-5g/day

Epilepsy

- *Armillaria mellea* - mycelium - 3-5g/day
- *Ganoderma lucidum* - shell-broken spore powder - 3-5g/day

Erectile Dysfunction

- *Ophiocordyceps sinensis* - mycelial biomass - 3g/day

Exercise-induced Immune Suppression

- *Polysaccharide extracts* - 1-3g/day

Fluid Retention

- *Polyporus umbellatus* - sclerotium - 6-15g/day

Gastric Ulcer

- *Hericium erinaceus* fruiting body - 25g/day or mycelial biomass - 5-10g/day

Hepatitis

- Polysaccharide extracts - 1.5-3g/day
- *Ophiocordyceps sinensis* - mycelial biomass - 3g/day

Herpes

- Polysaccharide extracts - 1-3g/day

HIV

- Polysaccharide extracts - 1-3g/day
- *Trametes versicolor* - mycelial biomass - 2-5g/day

HPV

- Polysaccharide extracts - 1-3g/day
- *Trametes versicolor* - mycelial biomass - 3g/day

Hypercholesterolaemia

- *Pleurotus ostreatus* - fruiting body - 15-20g/day
- *Lentinula edodes* - fruiting body or mycelial biomass - 9-15g/day

Hypertension

- *Ganoderma lucidum* - triterpene-rich extract - 2-3g/day

Infertility

- *Cordyceps militaris* - fruiting body - 3g/day
- *Ophiocordyceps sinensis* - mycelial biomass - 3g/day

Inflammatory Bowel Disease

- Polysaccharide extracts - 2-6g/day

Influenza

- Polysaccharide extracts - 1-3g/day

Insomnia/Anxiety

- *Ganoderma lucidum* - triterpene-rich extracts - 1-3g/day

Kidney Damage

- *Ophiocordyceps sinensis* - mycelial biomass - 3g/day

Liver Damage

- *Ophiocordyceps sinensis* - mycelial biomass - 3g/day
- *Antrodia camphorata* - fruiting body 1g/day or mycelium 1-3g/day

Meniere's Syndrome

- *Armillaria mellea* - mycelium - 3-5g/day

MRSA

- *Hericium erinaceus* - fruiting body - 25g/day or mycelial biomass - 5-10g/day

Multiple Sclerosis

- *Hericium erinaceus* - fruiting body or mycelial biomass - 3-5g/day

Nerve Damage

- *Hericium erinaceus* - fruiting body or mycelial biomass - 3-5g/day
- *Ganoderma lucidum* - sporoderm-broken spores - 1-3g/day

Parasitic Infection

- Polysaccharide extracts - 2-3g/day

Parkinson's Disease

- *Ganoderma lucidum* - triterpene-rich extract - 3g/day
- *Flammulina velutipes* - fruiting body - 3-5g/day

Polycystic Ovary Syndrome (PCOS)

- *Grifola frondosa* - polysaccharide extract - 3g/day

Psoriasis

- *Inonotus obliquus* - aqueous/ethanolic extract - 2-3g/day

Renal Health

- *Ophiocordyceps sinensis* - mycelial biomass - 2-5g/day

Rheumatoid Arthritis

- *Phellinus linteus* - polysaccharide extract - 3g/day
- *Ganoderma lucidum* - triterpene-rich extracts - 1-3g/day

Skin Repair

- *Sparassis crispa* - fruiting body - 1-3g/day

Stroke

- *Sparassis crispa* - fruiting body - 2-5g/day

Introduction

Mushrooms have a long history of therapeutic use in many cultures around the world. In Europe their medicinal use was documented by Dioscorides in his great work *De Materia Medica* (55AD) and by Gerrard in his influential 'Herbal' (1663)[2]. However, nowhere have their therapeutic properties been explored as comprehensively as in China and the Chinese herbal classic, the *Shen Nong Ben Cao*, dating to around 200AD, includes a number of mushrooms still in common use today, among them:

- Ling Zhi (*Ganoderma lucidum* - Reishi)
- Fu Ling (*Poria cocos*)
- Bai Me Er (*Tremella fuciformis* - Snow fungus)
- Zhu Ling (*Polyporus umbellatus*)

All of these are classified in the 'Superior' category of herbs, herbs which are considered safe to take for long periods of time without side effects and of which it is said that prolonged use will 'lighten the body and confer longevity'. Indeed, *G. lucidum* has long been thought to be the plant *Chi* mentioned in a number of Taoist texts as a plant that brings happiness and immortality, although it is now believed that *Chi* and its classical categorisation according to six colours actually refers to a number of different species[3].

Over time the incorporation of mushrooms into the materia medica expanded so that in Li Shi Zhen's authoritative work, the *Ben Cao Gang Mu* (1578), 21 mushrooms are listed as having medicinal properties and the reverence with which medicinal mushrooms, especially *G. lucidum*, are held in Chinese culture is attested to by their extensive depiction in paintings, carvings and embroidery[4].

Table Screen Mounted with *G. lucidum.*
THE PALACE MUSEUM, BEIJING

Imperial Ruyi Sceptre decorated with *G. lucidum*
THE PALACE MUSEUM, BEIJING

Portrait of the Kangxi Emperor in Court Dress featuring *G. lucidum*-shaped cloud motif.
THE PALACE MUSEUM, BEIJING

One of the main areas in which mushrooms have traditionally been

used in the Far East is in the treatment of cancer and this led Japanese researchers in the 1960s to investigate their anti-tumour properties. Early animal studies quickly confirmed the ability of mushroom extracts to extend survival times in a range of cancers and ultimately led to large scale clinical trials of commercial mushroom extracts, such as those on PSK, a proteoglycan extract from *Trametes versicolor* :

Selected Clinical trials with PSK

CANCER TYPE	DATE	PATIENT NUMBERS	RESULT
Stomach Cancer Stage IV	1976	66	PSK doubled 2-yr survival after surgery and chemotherapy
Advanced Stomach Cancer with Metastases	1982	450	PSK doubled 5-yr survival after surgery and chemotherapy
Advanced Stomach Cancer with Metastases	1990	255	PSK extended 15-yr survival after surgery and chemotherapy
Colorectal Cancer	1990	110	PSK extended 8-yr survival and disease-free period after surgery
Lung (NSCLC) Stages I-III	1993	185	PSK extended 5-yr survival 2-4x for all stages after radiotherapy
Oesophageal	1995	158	PSK extended 5-yr survival and normalised serum factors after surgery, radiotherapy and chemotherapy
Breast Stages I, II	1995	227	PSK trend to extend 10-yr survival and disease-free period with 100% survival in patients +ve for HLA B40 antigen

After Kidd P, 2000[5].

The positive results from these trials clearly confirmed their therapeutic potential and saw their routine prescription as ‘host defence potentiators’, or ‘biological response modifiers’ (BRMs) alongside conventional cancer treatment in Japan and China with sales in Japan of PSK or ‘Krestin’ exceeding US$600 million annually and by 1993 accounting for 25% of expenditure on anti-cancer agents[5, 6].

Although the lack of a defined mode of action or single active

chemical entity led to the failure of attempts to obtain pharmaceutical licensing in Europe and the US, the therapeutic efficacy and commercial success of these extracts has generated considerable interest in the clinical use of medicinal mushrooms and their potential for helping address some of the most pressing health issues we face today, including cancer, dementia and autoimmune disease.

Members of the fungal kingdom

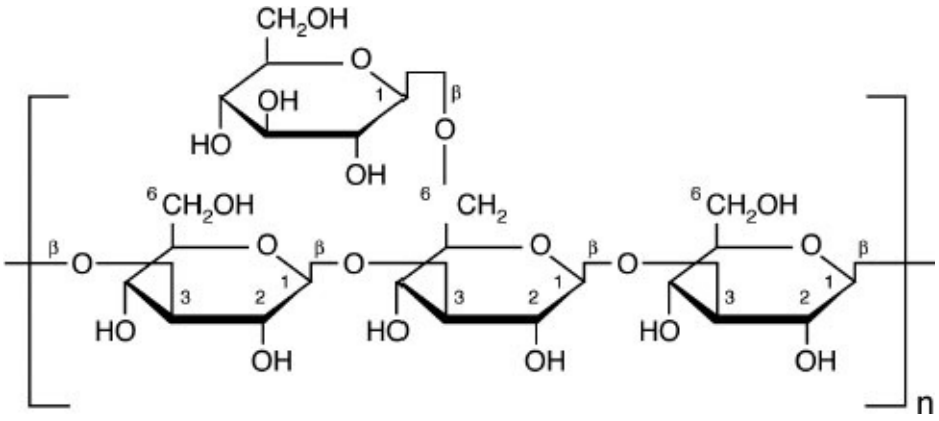
Neither plants nor animals, mushrooms form the most visible part of the fungal kingdom, being the above ground spore-bearing fruiting bodies of ‘higher fungi’. In the same way that some plants produce flowers as a means of reproduction, these fungi produce mushrooms as a means of disseminating their spores and colonizing new areas.

Although traditionally considered closer to plants, phylogenetic research has shown that fungi are in fact more closely related to animals[7]. Whereas plants derive carbon from carbon dioxide in the air and energy from sunlight through photosynthesis, both fungi and animals derive carbon and energy from the enzymatic breakdown of organic matter. While we as animals took the evolutionary route of ingesting food and breaking it down inside our bodies, fungi took the route of excreting enzymes into the surrounding substrate to break it down and then absorbing the smaller molecules resulting from the enzymatic hydrolysis.

Although metabolically closer to animals, structurally mushrooms are similar to plants. Like plants they possess a rigid cell wall formed largely of long sugar molecule chains (polysaccharides – ‘many sugars’) joined by beta linkages and hence resistant to degradation by our digestive enzymes, which are designed to deal with the alpha-linked polysaccharides (starch) that form much of our diet.

Unlike the cellulose in plant cell walls, which is formed by $\beta\ 1 \rightarrow 4$ linked glucose molecules (adjacent glucose molecules in the chain having bonds between the 1-position carbon of one molecule and the 4-position carbon of the next), in mushrooms the main polysaccharide

chain is typically β 1→3 linked with β 1→6 linked side chains, in other words a (1→3), (1→6) β-glucan.



Typical Fungal Beta-glucan. From Yanaki et al, 1983[8].

As will be discussed later, these mushroom polysaccharides have a significant impact on the immune system and the fact that they form an integral part of mushroom cell walls helps explain the broad immunomodulatory and anti-tumour activity observed in mushroom species.

Indeed, it is likely that most, if not all, of the classical mushrooms (fungi belonging to the class *Basidiomycota* that produce a spore-bearing fruiting body) contain pharmacologically active polysaccharides with polysaccharides from over 650 mushroom species already known to have anti-tumour activity[6].

In mushrooms the individual cells are joined together in long chains, or hyphae, which spread through the substrate on which the mushroom is growing, forming a tightly woven net or mycelium. The potential growth of the mycelium is limited only by the extent of the substrate and some soil growing mushrooms, such as *Armillaria* species, can cover an area of over a thousand acres (the largest reported to date covers an area of 2,400 acres in eastern Oregon, USA)[9].

The fungi's reproductive organs, their spore-bearing fruiting bodies or 'mushrooms', are then produced by the mycelium in order to propagate itself and spread to new sites, often in response to exhaustion of the substrate or other environmental stress.

Rich sources of pharmacologically active compounds

In common with other fungi, which are the source of several major pharmaceutical drugs, including major antibiotics such as penicillin and statins such as lovastatin, mushrooms produce a diverse array of compounds with widespread physiological activity.

In some cases these compounds are common to all mushrooms (and other fungi), *ie.* immunologically active beta-glucans and related polysaccharides, while others are restricted to one or a few species, *ie.* aromatic and diterpenoid compounds with the ability to stimulate production of nerve growth factor (NGF) found in *Hericium erinaceus*.

The major categories of pharmacologically active compounds found in mushrooms are discussed below with species-specific compounds covered under the individual mushrooms.

Polysaccharides (beta-glucans, proteoglycans and related compounds)

Water-soluble polysaccharides and related compounds form the major class of immunologically active molecule in mushrooms and other fungi and their action on the immune system has been extensively

reviewed[2,5,6].

Confusingly, several overlapping terms are in use: polysaccharides, proteoglycans (also called glycoproteins or protein-bound polysaccharides) and beta-glucans.

The term beta-glucan refers to the beta-linked glucose molecules that form the typical fungal polysaccharide. However, very few of the immunologically active polysaccharides from mushrooms are pure beta-glucans. Most are heteroglucans, containing other sugar molecules, such as galactose, xylose or mannose, as well as glucose.

Analysis of crude polysaccharide fractions from mushrooms also shows that all have some level of bound protein component (in the case of *Pleurotus citronopileatus*, the percentage of protein varies from 7-61%[6]).

Except where otherwise indicated I have therefore opted to use the broad term ‘mushroom polysaccharide’, including within it the beta-glucans, hetero-beta-glucans and proteoglycans/glycoproteins that fall under its umbrella and are present in mushroom polysaccharide extracts.

In contrast to the relatively inexpensive commercially available beta-glucans from yeast, mushroom beta-glucans have more diverse structures and, as a consequence, higher levels of immunological activity[7,8]. Of the mushroom polysaccharides reported to have immunological activity 77.5% are from mushroom fruiting body, 20.8% from mycelium and 2.0% from culture filtrate (broth).

The following table illustrates the structural diversity exhibited by some immunologically active polysaccharides from common medicinal mushrooms:

MUSHROOM	IMMUNOLOGICALLY ACTIVE POLYSACCHARIDES

Agaricus subrufescens	Various β-and α-linked glucans, Glucomannan, Riboglucan
Flammulina velutipes	Galactomannoglucan
Ganoderma lucidum	Mannogalactoglucan
Grifola frondosa	Xyloglucan, (1-6)-β-D-glucan with (1-3)-β-D-glucan side chains (MD fraction), Mannoxyloglucan, Mannogalactofucan
Hericium erinaceus	Glucoxylan, Xylan, Galactoxyloglucan, Mannoglucoxylan
Inonotus obliquus	Xylogalactoglucan
Lentinula edodes	(1-3)-β-D-glucan with (1-6)-β-D-glucosyl side chains (Lentinan), Galactoglucomannan
Trametes versicolor	Heteroglucans with α(1-4)- and β-(1-3) glycosidic linkages (with fucose in PSK and rhamnose and arabinose in PSP)
Tremella fuciformis	Glucoronoxylomannans (Tremellastin)

After Wasser SP, 2002[10]

Levels of anti-cancer activity appear to be related to degree of branching and to solubility in water, with higher solubility and a greater degree of branching being associated with higher activity (most active polysaccharides have degrees of branching between 0.20 and 0.33, *ie.* one side chain for every 3-5 main chain sugar units)[13].

It has also been suggested that activity may be related to molecular weight, although this may be connected to the means of administration with higher molecular weight polysaccharides from *Lentinula edodes* showing greater activity when delivered by injection. Other studies however, indicated greater activity for lower molecular weight polysaccharides from *Tremella fuciformis*, while a beta-glucan from *Agaricus subrufescens*, which showed anti-tumour activity when delivered by injection but was found to be ineffective by oral administration, became highly effective orally after acid hydrolysis to produce shorter chains of c.10kDa size[14, 15].

Higher levels of structure have also been investigated as possible determinants of biological activity with evidence that a triple-helical structure may be a contributing factor in the activity of some mushroom polysaccharides[10].

Recent research indicates that mushroom polysaccharides have a prebiotic effect on the gut microbiome with increases in *Bifidobacterium* and *Lactobacillus* species and decreases in *Clostridium*, *Staphylococcus* and *Enterococcus* species, together with increased concentration of organic acids (lactate and short-chain fatty acids), decreased pH and increased β-galactosidase and β-glucosidase activity and it has been suggested that this effect may also contribute to their diverse health benefits[16,17].

Proteins

As well as forming part of protein-bound polysaccharides, several mushroom proteins, including Ling Zhi-8 (LZ-8) from *Ganoderma lucidum* (Reishi) and Fve, EA-6 and Flammulin from *Flammulina velutipes* (Enokitake), have demonstrated biological activity in their own right[18-20], including:

- Immune modulation - mushroom proteins have been shown to act

directly on monocytes and to effect T-cell activation

- Ribosome inactivation - several exhibit ribosome inactivating activity
- Anti-viral - Velutin from *F. velutipes* inhibits HIV reverse transcriptase
- Anti-fungal - some have direct anti-fungal action
- Nuclease activity - a large number of proteins and peptides from mushrooms show nuclease activity
- Lectins have been isolated from many mushroom species, including *F. velutipes*, *Grifola frondosa* and *G. lucidum*[21],[22]

Proteins from *F. velutipes* have also been shown to have anti-allergic properties and to increase immune response to vaccination[23].

Triterpenes

Most triterpenes are highly biologically active and those found in mushrooms are no exception. The families of ganoderic and lucidenic acids from *Ganoderma lucidum* are the best known and are responsible for many of *G. lucidum's* unique therapeutic properties, having, among others, anti-cancer, anti-inflammatory, anti-histamine, hypotensive and sedative actions[24].

Another mushroom in which terpenoid compounds are important is *Inonotus obliquus*, which contains derivatives of betulin and betulinic acid from the bark of the host birch trees on which it grows. As with *Ganoderma lucidum* 's triterpenes betulin and betulinic acid demonstrate a wide range of biological activity including anti-cancer, anti-inflammatory and anti-viral properties[25].

High levels of triterpenes are also a major contributor to the therapeutic properties of the unique Taiwanese mushroom *Antrodia*

camphorata[26].

Phenols

High levels of phenolic components are found in certain mushrooms, especially *Inonotus obliquus*. Although polyphenols are known to be powerful antioxidants (the antioxidant activity of different mushrooms has been shown to be strongly correlated with their total concentrations of phenolic compounds[27]) recent publications have cast doubt on the relevance of the antioxidant properties of polyphenolic compounds such as flavonoids because of the low concentration achieved at a cellular level[28].

Instead it has been suggested that their physiological activity is a consequence of their effect on cell-signalling pathways (signal transduction pathways)[29].

Sterols

Mushrooms produce a number of sterols, principally ergosterol, with *H. erinaceus* fruiting bodies containing 381mg/100g ergosterol. In animal studies ergosterol has demonstrated activity against a number of different tumours as well as specific anti-angiogenic properties[30-32]. In addition, ergosterol derivatives have been reported to have anti-ageing activity on a par with that of resveratrol[33].

Although ergosterol is converted into ergocalciferol, vitamin D2, on exposure to UV light or γ-irradiation, few if any supplements are produced from mushrooms exposed to sunlight and, in the absence of UV exposure, levels of vitamin D are not significant.

Statins

First isolated from species of the fungus *Aspergillus*, lovastatin is also produced by many mushrooms because of the competitive advantage they derive from its strong anti-fungal properties[34,35].

Mushrooms with high levels of lovastatin include *Pleurotus* species and *Ganoderma lucidum*, with higher levels reported in the mycelium than the fruiting body[36,37].

Indole Compounds

A number of mushrooms including *Armillaria mellea* and *Pleurotus ostreatus* have been shown to produce indole compounds. These include L-tryptophan, 5-HTP and serotonin and it is likely that they may contribute to the reported neurological and anti-spasmodic effects of *A. mellea* in particular[38,39].

Chitin

The second most abundant polysaccharide in nature (after cellulose), chitin is a primary component of fungal and some bacterial cell walls, as well as the exoskeletons of insects, arachnids (spiders) and crustaceans. It is composed of beta 1,4 linked glucose units with attached acetylamine groups.

Chitin has demonstrated complex and size-dependent effects on innate and adaptive immune responses, including the ability to recruit and activate innate immune cells and induce cytokine and chemokine production via a number of cell surface receptors, including macrophage mannose receptor, TLR-2 and Dectin-1[40]. It has also demonstrated anti-bacterial and antioxidant activity and has been shown to help speed wound healing[41-43].

As some chitin derivatives are known to be non-toxic, non-allergenic and non-biodegradable, they are widely used in the

manufacture of prostheses such as artificial skin, contact lenses and surgical stitches. However, chitin is also a common component of allergy-triggering allergens, including those in shrimp, crab and house dust mite, and may be involved in the allergic reaction to eating mushrooms seen in a small number of people[44, 45].

Enzymes

Mushrooms produce a diverse array of enzymes, including digestive enzymes (proteases, lipases, etc.) and antioxidant enzymes (laccase, catalase, superoxide dismutase (S.O.D.), etc.), and it has been suggested that the enzymatic activity of mushrooms may contribute to the therapeutic activity of fruiting body/mycelial biomass dosage forms. S.O.D. is acid-labile however, and has been shown to have no bio-availability when delivered orally, even when administered as enteric-coated capsules[46].

Tyrosinase is found in some mushrooms and has been shown to exert a genoprotective effect *in vitro*[47].

Mushroom polysaccharides - Essential nutrients for our immune system?

Polysaccharides are not the sole category of therapeutically active compound present in mushrooms but they are the most widespread and, in many but not all mushrooms, the most important with a profound impact on the immune system mediated by a number of fungal polysaccharide-specific receptors on the surface of several classes of immune cell, including:

- Dectin-1 - expressed on macrophages, monocytes, neutrophils and dendritic cells
- CR3 - expressed on neutrophils and NK Cells
- TLR - expressed on macrophages, monocytes and dendritic cells
- SIGNR1 - expressed on macrophages and dendritic cells
- LacCer - expressed on neutrophils
- Scavenger - expressed on neutrophils

The fact that so many key categories of immune cells are hard-wired to respond to the presence of fungal polysaccharides is almost certainly a consequence of our immune system having evolved under the constant challenge of fungal pathogens, the presence of which now leads to broad increase in cytotoxic immune response, not only against fungi, but also against other pathogens and cancer cells.

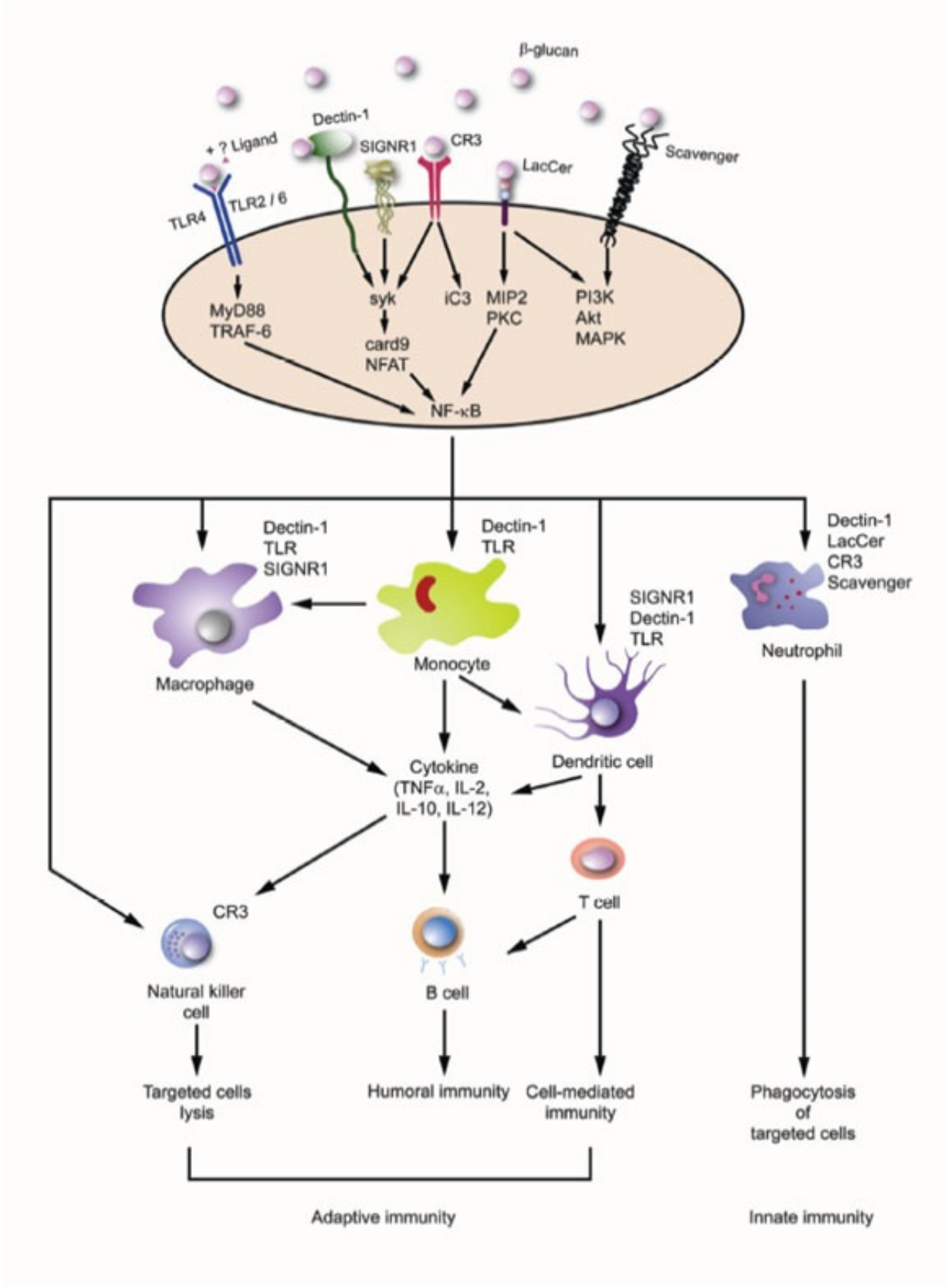
Uptake of fungal beta-glucans and related polysaccharides appears to occur through both receptor-dependent and independent routes.

As the component sugar molecules are primarily beta linked, like cellulose, rather than alpha linked, like starch, they are not broken down by digestive enzymes and so pass intact into the small intestine. There some of them come into contact with macrophages present in the areas of lymphoid tissue in the distal small intestine called Peyer’s patches or Gut Associated Lymphoid Tissue (GALT) and bind to the fungal polysaccharide-specific receptors, Dectin-1 and TLR 2/6, on their surface.

Once captured by the receptors, the polysaccharides are internalised, broken down into shorter chains and transported by the macrophages to the reticuloendothelial system where they are released to be taken up by other cells, including neutrophils, monocytes and dendritic cells, leading to activation of both the innate and specific immune systems.

As well as Dectin-1 dependent absorption of polysaccharides through GALT, it has been shown that there is Dectin-1 independent absorption through the intestinal mucosa and that polysaccharides absorbed in this way are also immunologically active, as indeed are mushroom polysaccharides delivered by injection, such as Lentinan and Schizophyllan.

Immune activation induced by beta-glucans

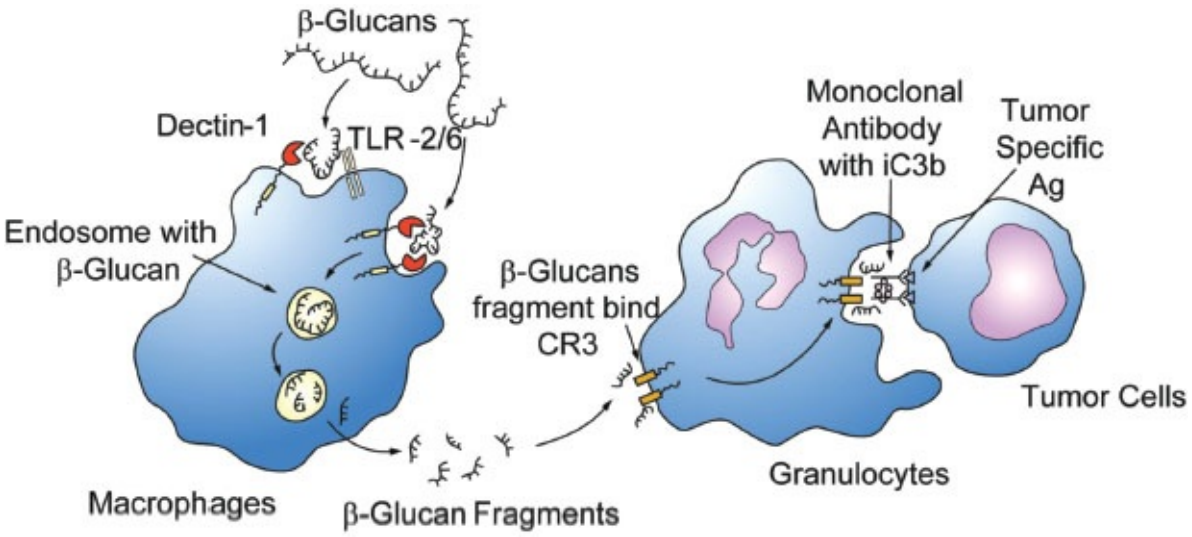

β-glucan
Dectin-1
+ ? Ligand
SIGNR1
CR3
LacCer
Scavenger
TLR4
TLR2 / 6
MyD88
TRAF-6
syk
iC3
MIP2
PKC
PI3K
Akt
MAPK
card9
NFAT
NF-κB
Dectin-1
TLR
SIGNR1
Macrophage
Dectin-1
TLR
Monocyte
SIGNR1
Dectin-1
TLR
Dendritic cell
Dectin-1
LacCer
CR3
Scavenger
Neutrophil
Cytokine
(TNFα, IL-2,
IL-10, IL-12)
CR3
Natural killer
cell
B cell
T cell
Targeted cells
lysis
Humoral immunity
Cell-mediated
immunity
Phagocytosis
of
targeted cells
Adaptive immunity
Innate immunity

From: ‘The effects of β-glucan on human immune and cancer cells’. Godfrey Chi-Fung Chan, Wing Keung Chan and Daniel Man-Yuen Sze[48].

It has been suggested that whereas small, soluble beta-glucans act primarily through binding to CR3, priming cells for cytotoxic activation (expressed on neutrophils and NK cells CR3 has two domains, one of which is specific for fungal polysaccharides and binding to which greatly enhances the ability of the cells to effectively target and destroy antibody-coated cancer cells and other pathogens), larger polysaccharide molecules are able to cross-link membrane CR3 receptors on neutrophils and monocytes, triggering respiratory bursts, degranulation and cytokine release[49].

Not only does binding of fungal polysaccharides to the aforementioned receptors lead to a significant increase in cytotoxic ability, it also initiates widespread activation of the immune system (see below), with the term ‘biological response modifier’ used to reflect the ability to modify, or modulate, immune response.

The uptake and subsequent actions of beta-glucans on immune cells



From: 'The effects of β-glucan on human immune and cancer cells'. Godfrey Chi-Fung Chan, Wing Keung Chan and Daniel Man-Yuen Sze[48].

Immune responses to fungal polysaccharides

- Increased Antibody Production
- Increased Lymphocyte Activating Factor (IL-1) Production
- Increased Tumour Necrosis Factor Production
- Increased Colony Stimulating Factor Production
- Increased Complement C3 Production
- Increased IFN-γ Production
- Increased IL-2 Production
- Reduction in the level of IL-2 needed to produce a cytotoxic response
- Th1 Activation
- Macrophage Activation
- Neutrophil Activation
- Natural Killer Cell Activation
- Cytotoxic T-cell Activation
- Lymphokine Activated Killer Cell Proliferation

- Enhanced maturation and tumour infiltration of Dendritic Cells
- Th2 Suppression
- Reduced IL-4 Production
- Inhibition of Prostaglandin Synthesis
- Inhibition of Delayed type Hypersensitivity

Of particular importance for the impact of medicinal mushrooms on many chronic health disorders is the ability of mushroom polysaccharides to promote a shift in the pattern of immune response in chronic conditions such as cancer, autoimmune conditions and allergies from a pro-inflammatory, Th2 dominant one to a cytotoxic, Th1 dominant one with increases in Th1 cytokines such as IL-2 and IFN-γ and decreases in Th2 cytokines such as IL-4.

Pharmacokinetics of Mushroom Polysaccharides

Studies with radio-labelled PSK showed it to be partially decomposed to smaller molecules in the digestive tract with the full molecular spectrum of radio-labelled PSK absorbed within 24 hrs following oral administration in mice. Peak plasma levels of low molecular weight substances occur at 0.5-1 hr in rats and 1-2 hr in rabbits, while PSK size molecules appear in the serum after 4, 10 and 24hr[46].

Radio-labelled PSK or its metabolites are detected in the intestinal tract, bone marrow, salivary glands, thymus, adrenal glands, brain, liver, spleen, pancreas and tumour tissue in sarcoma-bearing mice, with activity high for longest in the liver and bone marrow.

86% of PSK is excreted within 24hr (~70% excreted in expired air, 20% in faeces, 10% in urine and 0.8% in bile).

Th1-Th2, Mushroom Polysaccharides and Immune Balance

The terms Th1 and Th2 refer to two major populations of T-helper cells, a subset of lymphocytes (a type of white blood cell) that plays an important role in establishing and maximising the capabilities of the immune system. They are involved respectively in promoting cellular (cytotoxic) and humoral (pro-inflammatory) immune responses[50].

The balance between a Th1 and a Th2-mediated immune response appears to play an important role in immune regulation with a number of chronic disease states, including cancer, allergies and asthma, exhibiting elevated levels of the cytokines (chemical messengers) characteristic of a Th2 dominant immune response.

In a balanced state the immune system is able to maintain an equilibrium between Th1 and Th2 mediated immune responses but it appears that in these conditions a shift has taken place with the immune system becoming locked into a Th2 dominant pattern with increased levels of inflammation, metabolic activity and, in the case of cancer, angiogenesis (blood vessel formation), as well as reduced cytotoxic activity. Stress, elevated cortisol levels and exposure to organic pesticides have all been suggested as possible causes.

Supplementation with mushroom polysaccharides shows a clear shift in immune balance towards Th1 dominance with increased production of Th1 cytokines such as IL-2 and IFN-γ and suppression of Th2 cytokine production. As such it offers a valuable therapeutic tool for addressing a Th1→Th2 shift in conditions such as those mentioned above.

The concept of a Th1→Th2 shift in immune balance finds

parallels in the traditional Chinese medical concept of Retained Pathogenic Factor/Latent Heat, which describes many of the signs and symptoms characteristic of a Th2 dominant immune state, including fatigue, reduced resistance to infection, depression and chronic low-grade inflammation and medicinal mushrooms can likewise play an important role in treatment strategies to address this condition.

Understanding Mushroom Products

As well as having a large number of mushrooms with similar properties to choose from, the therapist is faced with an often bewildering variety of product forms produced through different growing and manufacturing processes.

Whereas traditionally only the fruiting body, or in some cases the sclerotium (underground hyphal mass - *ie. Polyporus umbellatus* and *Poria cocos*) or conk (sterile fungal growth on the trunk of the tree - *ie. Inonotus obliquus* - Chaga), was harvested and either been consumed whole in food, as with *Lentinula edodes* (Shiitake) and *Grifolafrondosa* (Maitake), or as teas made from aqueous decoctions of the fruiting body, as with *Ganoderma lucidum* (Reishi) and *I. obliquus*, nowadays many commercial mushroom products are produced from the mycelium of the mushroom grown either by liquid fermentation or as a mycelial biomass.

The following overview summarizes the features of the different dosage forms available.

Fruiting Body/Conk/Sclerotium

The traditional dosage form of medicinal mushrooms, the fruiting body, typically contains a higher level and number of different polysaccharides than the mycelium or culture broth with an increase in concentration with fruiting body growth until an optimum size is reached (approx. 17g for *L. edodes* and 180g for *G. frondosa*)[6,7,51].

In addition, concentrations of components such as triterpenes (*G. lucidum*) and other phenolic compounds (*I. obliquus*) tend to be higher in the fruiting body, where their bitter taste and natural

antimicrobial properties act to discourage unwanted predators. Data from *Antrodia camphorata* suggests the level of triterpenes in the mycelium is 40% of that in the fruiting body and for many mycelial biomass products the relative discrepancy is likely to be greater owing to the presence of residual substrate in the mycelial biomass. For this reason *G. lucidum* mycelial biomass products tend to lack the characteristic bitter flavour of the triterpenes found largely in the fruiting body.

Extracts

For mushrooms where triterpenoid and other phenolic components are therapeutically important such as *A. camphorata, G. lucidum* and *I. obliquus* products derived from the fruiting body/conk are usual with, given their indigestible nature, extracts often used in agreement with traditional practice.

Extracts are also used to deliver high concentrations of polysaccharides or other active components. They are usually made from either the fruiting body or the mycelium through one of two main methods:

- Aqueous (hot-water) extraction (traditional teas/decoctions) gives high polysaccharide concentrations but low levels of poorly water-soluble triterpenes. Crude polysaccharide extracts typically have around 30% polysaccharides with further purification possible.
- Ethanolic (alcohol) extraction (traditional tinctures) delivers higher levels of triterpenes but fewer polysaccharides (ethanol precipitates the polysaccharides out of solution).

As well as offering higher concentrations of polysaccharides and other clinically important compounds, extracts may be preferred in

cases of gut dysbiosis, from antibiotic use or otherwise, with resultant impaired ability to break down whole mushroom or mycelial biomass products (also in cases of colostomy).

For some mushrooms such as *G. lucidum*, aqueous extracts and ethanolic extracts can be combined to deliver high concentrations of both polysaccharides and triterpenes. Some practitioners such as Nanba have also reported good results from combining high concentration polysaccharide (beta-glucan) extracts with whole mushroom fruiting body[52].

Spores and Spore Oil

The fruiting body exists to spread the spores of the mushroom and generates them in amazing quantities with a single fruiting body of *Ganoderma applanatum* (the artist's conk) being estimated to produce up to 2.6 billion over its life at rates of up to 31,000 per second[53].

While all mushrooms produce spores only the spores from *Ganoderma lucidum* have so far been investigated for their clinical potential with polysaccharides, triterpenes and sterols all contributing to their therapeutic activity[54-57].

For increased bio-availability the hard outer shell of the spores (sporoderm) has to be ruptured using ultrasound or low temperature milling to produce shell-broken spore powder with a typical triterpene content of 2%. The oil can then extracted from the shell-broken spores to produce reishi spore oil, which can have a triterpene content of up to 30%.

Mycelium (liquid/submerged fermentation)

Liquid fermentation is the same technology used in the pharmaceutical industry to produce antibiotics and also to produce

other industrial products such as fungal enzymes.

The mushroom mycelium is cultured in a closed vessel with a liquid substrate containing all the essential nutrients for growth and growth parameters such as nutrient composition and temperature carefully controlled to optimise concentration of the desired components.

Because the substrate is a liquid the mycelium can easily be harvested and then either used as a therapeutic component itself or in most cases further processed to yield various extracts (eg. PSK). In addition, the extracellular metabolites secreted into the growth medium (broth) may also be harvested for their therapeutic properties (eg. Schizophyllan, an extracellular polysaccharide from *Schizophyllum commune*).

Mycelial Biomass

In mycelial biomass production the mushroom culture is inoculated into a sterile, grain-based substrate, often brown rice, and left to fully colonize the substrate. At the point at which it has exhausted the capacity of the substrate to support further growth and is about to produce fruiting bodies (primordia stage) the resultant mass of mycelium and residual substrate is dried and granulated to make a powder, which is then usually tabletted or encapsulated.

As well as mushroom mycelium and some residual grain, mycelial biomass products contain the full range of metabolites secreted into the substrate by the mycelium (especially antimicrobial compounds and exopolysaccharides), together with a wide variety of enzymes, including digestive enzymes (proteases, lipases etc.) and antioxidant enzymes (laccase, catalase and superoxide dismutase). They also contain substrate breakdown products such as arabinoxylans with therapeutic properties in their own right.

Indeed, in supplements such as Biobran™, also known as MGN-3™ (shiitake digested rice bran) and Avemar™ (yeast digested wheatgerm) the enzymatically transformed substrate itself is seen as the therapeutic entity and Stamets reports crude arabinoxylan content of mushroom mycelial biomass cultivated on short grain brown rice by his company, Fungi Perfecti, as ranging from 7.8% in *Agaricus subrufescens* to 24% in *Ophiocordceps sinensis.*

While mushroom mycelial biomass products contain a wide range of bioactive molecules, levels of the key immunomodulating beta-glucans and related heteropoly-saccharides are low. Stamets reports beta-glucan levels in the above form of mycelial biomass ranging from 1.23% in *Hericium erinaceus* to 2.96% in *Inonotus obliquus* with *A. subrufescens* 1.83%,*Grifola frondosa* 2.51% and *Ganoderma lucidum* 2.19%[7].

Combination Products

There is some evidence that combinations of mushrooms can have a greater effect on the immune system of both humans and mice than single mushrooms and that blends of mushrooms extracts have greater cytotoxicity against cancer cells than single extracts *in vitro*[58,59].

Sawai *et al* report greater immunological activity with higher levels of macrophage activation and INF-y induction by a mixture of mushroom polysaccharide extracts than by the single extracts[60]. Stamets also reports a blend of seven mushrooms (mycelial biomass) as having enhanced NK cell activation in human spleen cells when compared to the individual mushrooms[61].

Several commercial mushroom products are produced from multiple mushroom species including Active Hexose Correlated Compound (AHCC - an extract from the mycelia of several species of basidiomycete that has shown efficacy in clinical trials)[62,63].

Prescribing Medicinal Mushrooms

Prescribing medicinal mushrooms is not an exact science. Dosage depends on the condition and the individual being treated, as well as the product format being prescribed, and is discussed under the individual mushrooms and under the different clinical conditions, including at the end of the section on Medicinal Mushrooms in Cancer Therapy.

Although many of the medicinal mushrooms are also foods, for therapeutic purposes it is preferable to take them away from food to avoid interfering with their absorption. However, it can be appropriate to give together with juices, smoothies, pureed fruit or nut butter to assist with swallowing, depending on the format and the individual.

Although it is common to split the prescribed dose into two, with one taken a.m. and one p.m., it can be split into three if that is easier, especially for higher doses, or taken in a single dose if two is not possible. In all cases it is beneficial to take with water.

Side effects

Exhaustive analysis of data from several large scale clinical trials with mushroom polysaccharidee extracts confirms that side effects from mushroom supplements are minimal. In a study of 469 patients taking Lentinan only 32 reported any adverse reaction, none serious (most common were rash/redness, chest oppression and nausea), and a review in the Lancet of a well designed trial investigating the benefit of PSK for gastric cancer concluded that no toxic effects could be

observed ‘even after meticulous review of all the patient records’[5].

Clinically some change in bowel habit is seen in a few patients, especially at higher dosages but this is usually transient, lasting no more than 2-3 days.

Supplementation with medicinal mushrooms should of course be avoided in individuals with a history of confirmed or suspected mushroom allergy.

Candidiasis or other fungal conditions

The common myth that eating mushrooms will in some way facilitate the growth of candida or other fungal conditions is unsupported by clinical experience or research evidence.

Not only are mushrooms very low in the sugars that may help promote candidal growth but they also strengthen the body’s immune response to all fungi and in many cases contain compounds with direct anti-fungal activity (see Candidiasis for a more detailed discussion). While some mushrooms nourish Yin energy according to traditional Chinese energetics (ie. *Tremella fuciformis* - Bai Mu Er), none of them are considered to increase pathogenic Damp. Indeed for two of them (*Polyporus umbellatus* - Zhu Ling and *Poria cocos* - Fu Ling) the main use in TCM is as diuretics to Drain Damp and clinically mushrooms can be very beneficial in the treatment of conditions that are considered Damp in TCM.

Appendix I lists the TCM qualities of the main medicinal mushrooms.

With conventional treatment

In many cases the mushrooms used medicinally are also foodstuffs and in the vast majority of cases there are no reported interactions

with prescription medication. Indeed mushroom extracts are routinely prescribed alongside prescription drugs, especially chemotherapeutic agents, in China and Japan (see Medicinal Mushrooms in Cancer Therapy for a more detailed discussion of this area).

There is also *in vitro* and *in vivo* evidence that administration of polysaccharide extracts from *Ganoderma lucidum* and *Grifola frondosa* alongside antibiotics including vancomycin, ampicillin, ciprofloxacin, streptomycin, kanamycin and cephotaxamine increases the level of antibacterial activity compared to the antibiotic on its own[64,65].

Specific cautions are noted in the sections on the individual mushrooms.

With other nutritional supplements

There are no reported interactions with other classes of nutritional supplement and several studies indicating synergistic benefits between mushrooms and other supplements including vitamins C and vitamin K-3 as well as green tea[66,67].

While pregnant or breastfeeding

With the exception of *Auricularia auricula*, tests with commercial mushroom products show no adverse affect on male or female fertility, foetal abnormality, penetration into the foetus or excretion in breast milk, blood coagulation or arthritis from polysaccharide-based products. Neither do they possess teratogenic or genotoxic properties[69].

Anti-fertility action has been reported for *A. auricula* polysaccharides and for this reason neither *A. auricula* or *T. fuciformis*, whose polysaccharides have a similar structure, are

recommended for use during pregnancy or if pregnancy is planned[70].

Caution is also recommended when taking mushrooms with reported anti-coagulant activity such as *Ganoderma lucidum* during pregnancy.

REFERENCES

1. Medicinal mushroom science: history, current status, future trends and unsolved problems. Wasser SP. Int J Med Mushr. 2010; 12(1):1-16.
2. Medicinal mushrooms - An Exploration of Tradition, Healing and Culture. Hobbs C. 1986. Pub. Botanica Press, Williams. p.7-10.
3. Ancient Chinese People's Knowledge of Macrofungi as Medicinal Material During the Period from 581 to 979 AD. Lu D. Int J Med Mushr. 2014;16(2):189-204.
4. Reishi Mushroom - Herb of Spiritual Potency and Medical Wonder. Willard T. 1990 Sylvan Press. Issaquah
5. The use of mushroom glucans and proteoglycans in cancer treatment. Kidd P. Alt Med J. 2000;5(1):4-27.
6. Higher Basidiomycota as a source of antitumour and immuno-stimulating polysaccharides (Review). Reshetnikov SV, Tan KK. Int J Med Mushr. 2001;3(4):361-394.
7. Potentiation of cell-mediated host defense using fruitbodies and mycelia of medicinal mushrooms. Stamets P. Int J Med Mushr. 2003;5:179-191.
8. Correlation between the antitumour activity of a polysaccharide schizophyllan and its triple-helical conformation in dilute aqueous solution. Yanaki T, Ito W, Tabata K, Kojima T, Norisuye T, Takano N, Fujita H. Biophys Chem. 1983; 17(4):337-42.
9. Coarse-scale population structure of pathogenic Armillaria species in a mixed-conifer forest in the Blue Mountains of northeast Oregon. Ferguson BA, Dreisbach TA, Parks CG, Filip GM, Schmitt CL. Canadian Journal of Forest Research, 2003;33(4): 612-623.
10. Medicinal mushrooms as a source of antitumour and immunomodulating polysaccharides. Wasser SP. Appl. Environ Microbiol. 2002;60:258-274.
11. Evaluation of widely consumed botanicals as immunological adjuvants. Ragupathi G, Yeung KS, Leung PC, Lee M, Lau CB, Vickers A, Hood C, Deng G, Cheung NK, Cassileth B, Livingston P. Vaccine. 2008;26(37):4860-5.

12. Medicinal Mushroom Lingzhi or Reishi, *Ganoderma lucidum* (W.Curt.:Fr.) P. Karst., β-Glucan Induces Toll-like Receptors and Fails to Induce Inflammatory Cytokines in NF-κB Inhibitor-Treated Macrophages. Batbayar S, Kim MJ, Kim HW. Int J Med Mushr. 2011;13(3):213-225.
13. Medicinal mushrooms: their therapeutic properties and current medical usage with special emphasis on cancer treatments. Smith J, Rowan N, Sullivan R. May 2002. Cancer Research UK. p.101.
14. Effect of the molecular mass of tremella polysaccharides on accelerated recovery from cyclophosphamide-induced leucopenia in rats. Jiang RZ, Wang Y, Luo HM, Cheng YQ, Chen YH, Gao Y, Gao QP. Molecules. 2012 Mar 23;17(4):3609-17.
15. Peroral effect on tumour progression of soluble beta 1-6 glucans prepared by acid treatment from *Agaricus blazei*. Murr. Fujiyama Y, Yamomoto H, Noji M, Suzuki I. Int J Med Mush 2000;2:43-49.
16. *Trametes versicolor* extract modifies human fecal microbiota composition in vitro. Yu ZT, Liu B, Mukherjee P, Newburg DS. Plant Foods Hum Nutr. 2013 Jun;68(2):107-12.
17. Effects of polysaccharopeptide from *Trametes Versicolor* and amoxicillin on the gut microbiome of healthy volunteers: A randomized clinical trial. Pallav K.*et al*. Gut Microbes. 2014 Jul 9;5(4).
18. Mushroom proteins related to host defense. Ng T.B. Int J Med Mush. 2005;7(1,2):221-236.
19. Immunomodulatory capacity of fungal proteins on the cytokine production of human peripheral blood mononuclear cells. Jeurink PV, Noguera CL, Savelkoul HF, Wichers HJ. Int Immuno-pharmacol. 2008;8(8):1124-33.
20. Polysaccharides PS-G and protein LZ-8 from Reishi *(Ganoderma lucidum*) exhibit diverse functions in regulating murine macrophages and T lymphocytes. Yeh CH, Chen HC, Yang JJ, Chuang WI, Sheu F. J Agric Food Chem. 2010;58(15): 8535-44.
21. Lectins of higher fungi (Macromycetes)—their occurrence, physiological role, and biological activity. Konska G. Int J Med Mush. 2006;8(1):19-30.
22. Comparative study of lectin activity of higher Basidiomycetes. Nona A., Mikiashvili N.A, Elisashvili V, Wasser SP, Nevo E. Int J Med Mush. 2006;8(1):31-38.

23. Coadministration of the fungal immunomodulatory protein FIP-Fve and a tumour-associated antigen enhanced antitumour immunity. Ding Y, Seow SV, Huang CH, Liew LM, Lim YC, Kuo IC, Chua KY. Immunology. 2009;128(1Sup):881-94.
24. Biomedical triterpenoids of *Ganoderma lucidum* (Curt.: Fr.) P. Karst. (Aphyllophoromycetideae). Kim HW, Kim BK, Int J Med Mushr. 1999;1:121-13817.
25. Betulinic acid, a natural compound with potent anticancer effects. Mullauer FB, Kessler JH, Medema JP. Anticancer Drugs. 2010;21(3):215-27. 2010;24(1):90-114.
26. Review of pharmacological effects of *Antrodia camphorata* and its bioactive compounds. Geethangili M, Tzeng YM. Evid Based Complement Alternat Med. 2009.
27. Antioxidant properties of several medicinal mushrooms. Mau JL, Lin HC, Chen CC.J Agric Food Chem. 2002 Oct 9; 50(21):6072-7.
28. Flavonoids: antioxidants or signalling molecules?. Williams RJ, Spencer JP, Rice-Evans C. Free Radical Biology & Medicine. 2004;36(7):838–49.
29. Regulation of cellular signals from nutritional molecules: a specific role for phytochemicals, beyond antioxidant activity. Virgili F, Marino M. Free Radical Biology & Medicine. 2008;45(9):1205–16.
30. Isolation of an antitumour compound (Ergosterol) from *Agaricus blazei* Murill and its mechanism of action. Takaku T, Kimura Y, Okuda H. J Nutr. 2001;131:1409–1413.
31. Antihepatoma activity of the acid and neutral components from *Ganoderma lucidum*. Lu H, Song J, Jia XB, Feng L. Phytother Res. 2012 Sep;26(9):1294-1300.
32. Antitumor sterols from the mycelia of *Cordyceps sinensis*. Bok JW, Lermer L, Chilton J, *et al.* Phytochem 1999;51:891–898.
33. Ganodermasides A and B, two novel anti-aging ergosterols from spores of a medicinal mushroom *Ganoderma lucidum* on yeast via UTH1 gene. Weng Y, Xiang L, Matsuura A, Zhang Y, Huang Q, Qi J. Bioorg Med Chem. 2010;18(3):999-1002.
34. Crystal and molecular structure of compactin, a new antifungal metabolite from Penicillium brevicompactum. Brown AG, Smale TC, King TJ,

Hasenkamp R, Thompson RH. J Chem Soc Perkin 1. 1976;(11):1165-70.

35. Growth inhibition of Candida species and *Aspergillus fumigatus* by statins. Macreadie IG, Johnson G, Schlosser T, Macreadie PI. FEMS Microbiol Lett. 2006 Sep;262(1):9-1.
36. Comparative Study of Contents of Several Bioactive Components in Fruiting Bodies and Mycelia of Culinary-Medicinal Mushrooms. Lo YC *et al*. Int J Med Mushr. 2012;14(4):357-363.
37. Comparative Study of Contents of Several Bioactive Components in Fruiting Bodies and Mycelia of Culinary-Medicinal Mushrooms. Lin SY. Int J Med Mushr. 2013;15(3):315-323.
38. Indole Compounds in Some Culinary-Medicinal Higher Basidiomycetes from Poland. Bozena Muszynska, Katarzyna Sutkowska-Ziaja, Halina Ekiert Int J Med Mushr. 2011;13(5):449-454.
39. Analysis of indole compounds in *Armillaria mellea* fruiting bodies. Muszyńska B, Maślanka A, Ekiert H, Sułkowska-Ziaja K. Acta Pol Pharm. 2011 Jan-Feb;68(1):93-7.
40. Chitin Regulation of Immune Responses: An Old Molecule With New Roles. Lee CG, Da Silva CA, Lee JY, Hartl D, Elias JA. Curr Opin Immunol. 2008; 20(6):684–689.
41. Fungal chitin in medicine:prospects for its application. Burdyukova LI, Gorovoj LF. Int J Med Mush. 2001;3(2-3):126-127.
42. Wound-healing effect of micronized sacchachitin (mSC) nanogel on corneal epithelium. Chen RN, Lee LW, Chen LC, Ho HO, Lui SC, Sheu MT, Su CH. Int J Nanomedicine. 2012;7:4697-706.
43. Sacchachitin, a novel chitin-polysaccharide conjugate macro-molecule present in *Ganoderma lucidum*: purification, composition, and properties. Chuang CM *et al*. Pharm Biol. 2013 Jan;51(1):84-95.
44. Mushroom allergy. Koivikko A, Savolainen J. Allergy. 1988 Jan;43(1): 1-10.
45. Chitin induces accumulation in tissue of innate immune cells associated with allergy. Reese TA, Liang HE, Tager AM, Luster AD, Van Rooijen N, Voehringer D, Locksley RM. Nature. 2007;447;(7140):92–96.
46. Herb-Drug Interactions in Oncology. Cassileth BR, Yeung KS, Gubili J. Memorial Sloan-Kettering Cancer Center. 2010 People’s Medical Publishing

House, Shelton.

47. Role of tyrosinase in the genoprotective effect of the edible mushroom, Agaricus bisporus. Shi YL, Benzie IFF, Buswell JA. Life Sciences 2002;70(14):1595-1608.
48. The effects of β-glucan on human immune and cancer cells. Chan CH, Chan WK and Sze MY. Journal of Hematology & Oncology 2009, 2:25.
49. Therapeutic intervention with complement and beta-glucan in cancer. Ross GD, Vetvicka V, Yan J, Xia Y, Vetvickova J. Immuno-pharmacology. 1999;42:61-74.
50. TH1/Th2 Balance: the hypothesis, its limitations and implications for health and disease. Kidd P. Alt Med Rev. 2003;8(3):223-246.
51. Changes in immunomodulating activities and content of antitumour polysaccharides during the growth of two medicinal mushrooms, *Lentinus edodes* (Berk.) Sing, and *Grifola frondosa*(Dicks.: Fr.). Gray SF. Minato KI, Mizuno M, Kawakami S, Tatsuoka S, Denpo Y, Tokimoto K, Tsuchida H. Int J Med Mush. 2001;3(1):1-8.
52. Maitake extracts and their therapeutic potential - A review. Mayell M. Alt Med Rev, 2001;6(1).
53. Mushroom. Money NP. 2012 Oxford University Press, USA.
54. Antitumour activity of the sporoderm-broken germinating spores of *Ganoderma lucidum*. Liu X, Yuan JP, Chung CK, Chen XJ. Cancer Lett. 2002;182(2):155-61.
55. Sterols and triterpenoids from the spores of *Ganoderma lucidum*. Zhang CR, Yang SP, Yue JM. Nat Prod Res. 2008;22(13):1137-42.
56. Chemical constituents of the spores of *Ganoderma lucidum*. Zhang XQ, Pang GL, Cheng Y, Wang Y, Ye WC. Zhong Yao Cai. 2008;31(1):41-4.
57. Comparative studies on the immunomodulatory and antitumour activities of the different parts of fruiting body of *Ganoderma lucidum* and Ganoderma spores. Yue GG, Fung KP, Leung PC, Lau CB. Phytother Res. 2008;22(10):1282-91.
58. Cytotoxicity of Blended Versus Single Medicinal Mushroom Extracts on Human Cancer Cell Lines: Contribution of Polyphenol and Polysaccharide Content. Durgo K *et al*. Int J Med Mushr. 2013;15(5):435-448.
59. Regulation of cell cycle transition and induction of apoptosis in HL-60

leukemia cells by the combination of *Coriolus versicolor* and *Ganoderma lucidum*. Hsieh TC, Wu JM. Int J Mol Med. 2013 Jul;32(1):251-7.

60. Extraction of conformationally stable (1-6)-branched (1-3)-glucans from premixed edible mushroom powders by cold-alkaline solution. Sawai, M., Adachi, Y., Kanai, M., Matsui, S. and Yadomae, T. Int J Med Mushr. 2002;4:3.
61. Potentiation of cell-mediated host defense using fruitbodies and mycelia of medicinal mushrooms. P.Stamets. Int J Med Mushr. 2003;5:179-191.
62. Immunomodulatory and anticancer effects of active hemicellulose compound (AHCC). Ghoneum M, Wimbley M, Salem F, McKlain A, Attalah N, Gill G. Int J Immunotherapy. 1995;1,1:23-28.
63. An evidence-based systematic review of active hexose correlated compound (AHCC) by the Natural Standard Research Collaboration. Ulbricht C *et al*. J Diet Suppl. 2013 Sep;10(3):264-308.
64. Addition of Maitake D-fraction reduces the effective dosage of vancomycin for the treatment of Listeria-infected mice. Reese TA, Liang H, Tager AM, Luster AD, Van Rooijen N, Voehringer D, Locksley RM, Kodama N, Yamada M, Nanba H. Jpn J Pharmacol. 2001;87(4):327-32.
65. Antibacterial activity of the bio-multidrug (*Ganoderma lucidum*) on Multidrug resistant Staphylococcus aureus (MRSA). Prasad Y, Wesely WEG - Advanced Biotech, 2008.
66. Synergistic potentiation of D-fraction with vitamin C as possible alternative approach for cancer therapy. Konno S. Int J Gen Med. 2009 Jul 30;2:91-108.
67. Alternative therapeutic approach to renal-cell carcinoma: induction of apoptosis with combination of vitamin K3 and D-fraction. Degen M, Alexander B, Choudhury M, Eshghi M, Konno S. J Endourol. 2013 Dec;27(12):1499-503.
68. Dietary intakes of mushrooms and green tea combine to reduce the risk of breast cancer in Chinese women. Zhang M, Huang J, Xie X, Holman CD. Int J Cancer. 2009 Mar 15;124(6):1404-8.
69. Medicinal mushrooms: their therapeutic properties and current medical usage with special emphasis on cancer treatments. Smith J, Rowan N, Sullivan R. May 2002. Cancer Research UK. p.166-168.
70. Anti-fertility action of *Auricularia auricula* polysaccharide. He B. Chen Q.

Zhongguo Yaoke Daxue Xuebao. 1991;22:48-49.

Medicinal Mushrooms

To date around 14,000 species of mushroom have been described, although it is believed that the actual number is ten times as large. Of these it has been estimated that 5% may be therapeutically useful.

Any selection of medicinal mushrooms is therefore inevitably going to be a partial one but I have tried to include those mushrooms with significant therapeutic potential that is supported by traditional use and clinical research.

Agaricus subrufescens

(Agaricus blazei/Agaricus brasiliensis)

Japanese name
Himematsutake

Chinese name
Ji Song Rong

Portuguese name
Cogumela del sol

English name
Royal/Sun Agaric

Although commonly known as *A. blazei* Murrill (ABM), after a mushroom discovered in 1945 by the mycologist William A. Murrill growing on the lawn of his friend R.W. Blaze in Florida, the mushroom used therapeutically can be traced to spores and samples sent to Japan from the Piedade region of Brazil by a farmer of Japanese descent in 1965. It is now believed that the two are in fact different species with the name *Agaricus brasiliensis* proposed for the Brazilian mushroom[1]. Recent analysis however, indicates that this is the same mushroom first identified by Charles Horton Peck in 1893 and called *A. subrufescens* and that this name should therefore have precedence[2, 3].

Although one of the newest medicinal mushrooms, *A. subrufescens* is rapidly becoming one of the most popular. Reported in a recent survey as being taken by 31% of urological cancer patients in Japan[4], with the fastest growing US sales of any medicinal mushroom[5] and one of the three most popular medicinal mushrooms in Taiwan, this relative of the common button mushroom, *A. bisporus*, exhibits broad clinical activity[6].

Its polysaccharides include several immunologically active low molecular weight fractions, while an α-1,6 and α-1,4 glucan complex, several polysaccharide-protein complexes, a glucomannan with a main chain of beta 1,2 linked mannopyranosyle residues and a heteropolysaccharide composed mainly of glucose, arabinose and mannose all show anti-tumour activity[7-18]. Interestingly there appears

to be an increase in structural diversity of its polysaccharides with maturation of the fruiting body[19].

A. subrufescens also contains high levels of lipids, including linoleic acid, oleic acid, stearic acid and ergosterol[20].

CANCER - *A. subrufescens* polysaccharide extracts show strong *in vitro* and *in vivo* activity against a range of cancer cell lines, including lung and ovarian cancer, and *in vivo* studies show positive results for Ehrlich ascites cancer, Sarcoma 180, human ovarian cancer and mouse lung cancer cell lines, as well as synergistic benefits with chemotherapy and radiotherapy[21].

In a rat cachexia model *A. subrufescens* extracts, as well as powdered fruiting body, significantly reduced tumour size and promoted gain in body weight with reduction in AST levels and increased glycaemia[22], while an *in vivo* study using severely immunodeficient mice found *A. subrufescens* polysaccharides to directly inhibit the growth of prostate cancer cells via an apoptotic pathway and to suppress prostate tumour growth via anti-proliferative and anti-angiogenic mechanisms with the greatest activity found in the broth fraction (compounds extracted from the liquid growth medium in which the mycelium was grown) rather than the mushroom itself[23].

A 2008 study reported significant increases in the NK cell activity of human volunteers given *A. subrufescens* polysaccharide extract at a dose of 3g/day compared to placebo,[24] while Ahn reports increased NK-cell activity and reduced chemotherapy-related side effects (appetite loss, alopecia, emotional stability and general weakness) from *A. subrufescens* polysaccharide extract in one hundred cervical, ovarian, and endometrial cancer patients treated either with carboplatin plus VP16 (etoposide) or with carboplatin plus taxol[25].

In two small Chinese clinical studies, a dose of 20g *A. subrufescens*

fruiting body, taken twice daily as a tea, was reported to improve haematopoietic parameters and treatment outcomes in patients receiving chemotherapy for acute non-lymphocytic leukaemia in one study and improvement in immune status, haematopoietic parameters and quality of life measures in late stage alimentary tract tumours in another[26],[27].

The closely related *A. bisporus* shows *in vitro* anti-aromatase activity, with conjugated linoleic acid identified as the main active component, and Mizuno reports positive clinical results with *A. subrufescens* in a number of mainly breast cancer patients but at unspecified dosage[28-30].

Although most of the published research strongly supports the use of *A. subrufescens* in cancer therapy, two studies studies looking at the protective properties of *A. subrufescens* have been published with negative outcomes (in one *A. subrufescens* given at 5% of diet did not have a suppressive effect on colon carcinogenesis in rats exposed to dimethylhydrazine, in another an aqueous extract did not affect the development of liver cancer induced by diethylnitrosamine). In a third study *A. subrufescens* supplementation failed to produce significant change in TNF-α, IFN-γ or IL-10 levels in immunosuppressed mice and it appears that there may be significant variation in activity between different extracts, as well as between different strains[31-35].

DIABETES - To date little clinical data has been published although a 2008 study reported decreases in cholesterol and glucose levels together with increased natural killer cell activity at a dose of 3g/day polysaccharide extract[24].

ALLERGIES - As potent immune modulators mushroom polysaccharides can reduce the level of Th2-mediated allergic reactions and *A. subrufescens* is no exception with Andosan, a proprietary combination of polysaccharide extracts from *A.*

subrufescens (82%), *H. erinaceus* (15%) and *G. frondosa* (3%), causing a shift towards a Th1 cytokine profile with consequent reduced risk of allergies and *in vitro* inhibition of histamine release from mast cells[36,37].

HEPATOPROTECTIVE - There is evidence from a number of small clinical studies indicating possible application of *A. subrufescens* in the treatment of chronic hepatitis. In one study 1500mg of polysaccharide extract produced significant reductions in liver enzymes in a small number of hepatitis B patients over a 12 month period (AST reduced from 246 to 61 and ALT from 151 to 46)[38]. In another *A. subrufescens* extract reduced GTP in 80% of 20 patients with hepatitis C[39]. Wang et al also reported wide-ranging benefits in patients with chronic Hepatitis B at a dose of 20g fruiting body twice a day over a 3 month period, including reduction in abdominal distension, fatigue and hepatodynia, together with increased retraction of the liver and spleen[40].

One *in vivo* study also indicates therapeutic potential of *A. subrufescens* polysaccharide extract for alcoholic liver injury with 100mg/kg body weight producing improvements in liver enzymes as well as liver histology and mitochondrial membrane potential[41].

CLINICAL SUMMARY

Main Therapeutic Application - *Cancer*

Key Component - *Polysaccharides*

Dose - *3g/day polysaccharide extract has been used in clinical trials but the high activity of the culture broth also supports the use of mycelial biomass or of mycelial biomass/polysaccharide extract combinations*

Safety - *Although A. subrufescens (like the common button mushroom A. bisporus) contains agaritine, a hydrazine-derived mycotoxin and group 3*

carcinogen, this rapidly oxidises on exposure to air and during cooking with multiple studies confirming the safety of A. subrufescens as a functional food[42-45].

One animal study showed A. subrufescens to enhance local and systemic inflammation with possible implications for development of atherosclerosis although a randomized clinical trial in elderly women showed no changes in cytokine levels[46,47].

Another report suggested a possible connection between consumption of an A. subrufescens extract and three cases of hepatic dysfunction in cancer patients, although the authors state that several other causative factors cannot be completely ruled out[48]. *Cheilitis due to an A. subrufescens extract has also been reported*[49].

REFERENCES

1. Is a Widely Cultivated Culinary-Medicinal Royal Sun Agaricus (the Himematsutake Mushroom) Indeed *Agaricus blazei* Murrill? Ferreira da Eira A., Didukh MY, Stamets PE, Wasser SP, Angela L. de Amazonas M. Int J Med Mushr. 2002;4(4): 507-511
2. *Agaricus subrufescens*, a cultivated edible and medicinal mushroom, and its synonyms. Kerrigan RW. Mycologia. 2005;97(1):12-24.
3. *Agaricus subrufescens*: A review. Wisitrassameewong K, *et al*. Saudi J Biol Sci. 2012 Apr;19(2):131-46.
4. Use of complementary and alternative medicine by patients with urologic cancer: a prospective study at a single Japanese institution. Yoshinura W, Ueda N, Ichioka K, Matsui Y, Terai A, Arai Y. Support Care Cancer. 2005;13:685-90.
5. Uncloaking the mysteries of medicinal mushrooms: the U.S. medicinal mushroom market continues to grow and evolve rapidly but its size still pales in comparison to the rest of the world. Adams C. Nutraceuticals World. October 01, 2008.
6. The medicinal mushroom *Agaricus blazei* Murrill: Review of literature and Pharmaco-toxicological problems. Firenzuoli F, Gori L, Lombardo G. Evid Based Complement Alternat Med. 2008;5(1):3-15.
7. Characterization of chemical composition of *Agaricus brasiliensis* polysaccharides and its effect on myocardial SOD activity, MDA and caspase-3 level in ischemia-reperfusion rats. Zhang S, He B, Ge J, Zhai C, Liu X, Liu P. Int J Biol Macromol.2010;46(3):363-6.
8. Structural characterization of a water-soluble β-d-glucan from fruiting bodies of *Agaricus blazei* Murrill. Dong Q, Yao J, Yang X.T and Fang J.N. Carbohyd. Res. 2007;337:1417–1421.
9. Antitumour beta-glucan from the cultured fruit body of *Agaricus blazei*. Ohno N, Furukawa N, and Miura N. Biol Pharm Bull. 2004;24:820–828.
10. Tumour-specific cytocidal and immunopotentiating effects of relatively low molecular weight products derived from the basidiomycete *Agaricus blazei*

Murrill. Fujimiya Y, Suzuki Y, Katakura R, and Ebina T. Anticancer Res. 1999;19:113–118.

11. Immunostimulatory activities of a low molecular weight antitumoural polysaccharide isolated from *Agaricus blazei* Murill (LMPAB) in Sarcoma 180 ascitic tumour-bearing mice. Niu YC, Liu J.C, Zhao XM, Su F.Q, Cui HX. Pharmazie. 2009;64(7):472-6.
12. Isolation and characterization of polysaccharides from *Agaricus blazei* Murrill. Gonzaga MLC, Ricardo N.M.P.S, Heatley F, and Soares SA. Carbohyd. Polym. 2005;60:43–49.
13. Antitumour effect of a peptide-glucan preparation extracted from *Agaricus blazei* in a double-grafted tumour system in mice. Ebina T, and Fujimiya Y. Biotherapy. 1998;11:259–265.
14. Fractionation and antitumour activity of the water-insoluble residue of *Agaricus blazei* fruiting bodies. Kawagishi H, Inagaki R, Kanao T, Mizuno T, Shimura K, Ito H, Hagiwar T, and NakamuraT. Carbohyd. Res. 1989;186:267–273.
15. Oral administration of *Agaricus brasiliensis* S. Wasser *et al*. (Agaricomycetideae) extract downregulates serum immuno-globulin E levels by enhancing Th1 response. Morimoto T, Michihiro TM, Masashi MM. Int J Med Mushr 2008;10(1):30.
16. An extract based on the medicinal mushroom *Agaricus blazei* Murill stimulates monocyte-derived dendritic cells to cytokine and chemokine production *in vitro*. Førland DT, Johnson E, Tryggestad AM, Lyberg T, Hetland G. Cytokine. 2010 Mar;49 (3):245-50.
17. Effect of an extract based on the medicinal mushroom *Agaricus blazei* murill on release of cytokines, chemokines and leukocyte growth factors in human blood *ex-vivo* and *in vivo*. Johnson E, Førland DT, Saetre L, Bernardshaw SV, Lyberg T, Hetland G, Scand J. Immunol. 2009;69(3):242-50.
18. Peroral effect on tumour progression of soluble beta 1-6 glucans prepared by acid treatment from *Agaricus blazei* Murr. Fujiyama Y, Yamomoto H, Noji M, Suzuki I. Int J Med Mush 2000;2:43-4912.
19. Structural characterization of beta-glucans of *Agaricus brasiliensis* in different stages of fruiting body maturity and their use in nutraceutical products. Camelini CM, Maraschin M, de Mendonça MM, Zucco C, Ferreira AG, Tavares LA. Biotechnol Lett. 2005;27(17):1295-9.

20. Isolation of an antitumour compound (Ergosterol) from *Agaricus blazei* Murill and its mechanism of action. Takaku T, Kimura Y, Okuda HJ. Nutr. 2001;131:1409–1413.
21. Suppressing effects of daily oral supplementation of beta-glucan extracted from *Agaricus blazei* Murill on spontaneous and peritoneal disseminated metastasis in mouse model. Kobayashi H, Yoshida R, Kanada Y, Fukuda Y, Yagyu T, Inagaki K, Kondo T, Kurita N, Suzuki M, Kanayama N, Terao T. J Cancer Res Clin Oncol. 2005;131(8):527-38.
22. Effects of *Agaricus brasiliensis* mushroom in Walker-256 tumour-bearing rats. Jumes FM, Lugarini D, Pereira AL, de Oliveira A, Christoff Ade O, Linde GA, do Valle JS, Colauto NB, Acco A. Can J Physiol Pharmacol. 2010;88(1):21-7.
23. Inhibitory mechanisms of *Agaricus blazei* Murill on the growth of prostate cancer *in vitro* and *in vivo*. Yu CH, Kan SF, Shu CH, Lu TJ, Sun-Hwang L, Wang *PS*. J Nutr Biochem. 2009;20(10):753-64
24. Immunomodulating activity of *Agaricus brasiliensis* KA21 in mice and in human volunteers. Liu Y *et al*. Evid Based Complement Alternat Med. 2008;5(2):205-219
25. Natural killer cell activity and quality of life were improved by consumption of a mushroom extract, *Agaricus blazei* Murill Kyowa, in gynecological cancer patients undergoing chemotherapy. Ahn WS, *et al*. Int J Gynecol Cancer 2004;14(4):589-594.
26. Clinical observation on treatment of acute non lymphocytic leukaemia with *Agaricus blazei*. X. Tian, Z. Lun and H. Ito. J. Lanzhou Med. Coll. 20 (1994), pp. 169–171.
27. Observation on treatment effect of *Agaricus blazei* against alimentary tract tumour. Wang J, Mou XM and Cheng RZ Gansu Med J. 1994;13:5–7.
28. White button mushroom phytochemicals inhibit aromatase activity and breast cancer cell proliferation. Grube BJ, Eng ET, Kao YC, Kwon A, Chen S. J Nutr. 2001;131(12):3288-93.
29. Anti-aromatase activity of phytochemicals in white button mushrooms *(Agaricus bisporus*). Chen S *et al*. Cancer Res. 2006;66(24):12026-34.
30. Medicinal properties and clinical effects of culinary-medicinal mushroom *Agaricus blazei* Murrill (Agaricomycetideae) (Review). Mizuno T. Int J Med Mushr 2002;4:299–312.

31. *Agaricus blazei* (Himematsutake) does not alter the development of rat diethylnitrosamine-initiated hepatic preneoplastic foci. Barbisan L.F, Spinardi-Barbisan A.L, Moreira E.L, Salvadori D.M, Ribeiro L.R, da Eira A.F, de Camargo J.L. Cancer Sci. 2003;94(2):188-92.
32. Screening for *in vitro* and *in vivo* antitumour activities of the mushroom *Agaricus blazei*. Ziliotto L, Pinheiro F, Barbisan LF, Rodrigues MA. Nutr Cancer. 2009;61(2):245-50.
33. Aqueous Extract of Culinary-Medicinal Royal Sun Mushroom, *Agaricus brasiliensis* S. Wasser *et al*. (Agaricomycetideae) Effects on Immunodepression in Mice. Fantuzzi E. *et al*. Int J Med Mushr. 2010;12(3):227-234.
34. Variation of the antimutagenicity effects of water extracts of *Agaricus blazei* Murrill *in vitro*. Guterrez ZR, Mantovani MS, Eira AF, Ribeiro LR, Jordão BQ. Toxicol *in vitro*. 2004;18(3):301-9.
35. Effects of the medicinal mushroom *Agaricus blazei* Murill on immunity, infection and cancer. Hetland G, Johnson E, Lyberg T, Bernardshaw S, Tryggestad A.M, Grinde B. Scand J Immunol. 2008;68(4):363-70.
36. Oral Treatment with Extract of *Agaricus blazei* Murill Enhanced Th1 Response through Intestinal Epithelial Cells and Suppressed OVA-Sensitized Allergy in Mice. Bouike G *et al*. Evid Based Complement Alternat Med. Epub 2010 Sep 26.
37. An extract of the medicinal mushroom *Agaricus blazei* Murill can protect against allergy. Ellertsen LK, Hetland G. Clin Mol Allergy. 2009:5;7-6.
38. The mushroom *Agaricus blazei* Murill extract normalizes liver function in patients with chronic hepatitis B. Hsu CH, Hwang KC, Chiang YH, Chou P.J Altern Complement Med. 2008;14(3):299-301.
39. Clinical utility of ABCL (Agaricus Mushroom Extract) treatment for C-type hepatitis. Jpn Pharmacol Ther. 2002;30: 103-7.
40. Observation on the treatment effect of *Agaricus blazei* to the liver function of chronic hepatitis patients. Wang L. and Ma H. J Lanzhou Med Coll. 2004;20:24–26.
41. Effects of polysaccharide from fruiting bodies of *Agaricus bisporus*, *Agaricus brasiliensis*, and *Phellinus linteus* on alcoholic liver injury. Uyanoglu M *et al*. Int J Food Sci Nutr. 2014 Jun;65(4):482-8.

42. Medical mushrooms used for biochemical failure after radical treatment for prostate cancer: an open-label study. Yoshimura K *et al*. Int J Urol. 2010 Jun;17(6):548-54.
43. Phase I Clinical Study of the Dietary Supplement, *Agaricus blazei* Murill, in Cancer Patients in Remission. Ohno S, Sumiyoshi Y, Hashine K, Shirato A, Kyo S, Inoue M. Evid Based Complement Alternat Med. Epub 2011 Apr 18.
44. Safety study of culinary-medicinal Royal Sun Agaricus, *Agaricus brasiliensis* S. Wasser *et al*. KA21 (higher Basidiomycetes) assessed by prokaryotic as well as eukaryotic systems. Motoi M, Ohno N. Int J Med Mushrooms. 2012;14(2):135-48.
45. Royal sun medicinal mushroom, *Agaricus brasiliensis* Ka21 (higher Basidiomycetes), as a functional food in humans. Yamanaka D, Liu Y, Motoi M, Ohno N. Int J Med Mushr. 2013;15(4):335-43.
46. Pro-inflammatory effects of the mushroom *Agaricus blazei* and its consequences on atherosclerosis development. Gonçalves JL *et al*. Eur J Nutr. 2012 Dec;51(8):927-37.
47. *Agaricus blazei* Murrill and inflammatory mediators in elderly women: a randomized clinical trial. Lima CU1, Souza VC, Morita MC, Chiarello MD, Karnikowski MG. Scand J Immunol. 2012 Mar;75(3):336-41.
48. An alternative medicine, *Agaricus blazei*, may have induced severe hepatic dysfunction in cancer patients. Mukai H, Watanabe T, Ando M, Katsumata N. Jpn J Clin Oncol. 2006 Dec;36(12):808-10.
49. Cheilitis due to *Agaricus blazei* Murill mushroom extract. Suehiro M, Katoh N, Kishimoto S. Contact Dermatitis. May 2007;56(5): 293-294.

Antrodia camphorata

(Antrodia cinnamomea)

Taiwanese name
Niu Chang Chih

This native Taiwanese mushroom is starting to attract interest because of the exceptionally high concentration of its triterpenoid compounds and their structural diversity. Other important bioactive compounds include polysaccharides, maleic/succinic acid derivatives, benzenoids and benzoquinone derivatives[1-4].

In the wild *A. camphorata* grows solely on the tree *Cinnamomum kanehirai*, a species of cinnamon that grows at altitudes of between 450 and 2,000m in the mountains of Taiwan. As the fruiting body only develops fully once the tree is dead, in the past many trees were felled to supply demand for this unique and extremely lucrative mushroom (wild *A. camphorata* fetches up to US$15,000/kg) and this,

coupled with the fact that *C. kanehirai* itself is highly sought for furniture manufacture, has led to over-exploitation, with the result that *C. kanehirai* is now protected by the Taiwanese government[5].

To replace the wild-collected material, commercial cultivation of *A. camphorata* has been developed using a variety of techniques to produce either cultivated fruiting body, pure mycelium (grown by liquid fermentation), or mycelial biomass (mycelium and residual substrate). Levels of triterpenes are highest in the fruiting body products, which are also the most expensive, and lowest in the mycelial biomass products, with liquid fermentation mycelial products offering a cost-effective intermediate option.

A. camphorata has a wide range of traditional indications, including alcohol intoxication, cancer, hypertension, fatigue, viral infection and liver disease[1].

HEPATOPROTECTIVE - The use of *A. camphorata* by Taiwanese natives to counter the adverse effects of excessive alcohol consumption was first reported by a traditional Chinese medicine doctor, Wu-Sha in 1773. In animal experiments both the fruiting body and mycelium have been shown to protect against alcohol-induced hepatitis and liver steatosis (fatty liver), as well as CCl4 and cytokine induced liver damage, ameliorating increases in AST, ALT and ALP levels and histopathological changes in a dose-dependent manner with no observed lesions[5-9].

A. camphorata fruiting bodies also inhibited alcohol-induced rises in cholesterol, hepatic lipids and liver enzymes in rats with moderate effect at a dose of 0.025g/kg and increased efficacy at a dose of 0.1g/kg[10-12].

Separately it has been shown that *A. camphorata* possesses strong antioxidant activity and it has been suggested that this is a major contributor to its hepatoprotective properties[13,14]. Its antioxidant

activity is correlated with the presence of total polyphenols, crude triterpenoids and the protein/polysaccharide ratio of the polysaccharide extract[15].

A. camphorata polysaccharides also show hepatoprotective and anti-hepatitis B activity[16],[17], while a number of maleic/succinic acid derivatives showed potent inhibitory activity against hepatitis C protease through competitive inhibition[18].

In addition *A. camphorata* has been shown to suppress the invasive potential of liver cancer cells through inhibition of NF-kappaB[19] and to induce apoptosis in human hepatoma cells[20-23].

CANCER - As well as its effects on liver cancer, multiple *in vitro* and *in vivo* studies show inhibition of cancer cell growth and migration, together with increase in apoptosis, in various cancer cell lines including breast, prostate, liver, bladder, cervical and oral carcinoma[1],[24-29].

ASTHMA - The immune modulating and anti-inflammatory actions of *A. camphorata* offer potential in asthma treatment with animal experiments showing that *A. camphorata* polysaccharides dose-dependently inhibited the development of airway hyperresponsiveness, airway eosinophilia and Th2 immune status[30].

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) - A mycelial extract of *A. camphorata* reduced urine protein and creatinine levels and suppressed changes in the kidney glomerular basement membrane (a histological hallmark of SLE) at a dose of 400mg/kg in a mouse model of SLE, suggesting ability to protect the kidney from autoimmune disease[31],[32].

CARDIOVASCULAR DISEASE - *A. camphorata* has traditionally been used to treat a variety of heart conditions, including hypertension and atherosclerosis, and *A. camphorata* extracts have been reported to inhibit thickening of blood vessel walls and to promote vasodilation[33],[34].

CLINICAL SUMMARY

Main Therapeutic Application - *Liver disease.*

Key Component - *Triterpenes, Polysaccharides.*

Dose - *While the more expensive fruiting body contains the highest level of triterpenes and is preferred in Taiwan for cancer treatment, mycelium produced by liquid fermentation is increasingly available and has been shown to offer a cost effective alternative for treatment of liver conditions, with a recommended dose of 1-3g/day.*

Caution - *Patients on anti-coagulant medication.*

REFERENCES

1. Review of pharmacological effects of *Antrodia camphorata* and its bioactive compounds. Geethangili M, Tzeng YM. Evid Based Complement Alternat Med. Epub 2011 Jan 3.
2. Analysis of Taiwan patents for the medicinal mushroom 'Niu-Chang-Chih'. Chen YF, Lu WL, Wu MD, Yuan GF. Recent Pat Food Nutr Agric. 2013 Apr;5(1):62-9.
3. Immunomodulatory Effect of Polysaccharides Extracted from the Medicinal Mushroom *Antrodia camphorata* (Higher Basidiomycetes) in Specific Pathogen-Free Chickens. Ai-Rong Song, Dan Qin, Chen Zhao, Xiao-Le Sun, Fang Huang, Chao Kong, Song Yang. Int J Med Mushr. 2014;16(1):95-103.
4. New Anti-Inflammatory Aromatic Components from *Antrodia camphorata*. Chen YC, Chiu HL, Chao CY, Lin WH, Chao LK, Huang GJ, Kuo YH. Int J Mol Sci. 2013 Feb 26;14(3):4629-39.
5. Niuchangchih (*Antrodia camphorata*) and its potential in treating liver diseases. Ao ZH, Xu ZH, Lu ZM, Xu HY, Zhang XM, Dou WF. J Ethnopharmacol. 2009;121(2):194-212.
6. Further studies on the hepatoprotective effect of *Antrodia camphorata* in submerged culture on ethanol-induced acute liver injury in rats. Lu ZM, Tao WY, Xu HY, Ao ZH, Zhang XM, Xu ZH. Nat Prod Res. 2010 Jul 9:1-12.
7. Protective effects of *Antrodia cinnamomea* against liver injury. Liu YW, Lu KH, Ho CT, Sheen LY. J Tradit Complement Med. 2012 Oct;2(4):284-94.
8. Current evidence for the hepatoprotective activities of the medicinal mushroom *Antrodia cinnamomea*. Yue PY, Wong YY, Wong KY, Tsoi YK, Leung KS. Chin Med. 2013 Nov 1;8(1):21.
9. Hepatoprotective effects of eburicoic acid and dehydroeburicoic acid from *Antrodia camphorata* in a mouse model of acute hepatic injury. Huang GJ *et al*. Food Chem. 2013 Dec 1;141(3):3020-7.
10. Fruiting body of Niuchangchih (*Antrodia camphorata*) protects livers against chronic alcohol consumption damage. Huang CH, Chang YY, Liu CW, Kang WY, Lin YL, Chang HC, Chen YC. J Agric Food Chem.

2010;58(6):3859-66.

11. Effects of *Antrodia camphorata* on alcohol clearance and antifibrosis in livers of rats continuously fed alcohol. Wu MT, Tzang BS, Chang YY, Chiu CH, Kang WY, Huang CH, Chen YC. J Agric Food Chem. 2011 Apr 27;59(8):4248-54.
12. Further studies on the hepatoprotective effect of *Antrodia camphorata* in submerged culture on ethanol-induced acute liver injury in rats. Lu ZM, Tao WY, Xu HY, Ao ZH, Zhang XM, Xu ZH. Nat Prod Res. 2011 Apr;25(7):684-95.
13. Antioxidative and hepatoprotective effects of *Antrodia camphorata* extract. Hsiao G, Shen MY, Lin KH, Lan MH, Wu LY, Chou DS, Lin CH, Su CH, Sheu JR. J Agric Food Chem. 2003; 51(11):3302-8.
14. Protection of oxidative damage by aqueous extract from *Antrodia camphorate* mycelia in normal human erythrocytes. Hseu YC, *et al*. Life Sci.2002;71(4):469-482.
15. Antioxidant properties of *Antrodia camphorata* in submerged culture. Song TY, Yen GC. J Agric Food Chem. 2002;50(11): 3322-7.
16. Protective effects of a neutral polysaccharide isolated from the mycelium of *Antrodia cinnamomea* on Propionibacterium acnes and lipopolysaccharide induced hepatic injury in mice. Han HF, Nakamura N, Zuo F, Hirakawa A, Yokozawa T, Hattori M. Chem Pharm Bull (Tokyo). 2006;54(4):496-500.
17. *Antrodia camporata* polysaccharides exhibit anti-hepatitus B virus effects. Lee, IH, Huang RL, Chen CT, Chen HC, Hsu WC & Lu MK. FEMS Microbiol. Lett. 2002;209(1):63-67.
18. Inhibitory effects of antrodins A-E from *Antrodia cinnamomea* and their metabolites on hepatitis C virus protease. Phuong do T, Ma CM, Hattori M, Jin J.S. Phytother Res. 2009;23(4):582-4.
19. *Antrodia cinnamomea* fruiting bodies extract suppresses the invasive potential of human liver cancer cell line PLC/PRF/5 through inhibition of nuclear factor kappaB pathway. Hsu YL *et al*. Food Chem Toxicol. 2007;45(7):1249-57.
20. Induction of apoptosis in human hepatoma cells by mycelia of *Antrodia camphorata* in submerged culture. Song TY, Hsu SL, Yen GC. J Ethnopharmacol. 2005;100(1-2):158-67.

21. Mycelia from *Antrodia camphorata* in submerged culture induce apoptosis of human hepatoma HepG2 cells possibly through regulation of Fas pathway. Song TY, Hsu SL, Yeh CT, Yen GC. J Agric Food Chem. 2005;53(14):5559-64.
22. Methyl antcinate A from *Antrodia camphorata* induces apoptosis in human liver cancer cells through oxidant-mediated cofilin and Bax-triggered mitochondrial pathway. Hsieh YC, Rao YK, Wu CC, Huang CY, Geethangili M, Hsu SL, Tzeng YM. Chem Res Toxicol. 2010 Jul 19;23(7):1256-67.
23. Medicinal Fungus *Antrodia cinnamomea* Inhibits Growth and Cancer Stem Cell Characteristics of Hepatocellular Carcinoma. Liu YM, Liu YK, Lan KL, Lee YW, Tsai TH, Chen YJ. Evid Based Complement Alternat Med. 2013;2013:569737.
24. *Antrodia camphorata* extract induces replicative senescence in superficial TCC, and inhibits the absolute migration capability in invasive bladder carcinoma cells. Peng CC, Chen KC, Peng RY, Chyau CC, Su CH, Hsieh-Li HM. J Ethnopharmacol. 2007;109(1):93-103.
25. Inhibition of cyclooxygenase-2 and induction of apoptosis in estrogen-nonresponsive breast cancer cells by *Antrodia camphorata*. Hseu YC, *et al*. Food and Chemical Toxicology. 2006;45:1107-1115.
26. Unique Formosan mushroom *Antrodia camphorata* differentially inhibits androgen-responsive LNCaP and independent PC-3 prostate cancer cell. Chen, Kuan-Chou *et al*. Nutrition and Cancer 2007; 57(1):111-121.
27. Anti-metastatic activities of *Antrodia camphorata* against human breast cancer cells mediated through suppression of the MAPK signaling pathway. Yang HL *et al*. Food Chem Toxicol. 2011 Jan;49(1):290-8.
28. Cytotoxic effect and induction of apoptosis in human cervical cancer cells by *Antrodia camphorata*. Yang PY, Hu DN, Liu FS. Am J Chin Med. 2013;41(5):1169-80.
29. Anticancer effects of eleven triterpenoids derived from *Antrodia camphorata*. Lee YP *et al*. Anticancer Res. 2012 Jul;32(7):2727-34.
30. Administration of polysaccharides from *Antrodia camphorata* modulates dendritic cell function and alleviates allergen-induced T helper type 2 responses in a mouse model of asthma. Liu KJ, Leu SJ, Su CH, Chiang BL, Chen YL, Lee YL. Immunology. 2010; 129(3):351-62.

31. An extract of *Antrodia camphorata* mycelia attenuates the progression of nephritis in systemic lupus Erythematosus-prone NZB/W F1 mice. Chang JM, Lee YR, Hung LM, Liu SY, Kuo MT, Wen WC, Chen P. Evid Based Complement Alternat Med. Epub 2008 Sep 2.
32. Review of biological and pharmacological activities of the endemic Taiwanese bitter medicinal mushroom, *Antrodia camphorata* (M. Zang *et* CH. Su) Sh. H. Wu *et al*. (higher Basidiomycetes). Yue PY, Wong YY, Chan TY, Law CK, Tsoi YK, Leung KS. Int J Med Mushr. 2012;14(3):241-56.
33. A novel inhibitory effect of *Antrodia camphorata* extract on vascular smooth muscle cell migration and neointima formation in mice. Li YH, Chung HC, Liu SL, Chao TH, Chen JC. Int Heart J. 2009;50(2):207-20.
34. The vasorelaxation of *Antrodia camphorata* mycelia: involvement of endothelial Ca(2+)-NO-cGMP pathway. Wang GJ, Tseng HW, Chou CJ, Tsai TH, Chen CT, Lu MK. Life Sci. 2003;73(21): 2769-83.

Armillaria mellea

Japanese name
Naratake

Chinese nam
Mi Huan Jun

English name
Honey Mushroom

A. mellea is a common fungus that produces edible fruiting bodies with a distinctive golden colour. A single example can grow to cover a vast area and it is reported that the largest living organism in the world is a related species of honey fungus covering an area of 2400 acres in Oregon, USA, with estimates of its age ranging from 1900 to 8650 years[1].

Although responsible for the death of many trees and garden shrubs, *A. mellea* is essential for the growth of other plants, including the important Chinese herb *Gastrodia elata* (*Tian Ma*), which is used

to treat conditions including vertigo, dizziness, headache, stroke and convulsions and whose medical properties *A. mellea* mirrors. Indeed *A. mellea* is considered the more potent of the two with an effective dosage half that of *Tian Ma*[2,3].

Early reports indicated that *A. mellea* and *G. elata* shared the same active components but it is now known that they differ in their active metabolites.

As well as being essential for the growth of *G. elata*, it has been shown that Armillaria species are involved in sclerotium formation in *Polyporus umbellatus* (see *P. umbellatus* section).

A. mellea mycelium contains high levels of polysaccharides with anti-ageing, immune-modulating and anti-vertigo activity[4,5]. In addition, nucleoside analogues play a role in some of *A. mellea* 's functions and a number of indole compounds have been isolated including tryptamine, L-tryptophan and serotonin, with *A. mellea* fruiting bodies containing 2.207mg serotonin per 100g dry weight[6,7].

Several antibiotics, primarily sesquiterpene aryl esters, have been isolated from *A. mellea* and show strong action against gram-positive bacteria (*Staphylococcus*, *Streptococcus*, *Enterococcus* etc.), as well as yeasts and other fungi[8-10].

NEUROLOGICAL - Tablets composed of *A. mellea* mycelium are prescribed in China for treating a variety of neurological conditions including Meniere's Syndrome, vertigo, headache, insomnia, epilepsy, neurasthenia and hypertension[2,3,11-14].

A. mellea fermentation extract showed anti-convulsant properties, raising the seizure threshold in PTZ-induced seizures in mice[15], while an adenosine derivative from the mycelium abolished neurogenic twitch responses induced by electrical field stimulation with both pre- and post-synapse depression, as well as being found to be 1,000 times stronger than adenosine in its cerebral protecting activity[5]. In addition

A. mellea polysaccharide extract was shown to benefit vertigo induced by machinery rotation[16].

CLINICAL SUMMARY

Main Therapeutic Application - *Meniere's syndrome, vertigo, epilepsy.*

Key Components - *Polysaccharides, nucleoside derivatives and sesquiterpene aryl esters.*

Dose - *Mycelial tablets are used in China 3-4g/day.*

REFERENCES

1. Coarse-scale population structure of pathogenic Armillaria species in a mixed-conifer forest in the Blue Mountains of northeast Oregon. BA Ferguson, TA Dreisbach, CG Parks, GM Filip, CL Schmitt. Canadian Journal of Forest Research, 2003;33(4):612-623.
2. Modernizing chinese medicine - the case of armillaria as gastrodia substitute. Dharmananda S. www.itmonline.org/arts/gastrodia.htm.
3. Tian ma, an ancient Chinese herb, offers new options for the treatment of epilepsy and other conditions. Ojemann LM, Nelson WL, Shin DS, Rowe AO, Buchanan RA. Epilepsy & Behavior. 2006;8(2):376-383.
4. The cultivation, bioactive components and pharmacological effects of *Armillaria mellea*. Gao LW, Li WY, Zhao YL and Wang JW. Afr J Biotech. 2009;8(25):7383-7390.
5. A polysaccharide from *Armillaria mellea* exhibits strong *in vitro* anticancer activity via apoptosis-involved mechanisms. Wu J, Zhou J, Lang Y, Yao L, Xu H, Shi H, Xu S. Int J Biol Macromol. 2012 Nov;51(4):663-7.
6. A novel N6-substituted adenosine isolated from *mi huan jun (Armillaria mellea*) as a cerebral-protecting compound. Watanabe N, Obuchi T, Tamai M, Araki H, Omura S, Yang JS, Yu D.Q, Liang X.T, Huan J.H. Planta Med. 1990;56(1):48-52.
7. Analysis of indole compounds in *Armillaria mellea* fruiting bodies. Muszyńska B, Maślanka A, Ekiert H, Sułkowska-Ziaja K. Acta Pol Pharm. 2011 Jan-Feb;68(1):93-7.
8. Armillaric acid, a new antibiotic produced by *Armillaria mellea*. Obuchi T, Kondoh H, Watanabe N, Tamai M, Omura S, Yang J.S, Liang X.T. Planta Med. 1990;56(2):198-201.
9. Antimicrobial and antioxidant activities of mycelia of 10 wild mushroom species. Kalyoncu F, Oskay M, Sağlam H, Erdoğan TF, Tamer A.U. J Med Food. 2010;13(2):415-94.
10. Antibacterial sesquiterpene aryl esters from *Armillaria mellea*. Donnelly DM, Abe F, Coveney D, Fukuda N, O'Reilly J, Polonsky J, Prange T J Nat

Prod. 1985;48(1):10-6.

11. To use Armillaria fungus tablet to replace gastrodia tuber in treating 45 cases with syndrome of deficiency of yin and flourishing yang, Chinese Journal of Medicine, 1977;8:473-474.
12. Observation on curative effects of *Armillaria mellea* fungus tablet in treating 100 cases of neurasthenia and hypertension, *etc.* Zhou Linshen. Journal of New Medicine, 1978;10:13.
13. Curative effects of gastrodia tuber Armellaria fungus tablet in treating some diseases of the nervous system. Jiangsu Journal of TCM. 1980;1:35-37.
14. Antioxidant and Antiedema Properties of Solid-State Cultured Honey Mushroom, *Armillaria mellea* (Higher Basidiomycetes), Extracts and their Polysaccharide and Polyphenol Contents. Lai MN, Ng LT. Int J Med Mushr, 2013;15(1):1-8.
15. Pharmacological actions of gastrodia watery preparation and fermentation liquid of *Armellaria mellea* on nervous system. Chinese Journal of Medicine. 1977;8:470-472.
16. Study on the anti-vertigo function of polysaccharides of Gastrodia elata and polysaccharides of *Armillaria mellea*. Yu L. Shen YS, Miao HC. Chin J Information, TCM. 2006;13:29-36.

Auricularia auricula/Auricularia polytricha

Japanese Name
Kikurage

Chinese Name
Mu Er / Wood Ear

English Name
Jews Ear / Judas' Ear

A. auricula grows throughout Europe, Asia and the United States and is highly valued in Asian cooking for its crunchy, rubbery texture. A type of jelly fungus, it produces fruiting bodies that are translucent, brown in colour and 'ear'shaped, hence its Chinese name 'Wood Ear'. Both *A. auricula* and *A. polytricha* (*Mao Mu Er* 'Hairy Wood Ear', or *Yun Er* 'Cloud Ear') are considered as species of *Mu Er* in Chinese medicine and today are used interchangeably[1].

In common with other jelly fungi, *A. auricula* fruiting bodies

contain high levels of polysaccharides and these are the main bioactive component, although phenols have been shown to contribute to the total antioxidant and hypercholesterolaemic activity[2,3].

A. auricula is of particular interest as a functional food for the elderly, with polysaccharide extracts showing considerable promise and *Auricularia polytricha* in processed and unprocessed form exhibiting inhibitory activity against one of the key enzymes involved in Alzheimer's disease[4,5].

ANTI-INFLAMMATORY - *A. auricula* polysaccharides have anti-inflammatory activity, which correlates with *A. auricula*'s traditional use for soothing irritated or inflamed mucous membranes[6].

ANTIOXIDANT - *A. auricula* extracts show strong antioxidant properties with a positive correlation between levels of phenols and antioxidant capacity[7-9].

ANTI-THROMBOTIC - Polysaccharide extracts of *A. auricula* inhibit platelet aggregation and increase clotting times *in vitro* and *in vivo*. Its anti-coagulant activity is due to catalysis of thrombin inhibition by antithrombin but not by heparin cofactor II[10,11].

ANTI-CHOLESTEROL - *A. auricula* polysaccharides and polyphenols have been shown to lower blood total cholesterol (TC), triglyceride and LDL levels and enhance the level of blood HDL, as well as HDL/TC and HDL/LDL ratios at 5% of feed in rats suffering from hyperlipidaemia[3,12-14].

CARDIOPROTECTIVE - Together with *A. auricula*'s general

antioxidant properties, *A. auricula* polysaccharides show strong cardio-protective action, especially in aged mice, enhancing the activity of superoxide dismutase and reducing lipid peroxidation[15, 16].

CLINICAL SUMMARY

Main Therapeutic application - *Cardiovascular support.*

Key Component - *Polysaccharides.*

Dose - *2-3g/day polysaccharide extract.*

Caution - *Patients on anti-coagulant medication. Owing to possible anti-fertility effects it is recommended that A. auricula not be taken by pregnant or lactating women or those planning to conceive*[17].

REFERENCES

1. Hobbs C. Medicinal Mushrooms - An Exploration of Tradition, Healing and Culture. 1986. Botanica Press, Williams, Oregon.
2 Research progress in *Auricularia auricula* polysaccharide. Huang XG, Quan YL, Guan B, Hu Y. Science and Technology of Cereals, Oils and Foods. 2010-01.
3. Hypocholesterolemic effects of *Auricularia auricula* ethanol extract in ICR mice fed a cholesterol-enriched diet. Chen G, Luo YC, Ji BP, Li B, Su W, Xiao ZL, Zhang GZ. J Food Sci Technol. 2011 Dec;48(6):692-8.
4. Evaluation of antioxidant property and quality of breads containing *Auricularia auricula* polysaccharide flour. Fan L, Zhang S, Yu L. Li Ma Food Chemistry, 2007.
5. Heat-Stable Components of Wood Ear Mushroom, *Auricularia polytricha* (Higher Basidiomycetes), Inhibit *In Vitro* Activity of Beta Secretase (BACE1). Bennett L, Sheean P, Zabaras D, Head R. Int J Med Mushr. 2013;15(3):233-249.
6. Polysaccharides in fungi. XIV. Anti-inflammatory effect of the polysaccharides from the fruit bodies of several fungi. Ukai S, Kiho T, Hara C, Kuruma I, Tanaka Y. J Pharmacobiodyn. 1983;6(12):983-90.
7. Antioxidant capacity of fresh and processed fruit bodies and mycelium of *Auricularia auricula*-judae (Fr.) Quél. Kho Y.S, Vikineswary S, Abdullah N, Kuppusamy U.R, Oh H.I. J Med Food. 2009;12(1):167-74.
8. Antioxidant and nitric oxide synthase activation properties of *Auricularia auricula*. Acharya K, Samui K, Rai M, Dutta B.B, Acharya R. Indian J Exp Biol. 2004;42(5):538-40.
9. Antioxidant activity of submerged cultured mycelium extracts of higher Basidiomycetes mushrooms. Asatiani M *et al*. Int J Med Mush. 2007;9(2):151-158.
10. The nontoxic mushroom *Auricularia auricula* contains a polysaccharide with anticoagulant activity mediated by antithrombin. Yoon SJ, Yu MA, Pyun YR, Hwang JK, Chu DC, Juneja LR, Mourão P.A. Thromb Res.

2003;112(3):151-18.

11. Inhibition of human and rat platelet aggregation by extracts of Mu-er (*Auricularia auricula*). Thromb Haemost. Agarwal K.C, Russo F.X, Parks R.E Jr. 1982;48(2):162-5.
12. Effect of polysaccharide from *Auricularia auricula* on blood lipid metabolism and lipoprotein lipase activity of ICR mice fed a cholesterol-enriched diet. Chen G *et al*. J Food Sci. 2008 Aug;73(6):H103-8.
13. The hypocholester olemic effect of two edible mushrooms: *Auricularia auricula* (tree-ear) and *Tremella fuciformis* (white jelly-leaf) in hypercholesterolemic rats. Kaneda T and Tokuda S. Nutrition Research. 1996;1699(10):1721-1725.
14. Isolation and purification of polysaccharides from wood ear *(Auricularia auricular*) and their hypoglycemic, hypolipidemic and antioxidant activities. Yi M.A, Tang J, Han C. 2005 IFT Annual Meeting. ift.confex.com 18B-13.
15. Chemical characterization of *Auricularia auricula* polysaccharides and its pharmacological effect on heart antioxidant enzyme activities and left ventricular function in aged mice. Wu Q, Tan Z, Liu H, Gao L, Wu S, Luo J, Zhang W, Zhao T, Yu J, Xu X. Int J Biol Macromol. 2010 Apr 1;46(3):284-8.
16. *Auricularia auricular* polysaccharide protects myocardium against ischemia/reperfusion injury. Ye TM, Qian LB, Cui J, Wang HP, Ye ZG, Xia Q. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2010 May;26(2):154-8.
17. Anti-fertility action of *Auricularia auricula* polysaccharide. He B. Chen Q. Zhongguo Yaoke Daxue Xuebao. 1991;22:48-49.

Coprinus comatus

Japanese name
Sasakure Hitoyotake

Chinese name
Ji Tui Mo / Mao TouGui San

English name
Shaggy Inkcap /Lawyers Wig

A delicious culinary mushroom, especially when young, *C. comatus* is commonly found in woods and fields in the northern temperate zone. It gets its name from the maturing spores, which trigger deliquescence causing the gills to disintegrate into a black spore-rich mass[1].

Containing up to 25% protein when young, it is also rich in triglycerides of which linoleic acid is the most prominent[2].

Traditionally used in Chinese medicine to treat piles and improve digestion[3].

CANCER - As well as possessing broad polysaccharide-mediated immuno-modulatory activity, organic solvent extracts of *C. comatus* have been shown to possess anti-androgenic activity and to inhibit androgen-dependent prostate cancer cell proliferation through multiple mechanisms including inhibition of androgen receptor (AR)-mediated reporter activity, reduction in levels of AR and prostate-specific antigen (PSA) transcription and inhibition of Akt-mediated AR phosphorylation and binding of AR to the PSA enhancer region[4]-[6].

HEPATOPROTECTIVE - *C. comatus* has been shown in animal studies to have a marked hepatoprotective effect with daily administration of 50 mg/kg of *C. comatus* polysaccharide extract producing significant reduction in the negative effects of alcohol on liver structure and function[10],[11].

DIABETES - Several studies have examined the action of *C. comatus* in diabetes with *C. comatus* grown on media enriched with vanadium showing significant hypoglycaemic activity[12]-[17]. However, evaluation of the trace element content of *C. comatus* from different sites in China found no vanadium in any of the wild-harvested specimens and it remains to be determined whether *C. comatus* grown on unenriched substrate would be of any greater benefit in cases of diabetes than other mushrooms[18].

CLINICAL SUMMARY

Main Therapeutic application - *Prostate cancer, alcohol-induced liver damage.*

Key Component - *Polysaccharides, triglycerides.*

Dose - *3g/day polysaccharide and/or ethanolic extract.*

REFERENCES

1. The Fungal Pharmacy. Rogers R. NorthAtlantic Books. 2011:110-114.
2. Isolation and biological activity of triglycerides of the fermented mushroom of *Coprinus Comatus*. Ren J, Shi JL, Han CC, Liu ZQ, Guo JY. BMC Complement Altern Med. 2012 Apr 24;12:52.
3. Icons of Medicinal Fungi from China. Ying J. Science Press 1987.
4. *Coprinus comatus* and *Ganoderma lucidum* interfere with androgen receptor function in LNCaP prostate cancer cells. Zaidman BZ, Wasser SP, Nevo E, Mahajna J. Mol Biol Rep. 2008 Jun;35(2): 107-17.
5. The Culinary-Medicinal Mushroom *Coprinus comatus* as a Natural Antiandrogenic Modulator. Dotan N, Wasser SP, Mahajna J. Integr Cancer Ther. 2011 Jun;10(2):148-59.
6. Inhibition of the androgen receptor activity by *Coprinus comatus* substances. Dotan N, Wasser SP, Mahajna J. Nutr Cancer. 2011 Nov;63(8):1316-27.
7. The Shaggy Ink Cap Medicinal Mushroom, *Coprinus comatus* (O.F.Mull.: Fr.) Pers. (Agaricomycetideae) Substances Interfere with H2O2 Induction of the NF-κB Pathway through Inhibition of IκBα Phosphorylation in MCF7 Breast Cancer Cells. Asatiani MD *et al*. Int J Med Mushr. 2011;13(1):19-25.
8. Inhibitory Effect of Ethyl Acetate Extract of the Shaggy Ink Cap Medicinal Mushroom, *Coprinus comatus* (Higher Basidiomycetes) Fruit Bodies on Cell Growth of Human Ovarian Cancer. Amal Rouhana-Toubi, Solomon P. Wasser, Abed Agbarya, Fuad Fares. Int J Med Mushr. 2013;15(5):457-470.
9. *In vitro* effects on proliferation, apoptosis and colony inhibition in ER-dependent and ER-independent human breast cancer cells by selected mushroom species. Gu YH, Leonard J. Oncol Rep. 2006 Feb;15(2):417-23.
10. Curative effect of crude exopolysaccharides of some macrofungi on alcohol-induced liver damage. Uyanoglu M *et al*. Ultrastruct Pathol. 2013 May;37(3):218-26.
11. Consumption of *Coprinus comatus* polysaccharide extract causes recovery of alcoholic liver damage in rats. Ozalp FO *et al*. Pharm Biol. 2014 Aug;52(8):994-1002.

12. Hypoglycemic activity of fermented mushroom of *Coprinus comatus* rich in vanadium. Han C, Yuan J, Wang Y, Li L. J Trace Elem Med Biol. 2006;20(3):191-6.
13. The co-effect of vanadium and fermented mushroom of *Coprinuscomatus* on glycaemic metabolism. Zhou G, Han C. Biol Trace Elem Res. 2008 Jul;124(1):20-7.
14. Vanadium uptake by biomass of *Coprinus comatus* and their effect on hyperglycemic mice. Han C, Cui B, Wang Y. Biol Trace Elem Res. 2008 Jul;124(1):35-9.
15. A Comparison of Hypoglycemic Activity of Three Species of Basidiomycetes Rich in Vanadium. Han C, Liu T. Biol Trace Elem Res. 2009 Feb;127(2):177-82.
16. Comparison of Vanadium-Rich Activity of Three Species Fungi of Basidiomycetes. Han C, Cui B, Qu J. Biol Trace Elem Res. 2009 Mar;127(3):278-83.
17. Comparison of hypoglycemic activity of trace elements absorbed in fermented mushroom of *Coprinus comatus*. Lu Y, Han L, Yuan C, Guo J. Biol Trace Elem Res. 2009 Nov;131(2):177-85.
18. Determination of trace elements in three mushroom samples of basidiomycetes from Shandong, China. Wang C, Hou Y. Biol Trace Elem Res. 2011 Sep;142(3):843-7.

Cordyceps species/Ophiocordyceps sinensis

(Cordyceps sinesis)

Japanese name
Tochukas

Chinese name
Dong Chong Xia Cao

English name
Caterpillar Fungus

Cordyceps species are unique among the medicinal mushrooms in growing on an insect host rather than a plant host. To date over 700 species of cordyceps have been identified worldwide, in most cases growing parasitically on their insect hosts. However, it has also been suggested that in some cases a symbiotic relationship exists whereby the insect host derives a selective advantage from the fungal anamorph (the asexual form of the fungus), especially in marginal environments where energy efficiency is at a premium, such as the high Tibetan plateau above 3,000m where the main species used

traditionally, *Ophiocordyceps sinensis*, occurs naturally (although previously part of the *Cordyceps* genus, molecular phylogenetic analysis has now led to its being placed in a separate genus, the Ophiocordycipitaceae)[1],[2].

Although traditionally harvested cordyceps is still available, the vast majority of cordyceps on the market today is cultivated on non-insect, grain-based substrates leading to improved quality control and affordability. Despite the commercially cultivated cordyceps being grown on a different substrate from wild collected cordyceps, HPLC analysis shows identical chemical profiles and the two are seen to be interchangeable clinically[3].

As well as polysaccharides and lipids, cordyceps species contain a large number of nucleoside analogues, prominent among which is cordycepin, 3-deoxyadenosine, which is found in high levels in *Cordyceps militaris* and which differs from adenosine in the absence of oxygen at the 3 position of its ribose part[4-7]. Because of its close similarity to adenosine some enzymes cannot distinguish between the two and it is able to participate in certain biochemical reactions, including RNA/DNA synthesis, where its incorporation leads to the termination of the RNA/DNA molecule, there being no oxygen to bond with the next nucleotide[8-11].

This ability to interrupt RNA/DNA synthesis has led to the use of such nucleoside analogues, termed reverse transcriptase inhibitors, in the treatment of viral infections including HIV and hepatitis as well as cancer, under pharmaceutical names including AZT (Retrovir), Videx and Epivir. In normal healthy cells such reverse transcriptase inhibitors are out-competed by the corresponding nucleoside but in rapidly dividing cancer cells and virally infected cells they are able to exert effective inhibition of replication.

Adenosine in the form of adenosine monophosphate and adenosine triphosphate also plays a central role in energy metabolism and cyclic

nucleotides including cAMP play an important role in signal transduction and regulation of hormone production, actions which correlate well with the observed activity of cordyceps in these areas.

As well as *O. sinensis* and *Cordyceps militaris*, a large number of trials have been carried out using a fungal strain isolated from wild *O. sinensis* specimens by China's Academy of Sciences and selected for ease of cultivation by large-scale liquid fermentation technology. Termed Cs-4, this is currently identified as *Paecilomyces hepiali* and continues to be one of the main cordyceps related species used in China.

One *in vitro* study, however, showed Cs-4 to have immune-suppressive activity and the immune-suppressant drug Cyclosporin A has been shown to be present in other fungal strains isolated from wild *O. sinensis* specimens[12-14].

ANTI-AGEING - *O. sinensis* has traditionally been used as a supplement for the elderly and those recovering from long illness. Studies with Cs4 in healthy elderly subjects showed significant increases in oxygen uptake, aerobic capacity and resistance to fatigue.

Experimental evidence based on polysaccharide extracts indicates that *O. sinensis* is also able to improve brain function and antioxidative enzyme activity (superoxide dismutase, glutathione peroxidase and catalase), which, together with its beneficial effect on cardiovascular function, makes it an excellent supplement for the elderly[15].

ATHLETIC PERFORMANCE - The use of *O. sinensis*, together with other supplements, by the record breaking Chinese athletes of the early 1990s has attracted considerable interest in its potential to enhance athletic performance.

A 1996 study on long distance runners reported a significant improvement in 71% of participants and *O. sinensis* and *C. militaris* as well as the cordyceps anamorphs Cs-4 and Cs-HK1, have been shown to increase endurance in animal models. Studies on sedentary humans also show a significant increase in energy output and oxygen capacity[16-20]. However, three studies failed to demonstrate any effect on performance in competitive cyclists or other professional athletes and it has been suggested that this may be because such athletes are already operating at or close to their maximum aerobic capacity[21,22].

SEXUAL FUNCTION - *O. sinensis* produces clear benefits for male sexual hypofunction when taken over a period of time. Anecdotal evidence and reports from China also indicate possible benefits for female libido.

Based on animal studies *O. sinensis* and *C. militaris* have a clear effect on increasing levels of male sex hormones, improving testes morphology, sperm quantity and quality. *In vitro* research indicates that cordyceps affects the signal transduction pathway of steroidogenesis after the formation of cAMP[23-27].

FERTILITY - *O. sinensis* is increasingly being used by leading specialists in the field of infertility and clinical evidence suggests that cordyceps has a beneficial impact on female fertility and the success of IVF. In part this may be due to its ability to stimulate 17β-estradiol (oestrogen) production, through increased StAR (steroidogenic acute regulatory protein) and aromatase expression[28]. In common with other mushrooms, cordyceps' ability to regulate immune function and in particular NK cell activity may also play a part.

The ability of *O. sinensis* to increase oestrogen production also has potential for the management of postmenopausal osteoporosis[29].

DIABETES - Experimental evidence indicates that *O. sinensis* is able to:

- Trigger release of insulin
- Increase hepatic glucokinase
- Increase sensitivity of cells to insulin

In one randomized trial 95% of patients treated with 3g/day *O. sinensis* mycelial biomass saw improvements in their blood sugar profile compared with 54% treated by other methods. In addition it has been reported that consumption of 4.5g/day *O. sinensis* mycelial biomass by patients with alcohol induced diabetes also produced a reduced desire for alcohol[3,30-34].

Recent evidence indicates that cordycepin and related nucleoside derivatives play an active role in the anti-diabetic action of *O. sinensis* and that *C. militaris*, which has high levels of cordycepin, also has significant hypoglycaemic activity[35,36].

HEPATOPROTECTIVE - Multiple studies have shown the ability of both *O. sinensis* and *C. militaris* to inhibit hepatic fibrosis and help restore liver function[37-39]. One clinical study using 3g/day *O. sinensis* mycelial biomass to treat alcohol-induced liver steatosis in 14 patients showed reductions of 70% in AST levels, 63% in ALT levels and 64% in GGT levels over a 90 day period[40].

RENAL HEALTH - *O. sinensis* has traditionally been considered to support the kidneys and 3.5g/day has been shown to both improve kidney function in patients with chronic renal failure and speed recovery in patients with gentamycin-induced kidney damage[3].

RESPIRATORY DISEASE - Traditionally *O. sinensis* has been

used to treat respiratory ailments and is reported to be beneficial for asthma and COPD[3].

ANTI-VIRAL - As mentioned above, the nucleoside analogues present in cordyceps species are able to inhibit viral replication. At the same time the polysaccharides in cordyceps modulate the immune response to viral infections. This combination of enhanced immune response and interrupted viral replication makes cordyceps, especially *C. militaris*, one of the most effective mushrooms for tackling chronic viral infections[9, 10].

CANCER - Because of its combination of immune-modulating polysaccharides and nucleoside derivatives, many practitioners consider Cordyceps to be one of the most useful mushrooms for helping improve treatment outcomes in cancer, with cordycepin reported to induce apoptosis (cancer cell death) in multiple cancer cell lines, including: oral, colorectal, bladder, leukaemia, melanoma, multiple myeloma, breast and prostate[41-51].

CLINICAL SUMMARY

Main Therapeutic Applications - *Fertility and sexual function, energy, diabetes, lung function, kidney support, liver disorders.*

Key Component - *Nucleoside derivatives.*

Dose - *Cordyceps' unique properties are principally those of its nucleoside derivatives and as these are largely excreted (research on C. militaris shows that 98% of cordycepin is secreted into the growth medium[52]) mycelial biomass products offer the natural dosage format for cordyceps. 2-3g/day mycelial biomass is used in most cases while higher levels have been reported to give good results in a range of cancers[2].*

Some practitioners prefer to use C. militaris for cancer and viral infections

due to its higher cordycepin levels[53],[54].

Caution- *Hormone dependent cancers (prostate and breast) due to increased levels of oestrogen and testosterone.*

REFERENCES

1. Cordyceps fungi: natural products, pharmacological functions and developmental products. Zhou X, Gong Z, Su Y, Lin J, Tang K. J Pharm Pharmacol. 2009;61(3):279-91.
2. What is the Chinese caterpillar fungus *Ophiocordyceps sinensis* (Ophiocordycipitaceae)?. Shrestha B, Weimin Z, Yongjie Z & Xingzhong L. Mycology, 2010; 1(4):228-236.
3. Medicinal value of the caterpillar fungi species of the genus Cordyceps (Fr.) Link (Ascomycetes). A Review. Holliday J, Cleaver M. Int J Med Mushr, 2008;10(3):219–234.
4. Analysis of the main nucleosides in *Cordyceps sinensis* by LC/ESI-MS. Xie JW, Huang LF, Hu W, He YB, Wong KP. Molecules. 2010;15(1):305-14.
5. Measurement of cordycepin and adenosine in stroma of Cordyceps sp. by capillary zone electrophoresis (CZE). Ling YJ, Sun YJ, Zhang LP, Zhang CK. J Biosci Bioeng 2002;94:371–74.
6. Chemical Screening and Identification of High Cordycepin Containing Cultured Isolate(s) of Medicinal Chinese Caterpillar Mushroom, *Ophiocordyceps sinensis* (Berk.) GH Sung *et al*. Varshney VK, Pandey A, Kumar A, Rathod D, Kannojia P. Int J Med Mushr. 2011; 13(4):327-333.
7. Chemical composition and nutritional and medicinal value of fruit bodies and submerged cultured mycelia of culinary-medicinal higher Basidiomycetes mushrooms. Cohen N *et al*. Int J Med Mushrooms. 2014;16(3):273-91.
8. Some biologically active substances from a mycelial biomass of medicinal ‘Caterpillar fungus’ *Cordyceps sinensis* (Berk.) Sacc. (Ascomycetes). Smirnov DA, Babitskaya VG, Puchkova TA, Shcherba VV, Bisko NA, Poyedinok NL. Int J Med Mushr. 2009;11(1):80.
9. Effect of Cordycepin Triphosphate on *in vitro* RNA synthesis by plant viral replicases. White JL, Dawson WO. J Virol. 1979;29(2): 811-814.
10. Cordycepin interferes with 3’end formation in yeast independently of its potential to terminate RNA chain elongation. RNA. 2009; 15(5): 837-49.

11. Cordycepin inhibits (collagen induced) human platelet platelet aggregation in a cAMP-and cGMP-dependent manner. Eur J Pharmacol. 2007;558:43-51.
12. Immunosuppressive effect of Cordyceps CS-4 on human monocyte derived dendritic cells *in vitro*. Tang J, Tian D, Liu G. Am J Chin Med. 2010;38(5):961-72.
13. Mycelium cultivation, chemical composition and antitumour activity of a Tolypocladium sp. fungus isolated from wild *Cordyceps sinensis*. Leung PH1, Zhang QX, Wu JY. J Appl Microbiol. 2006 Aug;101(2):275-83.
14. Botanical Medicines: The Desk Reference for Major Herbal Supplements, Second Edition. Mckenna DJ, Jones K, Hughes K, Tyler VM. Pub. Routledge, 2012. p. 170.
15. Antiaging effect of *Cordyceps sinensis* extract. Ji DB, Ye J, Li CL, Wang YH, Zhao J, Cai SQ. Phytother Res. 2009;23(1):116-22.
16. Increased aerobic capacity in healthy elderly humans given a fermentation product of Cordyceps CS-4. Xiao Y, Huang XZ, Chen G, Wang, MB, Zhu, JS, Cooper CB. FACSM Medicine & Science in Sports & Exercise: May 1999; 31(5):174.
17. Randomized double-blind placebo-controlled clinical trial and assessment of fermentation product of *Cordyceps sinensis* (Cs-4) in enhancing aerobic capacity and respiratory function of the healthy elderly volunteers. Xiao Y, Huang XZ and Zhu JS. Chinese Journal of Integrative Medicine. 2004;10,3:187-192.
18. Effect of medicinal plant extracts on forced swimming capacity in mice. Jung K, Kim IH, Han D. J Ethnopharmacol. 2004 Jul; 93(1):75-81.
19. CordyMax enhances aerobic capability, endurance performance, and exercise metabolism in healthy, mid-age to elderly sedentary humans. JS Zhu, JM Rippe - Gerontology, 2001.
20. Effect of Cs-4 (*Cordyceps sinensis*) on exercise performance in healthy older subjects: a double-blind, placebo-controlled trial. Chen S, Li Z, Krochmal R, Abrazado M, Kim W, Cooper CB. J Altern Complement Med. 2010 May;16(5):585-90.
21. *Cordyceps Sinensis* Supplementation Does Not Improve Endurance Performance in Competitive Cyclists. Parcell AC, Smith JM, Schulthies SS, Myrer JW, Fellingham G. Medicine & Science in Sports & Exercise:

2002;34(5):231.

22. Does *Cordyceps sinensis* Ingestion Aid Athletic Performance? TB Walker. Strength and Conditioning Journal, 2006
23. Effect of *Cordyceps militaris* supplementation on sperm production, sperm motility and hormones in Sprague-Dawley rats. Am J Chin Med. 2008;36(5):849-59.
24. *In vivo* and *in vitro* stimulatory effects of *Cordyceps sinensis* on testosterone production in mouse Leydig cells. Life Sci. 2003 Sep 5;73(16):2127-36.
25. Influence of *Cordyceps Sinensis* on Reproduction and Testis Morphology in Mice. Shenzhen Journal of Integrated Chinese and Western Medicine. 2005-6.
26. Improvement of sperm production in subfertile boars by *Cordyceps militaris* supplement. Am J Chin Med. 2007;35(4): 631-41.
27. Estrogenic Substances from the Mycelia of Medicinal Fungus Cordyceps ophioglossoides (Ehrh.) Fr. (Ascomycetes). Hirokazu Kawagishi, Kentaro Okamura, Fumio Kobayashi, Noriko Kinjo. Int J Med Mushr.2004;6(3): 28. Upregulation of Steroidogenic Enzymes and Ovarian 17β-Estradiol in Human Granulosa-Lutein Cells by *Cordyceps sinensis* Mycelium. Biology of Reproduction May 1, 2004 vol. 70 no. 5 1358-1364.
29. The Co-effect of *Cordyceps sinensis* and Strontium on Osteoporosis in Ovariectomized Osteopenic Rats. Qi W, Yan YB, Wang PJ, Lei W. Biol Trace Elem Res. 2010 May 5.
30. Hypoglycemic Activity of a Polysaccharide (CS-F30) from the Cultural Mycelium of *Cordyceps sinensis* and Its Effect on Glucose Metabolism in Mouse Liver. Kiho T, *et al*. Biol Pharm Bull. Feb 1996;19(2):294-96.
31. Structural Features and Hypoglycemic Activity of a Polysaccharide (CS-F10) from the Cultured Mycelium of *Cordyceps sinensis*. Kiho T, Ookubo K, Usui S, *et al*. Biol Pharm Bull. Sep 1999;22(9):966-70.
32. Anti-hyperglycemic activity of natural and fermented in rats with diabetes induced by nicotinamide and streptozotocin. Lo HC, Hsu TH, Tu ST, Lin KC. Am J Chin Med. 2006;34(5):819-32.
33. Hypoglycemic activity of polysaccharide, with antioxidation, isolated from cultured *Cordyceps mycelia*. Li SP, Zhang GH, Zeng Q, Huang ZG, Wang YT, Dong TT, Tsim KW. Phytomedicine. 2006 Jun;13(6):428-33.

34. Cordycepin Suppresses Expression of Diabetes Regulating Genes by Inhibition of Lipopolysaccharide-induced Inflammation in Macrophages. Shin S, Lee S, Kwon J, Moon S, Lee S, Lee CK, Cho K, Ha NJ, Kim K. Immune Netw. 2009 Jun;9(3):98-105.
35. Aqueous Extracts of *Cordyceps militaris* (Ascomycetes) Lower the Levels of Plasma Glucose by Activating the Cholinergic Nerve in Streptozotocin-Induced Diabetic Rats. Cheng YW. Int J Med Mushr. 2013;15(3):277-286.
36. Studies on the antidiabetic activities of *Cordyceps militaris* extract in diet-streptozotocin-induced diabetic Sprague-Dawley rats. Dong Y *et al*. Biomed Res Int. Published online 2014 March 11.
37. Inhibitive Effect of *Cordyceps sinensis* on Experimental Hepatic Fibrosis and its Possible Mechanism-Liu YK, Shen W. Department of Gastrointerology, the Second Affiliated Hosptial, Chongqing University of Medicial Sciences, Chongqing 400010, Chinga World J Gastroenterol. 2003. 2003 Mar;9(3): 529-33.
38. Dynamical Influence of *Cordyceps sinensis* on the Activity of Hepatic Insulinase of Experimental Liver Cirrhosis-Zhang X, Liu YK, Shen W, Shen DM. Hepatobiliary Pancreat Dis Int. 2004 Beb;3(1):99-101.
39. *Cordyceps militaris* alleviates non-alcoholic fatty liver disease in ob/ob mice. Choi HN, Jang YH, Kim MJ, Seo MJ, Kang BW, Jeong YK, Kim JI. Nutr Res Pract. 2014 Apr;8(2):172-6.
40. *Cordyceps sinensis* Supplementation as Immunonutrition in Alcohol Induced Liver Steatosis-II. Santos C. Mycology News, 2004;1(9):2-3.
41. RNA-directed agent, cordycepin, induces cell death in multiple myeloma cells. Chen LS, Stellrecht CM, Gandhi V. Br J Haematol. 2008 Mar;140(6):682-391. 30. Antitumour activity of Cordycepin in mice. Clin Exp Pharmacol Physiol. 31, S51-S53. 2004.
42. Cordycepin inhibits protein synthesis and cell adhesion through effects on signal transduction. J Biol Chem. 2010 Jan 22;285(4): 2610-21.
43. Effect of cordycepin on interleukin-10 production of human peripheral blood mononuclear cells. European Journal of Pharmacology, volume 453, Issues 2-3, 25 October 2002, Pages 309-317.
44. Cordycepin suppresses TNF-alpha-induced invasion, migration and matrix metalloproteinase-9 expression in human bladder cancer cells. Lee EJ, Kim WJ, Moon SK. Phytother Res. 2010 Jun 17.

45. Role of Cordycepin and Adenosine on the Phenotypic Switch of Macrophages via Induced Anti-inflammatory Cytokines. Shin S, Moon S, Park Y, Kwon J, Lee S, Lee CK, Cho K, Ha NJ, Kim K.Immune Netw. 2009 Dec;9(6):255-64.
46. Involvement of autophagy in cordycepin-induced apoptosis in human prostate carcinoma LNCaP cells. Lee HH *et al*. Environ Toxicol Pharmacol. 2014 Jul;38(1):239-50.
47. Cordycepin: a bioactive metabolite with therapeutic potential. Tuli HS, Sharma AK, Sandhu SS, Kashyap D. Life Sci. 2013 Nov 26;93(23):863-9.
48. Anti-cancer effect and apoptosis induction of cordycepin through DR3 pathway in the human colonic cancer cell HT-29. Lee SY, Debnath T, Kim SK, Lim BO. Food Chem Toxicol. 2013 Oct;60:439-47.
49. Medicinal uses of the mushroom *Cordyceps militaris*: current state and prospects. Das SK, Masuda M, Sakurai A, Sakakibara M. Fitoterapia. 2010 Dec;81(8):961-8.
50. Advances on *Cordyceps militaris* constituents and pharmacological effect. Fan HT, Lin HS. Zhongguo Zhong Yao Za Zhi. 2013 Aug;38(15):2549-52.
51. Extract of *Cordyceps militaris* inhibits angiogenesis and suppresses tumor growth of human malignant melanoma cells. Ruma IM *et al*. Int J Oncol. 2014 Jul;45(1):209-18.
52. Production of cordycepin by surface culture using the medicinal mushroom *Cordyceps militaris*. Masuda M, Urabe E, Akihiko Sakurai A, Sakakibara M. Enzyme and Microbial Technology 2006;39(4):641-646.
53. Cultivation of Medicinal Caterpillar Fungus, *Cordyceps militaris* (Ascomycetes), and Production of Cordycepin Using the Spent Medium from Levan Fermentation. Wu FC, Chen YL, Chang SM, Shih IL. Int J Med Mushr. 2013;15(4):393-405.
54. Determination of nucleosides and nucleobases in different species of Cordyceps by capillary electrophoresis-mass spectrometry. Yang FQ, Ge L, Yong JW, Tan SN, Li SP. J Pharm Biomed Anal. 2009 Oct 15;50(3):307-14.

Flammulina velutipes

Japanese name
Enokitake

Chinese name
Jin Zhen Gu/Dong Gu

English name
Velvet Foot/Winter Mushroom/Golden Needle Mushroom

A common culinary mushroom, *F. velutipes* was the second earliest mushroom to be cultivated (cultivation started around 800 AD, after *Auricularia auricula* -600 AD, and before *Lentinula edodes* -1000 AD).

It shows considerable clinical promise, especially for cancer prevention protocols.

A study of 174,505 inhabitants of the Nagano area of Japan

compared the cancer death rates among *F. velutipes* farmers with rates in the general population over a 15 year period (1972-86) and found that the *F. velutipes* farmers had a much lower death rate of 97.1 per 100,000, compared to 160.1 per 100,000 in the general population, with the suggestion that this was due to increased consumption of *F. velutipes*[1].

Following on from the above a case-control study investigated the relationship between risk reduction of stomach cancer and intake of edible mushrooms in the same prefecture from 1998 to 2002. While the odds ratio (OR) of subjects who were eating hardly any mushrooms or mushrooms less than once a week was 1.00, consumption of *F. velutipes* more than three times a week produced a reduction to 0.66 (the OR of those taking *L. edodes* more than three times a week was 0.95)[2].

As well as immunomodulatory polysaccharides[3,5], *F. velutipes* is notable for its high protein content (31.2%), which includes a large number of protein-rich components with strong immunomodulatory and anticancer activity[6-11].

F. velutipes extracts also demonstrate strong tyrosinase inhibition[12].

CANCER -*F. velutipes* extracts show exceptionally high anticancer activity *in vitro*. In one study of extracts from 38 mushrooms carried out by Bastyr University, *F. velutipes* had one of the highest levels of inhibitory activity against two oestrogen-dependent and one oestrogen-independent breast cancer cell lines[13]. In a separate study of aqueous extracts from 20 mushrooms and three mushroom polysaccharides, the aqueous extract from *F. velutipes*, together with that from *Pleurotus ostreatus*, showed the highest level of cytotoxic activity against androgen-independent prostate cancer cells[14].

In vivo, EA6, a protein-bound polysaccharide isolated from the fruiting body of *F. velutipes*, augmented humoral immunity, cellular

immunity, and IL-2 production in mice bearing Meth-A fibrosarcoma at 10mg/kg and administration after surgery markedly inhibited growth of the rechallenged Meth-A solid tumour, while Proflammin (90% protein, 10% polysaccharide) isolated from the mycelium of *F. velutipes* abolished suppression of immunocompetence after cryosurgery at 10mg/kg/day[15].

Another protein from *F. velutipes*, Fve, protected mice against liver cancer through activation of both innate and adaptive immune responses when administered orally at a dose of 10mg/kg[16].

In clinical studies EEM, a combination of extracts from *F. velutipes* and *Hypsizygus marmoreus*, revealed superior results to MPA (methyl-acetoxy-progesterone) on the cachexia of advanced cancer patients with better clinical response, performance status (PS), and quality of life (QOL). EEM supplementation in combination with anticancer drugs improved the clinical response rate, PS, and QOL of advanced cancer patients compared to patients treated with anticancer drugs alone. EEM supplementation also reduced precancerous lesions on the oesophageal mucosa[2].

ANTI-VIRAL - Co-administration of Fve, a protein from *F. velutipes*, with immunization against HPV-16 led to 60% of mice remaining tumour-free 167 days after challenge with tumour cells compared to 20% of those receiving immunization alone. The co-immunized mice showed enhanced production of HPV-16 E7 oncoprotein-specific antibodies as well as expansion of HPV-16 E7-specific interferon (IFN)-gamma-producing CD4(+) and CD8(+) T cells compared to mice immunized with HPV-16 E7 alone[17].

Proteins from *F. velutipes* also show direct anti-viral activity, including ribosome inactivating activity and inhibition of HIV-1 reverse transcriptase, beta-glucosidase and beta-glucuronidase[18].

FOOD ALLERGIES - Mice orally given five daily 200 µg doses of protein from *F. velutipes* before and after each of two intraperitoneal injections of ovalbumin significantly reduced symptoms of anaphylaxis and levels of plasma histamine on subsequent oral challenge with ovalbumin and demonstrated an impaired OVA-specific IgE response with a Th1-predominant cytokine profile[19]. Other research has demonstrated the ability of the *F. velutipes* protein Fve to enhance eosinophil apoptosis, with therapeutic implications for eosinophil-related allergic inflammation, and of an ethanol extract to suppress hypersensitive immune response[20-22].

CLINICAL SUMMARY

Main Therapeutic Application - *Dietary supplementation in patients at risk of cancer or with chronic viral conditions.*

Key Component - *Proteins and polysaccharides.*

Dose - *F. velutipes fruiting body contains high levels of the therapeutically active proteins at a reasonable cost and is the preferred dosage form in most cases with 3-5g dried fruiting body equating to 30-50g fresh mushroom.*

Safety - *Flammutoxin, a protein found in F. velutipes that is cytolytic and cardiotoxic when injected has been shown to be non-toxic when absorbed orally*[23].

REFERENCES

1. Beneficial effects of edible and medicinal mushrooms on health care. Ikekawa T - Int J Med Mushr. 2001;3(4):8-12.
2. Cancer Risk Reduction by Intake of Mushrooms and Clinical Studies on EEM. Ikekawa T. Int J Med Mush. 2005;7(3):347.
3. Inhibitory activity of polysaccharide extracts from three kinds of edible fungi on proliferation of human hepatoma SMMC-7721 cell and mouse implanted S180 tumour. Jiang SM, Xiao ZM, Xu ZH. World J Gastroenterol. 1999;5(5):404-407.
4. Investigation of immunomodulating activity of the medicinal mushroom *Flammulina velutipes* (Curt.: Fr.) P. Karst. *in vitro*. Cytokine induction by fruiting body extract Badalyan S, Hambardzumyan L.A. Int J Med Mush. 2001;3(2-3):110-111.
5. Purification, characterization and immunomodulating properties of polysaccharides isolated from *Flammulina velutipes* mycelium. Yin H, Wang Y, Wang Y, Chen T, Tang H, Wang M. Am J Chin Med. 2010;38(1):191-204.
6. Effect of *Flammulina velutipes* polysaccharides on production of cytokines by murine immunocytes and serum levels of cytokines in tumour-bearing mice. Chang HL, Lei LS, Yu CL, Zhu ZG, Chen NN, Wu SG. Zhong Yao Cai. 2009;32(4):561-3.
7. FIP-fve stimulates interferon-gamma production via modulation of calcium release and PKC-alpha activation. Ou CC, Hsiao YM, Wu WJ, Tasy GJ, Ko JL, Lin MY. J Agric Food Chem. 2009;57(22):11008-13.
8. Fungal immunomodulatory protein from *Flammulina velutipes* induces interferon-gamma production through p38 mitogen-activated protein kinase signaling pathway. Wang PH, Hsu CI, Tang SC, Huang YL, Lin JY, Ko JL. J Agric Food Chem. 2004;52(9):2721-5.
9. Flammulin: a novel ribosome-inactivating protein from fruiting bodies of the winter mushroom *Flammulina velutipes*. Wang HX, Ng TB. Biochem Cell Biol. 2000;78(6):699-702.

10. High processing tolerances of immunomodulatory proteins in Enoki and Reishi mushrooms. Tong MH, Chien PJ, Chang HH, Tsai MJ, Sheu F. J Agric Food Chem. 2008;56(9):3160-6.
11. Interruption of lung cancer cell migration and proliferation by fungal immunomodulatory protein FIP-fve from *Flammulina velutipes*. Chang YC, Hsiao YM, Wu MF, Ou CC, Lin YW, Lue KH, Ko JL. J Agric Food Chem. 2013 Dec 11;61(49):12044-52.
12. Isolation of 1', 3'-dilinolenoyl'-2'-linoleoylglycerol with tyrosinase inhibitory activity from *Flammulina velutipes*. Jang SG, Jeon KS, Lee EH, Kong WS, Cho JY. J Microbiol Biotechnol. 2009;19(7):681-4.
13. *In vitro* effects on proliferation, apoptosis and colony inhibition in E-dependent and ER-independent human breast cancer cells by selected mushroom species. Gu YH, Leonard J. Oncology Reports. 2006;15:417-423.
14. Cytotoxic effect of oyster mushroom *Pleurotus ostreatus* on human Androgen-independent prostate cancer PC-3 Cells. Gu YH, Sivam G. J Med Food. 2006;9(2):196-204.
15. Immunomodulation and antitumour activity of a mushroom product, Proflamin, isolated from *Flammulina velutipes* (W. Curt.: Fr.) Singer (Agaricomycetideae). Maruyama H, Ikekawa T. Int J Med Mushr. 2007;9(2):20.
16. Oral administration of an Enoki mushroom protein FVE activates innate and adaptive immunity and induces antitumour activity against murine hepatocellular carcinoma. Chang HH, Hsieh KY, Yeh CH, Tu YP, Sheu F. Int Immunopharmacol. 2010;10(2):239-46.
17. Coadministration of the fungal immunomodulatory protein FIP-Fve and a tumour-associated antigen enhanced antitumour immunity. Ding Y, Seow SV, Huang CH, Liew LM, Lim YC, Kuo IC, Chua KY. Immunology. 2009;128(1Sup):881-94.
18. Isolation and characterization of velutin, a novel low-molecular-weight ribosome-inactivating protein from winter mushroom *(Flammulina velutipes*) fruiting bodies. Wang H, Ng TB. Life Sci. 2001;68(18):2151-8.
19. Oral administration of an edible-mushroom-derived protein inhibits the development of food-allergic reactions in mice. Hsieh KY, Hsu C, Lin JY, Tsai CC, Lin RH. Clin Exp Allergy. 2003;33(11):1595-602.
20. The modulatory effect of FIP-fve on eosinophil apoptosis *in vitro* indicates

that it may have some therapeutic effect on eosinophil-related allergic inflammation *in vivo*. J Formos Med Assoc. 2007; 106(1):36-43.

21. Eosinophil apoptosis induced by fungal immunomodulatory peptide-fve via reducing IL-5alpha receptor. Hsieh CW, Lan JL, Meng Q, Cheng YW, Huang HM, Tsai JJ. J Formos Med Assoc. 2007;106(1):36-43.
22. Inhibitory effects of edible higher Basidiomycetes mushroom extracts on mouse type IV allergy. Sano M, Yoshino K, Matsuzawa T, Ikekawa T. Int J Med Mushr. 2002;4(1):37-41.
23. Handbook of Mushroom Poisoning: Diagnosis and Treatment. Rumack BH, Spoerke DG. CRC Press 1994, p.394.

Ganoderma lucidum

Japanese name
Reishi or Mannetake (10,000 year mushroom/mushroom of immortality)

Chinese name
Ling Zhi (spirit mushroom - mushroom of spritual potency)

The most famous of all the medicinal mushrooms with annual sales of over US$2billion, *G. lucidum's* wide-ranging health benefits are due to its combination of high polysaccharide content (Stamets reports the fruiting body to contain 41% beta-glucan) and triterpenoid compounds[1-4]. Over 130 of these have been identified, belonging primarily to two families: ganoderic and lucidenic acids with functions including:

- Inhibiting histamine release
- Hepatoprotective
- Anti-hypertensive (ACE inhibiting)
- Inhibiting cholesterol synthesis

- Anti-inflammatory
- Inducing apoptosis
- Inhibiting viral induction
- Antioxidant
- Anti-tumour
- CNS sedation
- Antimicrobial
- Immune modulation

Levels of triterpenes are particularly high in *G. lucidum* spores, typically >2.0% in shell-broken spore powder and >30% in the spore oil and recent studies report promise for the spores and spore oil as anti-cancer and neuroprotective agents[5-8].

G. lucidum shows exceptionally high tyrosinase inhibition with the highest activity in the aqueous extract. This has led to its inclusion in many commercial skin whitening products and has medical implications, especially in relation to Parkinson's Disease (see discussion under Parkinson's Disease)[9-11].

A number of related species have also been investigated with polysaccharides and triterpenes from both *Ganoderma tsugae* and *Ganoderma applanatum* showing similar anti-tumour, anti-inflammatory, immune-modulatory and hepatoprotective activity to those from *G. lucidum* and *Ganoderma japonicum* showing neuroprotective properties[12-21].

CANCER - *G. lucidum* has a long history of traditional use in the treatment of cancer and is credited with many cases of spontaneous remission[22,23]. As well as the immune modulating effect of its high polysaccharide content, its triterpenes show significant cytotoxic activity against different cancer cell lines, as well as inhibitory effects against Epstein-Barr virus, known to be associated with some cancers[24-35]. In addition triterpenes from *G. lucidum* show inhibition of

the nuclear transcription factor, NF-kappaB (NF-kB), which is overexpressed in various cancer cell lines, and also the AP-1 signalling pathway[36].

Inhibition of NF-kB is of particular importance in the activity of *G. lucidum* against breast and prostate cancers as it is considered to play an essential role in the hormone independent growth and spread of these cancers[37],[38]. In addition *G. lucidum* triterpenes have been shown to block the androgen receptor on prostate cancer cells, supporting *G. lucidum*'s use in the treatment of prostate cancer.

Clinical studies with *G. lucidum* polysaccharide extract confirm its ability to enhance immune status in cancer patients with increases in NK cell activity and Th1 cytokine levels and decreases in Th2 cytokine levels in advanced lung cancer patients, and reduction in side effects when given alongside chemotherapy and radiotherapy[39-41].

In vitro and *in vivo* studies also indicate significant anti-tumour activity for the triterpene-rich *G. lucidum* spore powder and spore oil[42-47]. A randomized controlled trial of 48 breast cancer patients reported reductions in fatigue, anxiety and depression in the treatment group (3g/day *G. lucidum* spore powder), together with improvements in immune parameters[48].

ALLERGIES - As well as immunomodulatory activity, *G. lucidum* demonstrates strong anti-inflammatory activity with suppression of tumour necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), the inflammatory mediator nitric oxide (NO) and prostaglandin E2, mediated through inhibition of the NF-kB and AP-1 signaling pathways. This combination of immunomodulatory and anti-inflammatory activity contributes to its efficacy in the treatment of allergies and other inflammatory conditions[49-52].

G. lucidum is a component of FAHF-2, a Chinese herbal formula that has been reported to completely block anaphylactic reactions in a

mouse model of peanut allergy[53].

LIVER DISEASE - The fruiting body of *G. lucidum* has long been a popular traditional treatment for liver diseases and demonstrates wide hepatoprotective properties[54-60]. It appears that at least part of its action in this regard may be through the ability of *G. lucidum* triterpenes to block platelet-derived growth factor beta receptor (PDGFbetaR), thus inhibiting the activation and proliferation of hepatic stellate cells, a key event in hepatic fibrosis[61].

G. lucidum is also traditionally used in the treatment of hepatitis and in a clinical study of 355 cases of hepatitis B treated with Wulingdan Pill, of which *G. lucidum* is the major component, 92.4% of patients were reported to have positive results[62]. Again, it appears that triterpenes are the key components[63, 64].

HYPERTENSION - *G. lucidum* has a broad range of action on cardiovascular health. Polysaccharides and triterpenes isolated from *G. lucidum* have shown hyperlipidaemic, hypotensive, and anti-thrombotic effects while a polysaccharide preparation (Ganopoly) led to improved ECG and lowered chest pain, palpitation and shortness of breath in a double-blind, randomized, multi-centre study[65]. Mild ACE-inhibitory activity has also been demonstrated for some of *G. lucidum*'s triterpenoid compounds[66, 67].

INSOMNIA/ANXIETY - The traditional name 'spirit mushroom' points to the sedative action of its triterpenoid components and many herbalists value its benefits in cases of insomnia. Christopher Hobbs recommends *G. lucidum* for deficiency insomnia while Mizuno recommends it for 'mental stabilisation'[68-71].

RHEUMATOID ARTHRITIS - *G. lucidum*'s combination of immunomodulatory and anti-inflammatory action suggests potential application in the treatment of autoimmune conditions such as rheumatoid arthritis and a proteoglycan fraction from *G. lucidum* has been shown to inhibit production of rheumatoid arthritis synovial fibroblasts *in vitro*, in part through inhibition of the NF-kB transcription pathway[72].

NEUROPROTECTIVE - Traditionally considered to promote longevity, *G. lucidum* extract has been shown to inhibit beta-amyloid synaptic toxicity with potential benefits in Alzheimer's disease[73]. Both polysaccharides and triterpenes from *G. lucidum* exhibit neuroprotective and anticonvulsant effects at levels of 10-80mg/kg while *G. lucidum* spores have shown ability to protect neurons from apoptosis and improve cognitive dysfunction *in vivo*[74-78].

ANTI-AGEING - Traditionally known as the 'mushroom of immortality', *G. lucidum*'s broad-spectrum cardiovascular, neurological and immunological benefits, together with its support for blood sugar and cholesterol control[79-82], contribute to its anti-ageing properties.

CLINICAL SUMMARY

Main Therapeutic Applications - *Allergies, liver support, cancer (especially breast and prostate), hypertension, anxiety/insomnia.*

Together with Cordyceps sinensis, G. lucidum has the most extensive range of indications and combines well with it in treatment of lung and liver conditions, as well as to provide all-round adaptogenic support.

Key Components - *Triterpenes and polysaccharides.*

Dose - *Traditional materia medica recommend a dose range for crude G.*

lucidum of 3-15g/day in decoctions or 1.5-3g as powder or in pills while doses of up to30g/day have been reported and 5.4g/day of polysaccharide extract and 3.0g/day and G. lucidum spore powder have been used in clinical trials[23],[48],[83-85].

Dose range for dual-extraction products combining polysaccharide-rich hot-water and triterpene-rich ethanolic (alcohol-based) extracts is typically 1-3g/day while 500-1,000mg/day is normal for G. lucidum spore oil products.

Caution - *Patients on anti-coagulant medication should be monitored due to G. lucidum's actions in this area although a study of G. lucidum supplementation (1.5g/day) in healthy volunteers showed no effect on haemostatic function*[86],[87].

REFERENCES

1. Reishi mushroom: herb of spiritual potency and medical wonder. Willard T. 1990. Pub. Sylvan Press, Issaquah.
2. Global marketing of medicinal ling zhi mushroom *Ganoderma lucidum* (W.Curt.:Fr.) Lloyd (Aphyllophoromycetideae) Products and Safety Concerns. Lai T, Gao Y, Zhou S. Int J Med Mushr. 2004;6(2):100.
3. *Ganoderma lucidum* and its pharmaceutically active compounds. Boh B, Berovic M, Zhang J, Zhi-Bin L. Biotechnol Annu Rev. 2007;13:265-301.
4. Ganoderma - a therapeutic fungal biofactory. Paterson R.R. Phytochemistry. 2006;67(18):1985-2001.
5. Antitumour activity of the sporoderm-broken germinating spores of *Ganoderma lucidum*. Liu X, Yuan JP, Chung CK, Chen XJ. Cancer Lett. 2002;182(2):155-61.
6. Sterols and triterpenoids from the spores of *Ganoderma lucidum*. Zhang CR, Yang SP, Yue JM. Nat Prod Res. 2008;22(13):1137-42.
7. Chemical constituents of the spores of *Ganoderma lucidum*. Zhang XQ, Pang GL, Cheng Y, Wang Y, Ye WC. Zhong Yao Cai. 2008;31(1):41-4.
8. Comparative studies on the immunomodulatory and antitumour activities of the different parts of fruiting body of *Ganoderma lucidum* and Ganoderma spores. Yue GG, Fung KP, Leung PC, Lau CB. Phytother Res. 2008;22(10):1282-91.
9. Inhibition of tyrosinase from *Ganoderma lucidum*. Chu HL, Wu HC, Yen-Chin Chen YC, Kuo JM. 12th World Food Congress. 2003;166(2):117-20.
10. Effects on tyrosinase activity by the extracts of *Ganoderma lucidum* and related mushrooms. Chien CC, Tsai ML, Chen CC, Chang SJ, Tseng CH. Mycopathologia. 2008;166(2):117-20.
11. Dopamine-or L-DOPA-induced neurotoxicity: the role of dopamine quinone formation and tyrosinase in a model of Parkinson’s disease. Asanuma M, Miyazaki I, Ogawa N. Neurotox Res. 2003;5(3): 165-76.
12. Effect of polysaccharides from *Ganoderma applanatum* on immune

responses. I. Enhancing effect on the induction of delayed hypersensitivity in mice. Nakashima S, Umeda Y, Kanada T. Microbiol Immunol. 1979;23(6):501-13.

13. Antitumor active protein-containing glycans from the Chinese mushroom songshan lingzhi, *Ganoderma tsugae* mycelium. Zhang J *et al*. Biosci Biotechnol Biochem. 1994 Jul;58(7):1202-5.
14. Effect of *Ganoderma tsugae* on chronically carbon tetrachloride-intoxicated rats. Wu YW, Chen KD, Lin WC. Am J Chin Med. 2004;32(6):841-50.
15. Effects of triterpenoid-rich extracts of *Ganoderma tsugae* on airway hyperreactivity and Th2 responses *in vivo*. Chen ML, Lin BF. Int Arch Allergy Immunol. 2007;143(1):21-30.
16. A comparison study on the physical/chemical properties and immunomodulatory activities of mycelial polysaccharide extracts from five Ganoderma species. Chen CF, Yang XT, Li XQ, Mi K, Yang QY. Wei Sheng Wu Xue Bao. 2007 Aug;47(4):628-33.
17. Antiinflammatory triterpenoids and steroids from *Ganoderma lucidum* and *G. tsugae*. Ko HH, Hung CF, Wang JP, Lin CN. Phytochemistry. 2008 Jan;69(1):234-9
18. *Ganoderma applanatum*: a promising mushroom for antitumor and immunomodulating activity. Jeong YT, Yang BK, Jeong SC, Kim SM, Song CH. Phytother Res. 2008 May;22(5):614-9.
19. *Ganoderma tsugae* extracts inhibit colorectal cancer cell growth via G(2)/M cell cycle arrest. Hsu SC *et al*. J Ethnopharmacol. 2008 Dec 8;120(3):394-401.
20. *Ganoderma applanatum* terpenes protect mouse liver against benzo(α)pyrene-induced oxidative stress and inflammation. Ma JQ, Liu CM, Qin ZH, Jiang JH, Sun YZ. Environ Toxicol Pharmacol. 2011 May;31(3):460-8.
21. *Ganoderma tsugae* Extract Inhibits Growth of HER2-Overexpressing Cancer Cells via Modulation of HER2/PI3K/Akt Signaling Pathway. Kuo HP *et al*. Evid Based Complement Alternat Med. Epub 2013 Apr 7.
22. Anticancer effects of *Ganoderma lucidum*: a review of scientific evidence. Yuen JW, Gohel MD. Nutr Cancer. 2005; 53(1):11-7.
23. Regression of gastric large B-Cell lymphoma accompanied by a florid

lymphoma-like T-cell reaction: immunomodulatory effect of *Ganoderma lucidum* (Lingzhi) Cheuk W, Chan JK, Nuovo G, Chan MK, Fok M. Int J Surg Pathol. 2007;15(2):180-6.

24. Potential of a novel polysaccharide preparation (GLPP) from Anhui-grown *Ganoderma lucidum* in tumour treatment and immuno-stimulation. Pang X, Chen Z, Gao X, Liu W, Slavin M, Yao W, Yu L.L. J Food Sci. 2007;72(6):S435-42.
25. Cytotoxic triterpenoids from *Ganoderma lucidum*. Cheng CR, Yue QX, Wu ZY, Song XY, Tao SJ, Wu XH, Xu PP, Liu X, Guan SH, Guo DA. Phytochemistry. 2010;71(13):1579-1585.
26. Triterpenes from *Ganoderma lucidum* induce autophagy in colon cancer through the inhibition of p38 mitogen-activated kinase (p38 MAPK). Thyagarajan A, Jedinak A, Nguyen H, Terry C, Baldridge L.A, Jiang J, Sliva D. Nutr Cancer. 2010;62(5):630-40.
27. Ganoderic acid T inhibits tumour invasion *in vitro* and *in vivo* through inhibition of MMP expression. Chen NH, Liu JW, Zhong JJ. Pharmacol Rep. 2010;62(1):150-63.
28. Inhibitory effects of *Ganoderma lucidum* on tumourigenesis and metastasis of human hepatoma cells in cells and animal models. Weng CJ, Chau CF, Yen GC, Liao JW, Chen DH, Chen KD. J Agric Food Chem. 2009;57(11):5049-57.
29. Cytotoxic lanostanoid triterpenes from *Ganoderma lucidum*. Guan SH, Xia JM, Yang M, Wang XM, Liu X, Guo DA. J Asian Nat Prod Res. 2008;10(7-8):705-10.
30. The anti-invasive effect of lucidenic acids isolated from a new *Ganoderma lucidum* strain. Weng CJ, Chau CF, Chen KD, Chen DH, Yen GC. Mol Nutr Food Res. 2007;51(12):1472-7.
31. Lucidenic acids P and Q, methyl lucidenate P, and other triterpenoids from the fungus *Ganoderma lucidum* and their inhibitory effects on Epstein-Barr virus activation. Iwatsuki K *et al*. J Nat Prod. 2003 Dec;66(12):1582-5.
32. *Ganoderma lucidum* polysaccharides: immunomodulation and potential antitumor activities. Xu Z, Chen X, Zhong Z, Chen L, Wang Y. Am J Chin Med. 2011;39(1):15-27.
33. Antitumor and anti-inflammatory activities of polysaccharides isolated from *Ganoderma lucidum*. Joseph S, Sabulal B, George V, Antony KR,

Janardhanan KK.Acta Pharm. 2011 Sep 1;61(3):335-42.

34. Anticancer properties of triterpenoids isolated from *Ganoderma lucidum* - a review. Wu GS, Guo JJ, Bao JL, Li XW, Chen XP, Lu JJ, Wang YT. Expert Opin Investig Drugs. 2013 Aug;22(8): 981-92.
35. Triterpenoids from *Ganoderma lucidum* and their cytotoxic activities. Li P, Deng YP, Wei XX, Xu JH. Nat Prod Res. 2013;27(1):17-22.
36. Suppression of the inflammatory response by triterpenes isolated from the mushroom *Ganoderma lucidum*. Dudhgaonkar S, Thyagarajan A, Sliva D.Int Immunopharmacol. 2009;9(11): 1272-80.
37. *Ganoderma lucidum* suppresses motility of highly invasive breast and prostate cancer cells. Sliva D, Labarrere C, Slivova V, Sedlak M, Lloyd F.P Jr, Ho N.W. Biochem Biophys Res Commun. 2002;298(4):603-12.
38. *Ganoderma lucidum* suppresses growth of breast cancer cells through the inhibition of Akt/NF-kappaB signaling. Jiang J, Slivova V, Harvey K, Valachovicova T, Sliva D. Nutr Cancer. 2004;49(2):209-16.
39. Effects of ganopoly (a *Ganoderma lucidum* polysaccharide extract) on the immune functions in advanced-stage cancer patients. Gao Y, Zhou S, Jiang W, Huang M, Dai X. Immunol Invest. 2003;32(3): 201-15.
40. Effects of water-soluble *Ganoderma lucidum* polysaccharides on the immune functions of patients with advanced lung cancer. Gao Y *et al*. J Med Food. 2005;8(2):159-68.
41. *Ganoderma lucidum* (Reishi mushroom) for cancer treatment. Jin X, Ruiz Beguerie J, Sze DM, Chan GC. Cochrane Database Syst Rev. 2012 Jun 13.
42. Antitumor activity of the sporoderm-broken germinating spores of *Ganoderma lucidum*. Liu X, Yuan JP, Chung CK, Chen XJ. Cancer Lett. 2002 Aug 28;182(2):155-61.
43. Glossy ganoderma spore oil promotes apoptosis of human lung adenocarcinoma SPC-A1 through downregulation of miR-21. Zhao G, Guo W, Zhao X, Wang Y, Hou Y. Zhongguo Zhong Yao Za Zhi. 2011 May;36(9):1231-4.
44. Inhibitory effects of sporoderm-broken *Ganoderma lucidum* spores on growth of lymphoma implanted in nude mouse. Chen J, Yu YH. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2012 Apr; 20(2):310-4.
45. Extract of sporoderm-broken germinating spores of *Ganoderma lucidum*

activates human polymorphonuclear neutrophils via the P38 mitogen-activated protein kinase pathway. Hsu PY, Chern JL, Chen HY, Yang SH. Chang Gung Med J. 2012 Mar-Apr; 35(2):140-7.

46. Study the rudimentary immunoregulatory mechanisms of Ganoderma Spore oil on immunocompromized mice. Yi Y, Hu S, Xiong X, Liu D, Zhong Y. Wei Sheng Yan Jiu. 2012 Sep; 41(5):833-9.
47. Ganoderma spore induced increased CA72-4 in three gastroenteric tumor patients and literature analysis. Yan B, He ZH, Qin ZF. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2012 Oct; 32(10):1426-7.
48. Spore Powder of *Ganoderma lucidum* Improves Cancer-Related Fatigue in Breast Cancer Patients Undergoing Endocrine Therapy: A Pilot Clinical Trial. Zhao H, Zhang Q, Zhao L, Huang X, Wang J, Kang X. Evid Based Complement Alt Med. Epub 2011 Dec 10.
49. Anti-allergic constituents in the culture medium of *Ganoderma lucidum*. (I). Inhibitory effect of oleic acid on histamine release. Tasaka K, Akagi M, Miyoshi K, Mio M, Makino T. Inflammation Research. 1988;23(3-4):153-6.
50. Anti-allergic constituents in the culture medium of *Ganoderma lucidum*. (II). The inhibitory effect of cyclooctasulfur on histamine release. Tasaka K, Mio M, Izushi K, Akagi M, Makino T. Inflammation Research. 1988;23(3-4):157-60.
51. Effectiveness of Dp2 nasal therapy for Dp2-induced airway inflammation in mice: using oral *Ganoderma lucidum* as an immunomodulator. Liu Y.H, Tsai C.F, Kao M.C, Lai Y.L, Tsai J.J. J Microbiol Immunol Infect. 2003;36(4):236-428.
52. The use of *Ganoderma lucidum* (Reishi) in the management of Histamine-mediated allergic responses. Powell M. Nutritional Practitioner Magazine. October 2004.
53. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in murine model of peanut allergy. Srivastava KD *et al*. J Allergy Clin Immunol. 2005;115(1):171-8.
54. Antimutagenic activity of methanolic extract of *Ganoderma lucidum* and its effect on hepatic damage caused by benzo[a]pyrene. Lakshmi B, Ajith T.A, Jose N, Janardhanan K.K. J Ethnopharmacol. 2006;107(2):297-303.
55. Effects of *Ganoderma lucidum* polysaccharide on CYP2E1, CYP1A2 and CYP3A activities in BCG-immune hepatic injury in rats. Wang X, Zhao X,

Li D, Lou Y.Q, Lin Z.B, Zhang G.L. Biol Pharm Bull. 2007;30(9):1702-6.

56. Post-treatment of *Ganoderma lucidum* reduced liver fibrosis induced by thioacetamide in mice. Wu Y.W, Fang H.L, Lin W.C. Phytother Res. 2010;24(4):494-9.
57. *In vitro* and *in vivo* protective effects of proteoglycan isolated from mycelia of *Ganoderma lucidum* on carbon tetrachloride-induced liver injury. Yang XJ, Liu J, Ye LB, Yang F, Ye L, Gao JR, Wu ZH. World J Gastroenterol. 2006;12(9):1379-85.
58. Antifibrotic effects of a polysaccharide extracted from *Ganoderma lucidum*, glycyrrhizin, and pentoxifylline in rats with cirrhosis induced by biliary obstruction. Park EJ, Ko G, Kim J, Sohn DH. Biol Pharm Bull. 1997;20(4):417-20.
59. Hepatoprotective effects of mushrooms. Soares AA, de Sá-Nakanishi AB, Bracht A, da Costa SM, Koehnlein EA, de Souza CG, Peralta RM. Molecules. 2013 Jul 1;18(7):7609-30.
60. Hepatoprotective Effects of Aqueous Extract from Lingzhi or Reishi Medicinal Mushroom *Ganoderma lucidum* (Higher Basidiomycetes) on α-Amanitin−Induced Liver Injury in Mice. Wu X, Zeng J, Hu JS, Liao Q, Zhou R, Zhang P, Chen ZH. Int J Med Mushr. 2013;15(4):383-391.
61. *Ganoderma lucidum* extract attenuates the proliferation of hepatic stellate cells by blocking the PDGF receptor. Wang GJ, Huang YJ, Chen DH, Lin YL. Phytother Res. 2009;23(6):833-9.
62. Treatment of chronic hepatitis B with Wulingdan Pill. Journal of the fourth Military Medical College. 8:380-383. From Abstracts of Chinese Medicines 2:188.
63. Effects of total Triterpenoids extract from *Ganoderma lucidum* (Curt.: Fr.) P. Karst. (Reishi Mushroom) on experimental liver injury models induced by Carbon Tetrachloride or D-Galactosamine in mice. Lin ZB, Wang MY, Liu Q, Che QM. Int J Med Mushr. 2002;4(1):37-41.
64. Anti-hepatitis B activities of ganoderic acid from *Ganoderma lucidum*. Li YQ, Wang SF. Biotechnol Lett. 2006;28(11):837-41.
65. A phase I/II study of ling zhi mushroom *Ganoderma lucidum* (W.Curt.:Fr.) Lloyd (Aphyllophoromycetideae) extract in patients with coronary heart disease. Gao Y, Chen G, Dai X, Ye J, Zhou S. Int J Med Mushr. 2004;6(4):30.

66. Effect of *Ganoderma lucidum* on the quality and functionality of Korean traditional rice wine, yakju. Kim JH, Lee DH, Lee SH, Choi SY, Lee JS. J Biosci Bioeng. 2004;97(1):24-8.
67. Anti-angiotensin converting enzyme (ACE) proteins from mycelia of *Ganoderma lucidum* (Curtis) P. Karst. Mohamad Ansor N, Abdullah N, Aminudin N. BMC Complement Altern Med. 2013 Oct 4;13:256.
68. A preliminary study on the sleep-improvement function of the effective ingredients of *Ganoderma lucidum* fruitbody. Jia W, Wu M, Zhang JS, Liu YF. Acta Edulis Fungi. 2005;12(3):43-47.
69. Sleep-promoting effects of Ganoderma extracts in rats: comparison between long-term and acute administrations. Honda K, Komoda Y, Inoué S. Tokyo Ika Shika Daigaku Iyo Kizai Kenkyusho Hokoku. 1988;22:77-82.
70. Extract of *Ganoderma lucidum* potentiates pentobarbital-induced sleep via a GABAergic mechanism. Chu QP, Wang LE, Cui XY, Fu HZ, Lin ZB, Lin SQ, Zhang YH. Pharmacology Biochemistry and Behavior 2007;86(4):693-698.
71. Extract of *Ganoderma lucidum* prolongs sleep time in rats. Cui XY *et al*. J Ethnopharmacol. 2012 Feb 15;139(3):796-800.
72. *Ganoderma lucidum* polysaccharide peptide reduced the production of proinflammatory cytokines in activated rheumatoid synovial fibroblast. Ho YW *et al*. Mol Cell Biochem. 2007; 301(1-2):173-9.
73. Antagonizing beta-amyloid peptide neurotoxicity of the anti-aging fungus *Ganoderma lucidum*. Lai CS, Yu MS, Yuen WH, So KF, Zee SY, Chang RC. Brain Res. 2008;1190:215-24.
74. Neuroprotective effects of water-soluble *Ganoderma lucidum* polysaccharides on cerebral ischemic injury in rats. Zhou ZY *et al*. J Ethnopharmacol. 2010 Aug 19;131(1):154-64.
75. *Ganoderma lucidum* reduces kainic acid-induced hippocampal neuronal damage via inflammatory cytokines and glial fibrillary acid protein expression. Aguirre MAC, Campos PV, Villeda HJ, León RI, Montiel AE. Proc West Pharmacol Soc. 2011;54:78-9.
76. Triterpenoids with neurotrophic activity from *Ganoderma lucidum*. Zhang XQ *et al*. Nat Prod Res. 2011 Oct;25(17):1607-13.
77. Anticonvulsant and Neuroprotective Effects of Oligosaccharides from

Lingzhi or Reishi Medicinal Mushroom, *Ganoderma lucidum* (Higher Basidiomycetes). Aguirre-Moreno A *et al*. Int J Med Mushr. 2013;15(6):555-568.

78. Neuroprotective effect of preadministration with *Ganoderma lucidum* spore on rat hippocampus. Zhou Y *et al*. Exp Toxicol Pathol. 2012 Nov;64(7-8):673-80.
79. Novel hypoglycemic effects of *Ganoderma lucidum* water-extract in obese/diabetic (+db/+db) mice. Seto SW, Lam TY, Tam HL, Au AL, Chan SW, Wu JH, Yu PH, Leung GP, Ngai SM, Yeung JH, Leung PS, Lee SM, Kwan YW. Phytomedicine. 2009; 16(5):426-36.
80. Cholesterol-lowering properties of *Ganoderma lucidum in vitro*, *ex-vivo*, and in hamsters and minipigs. Berger A *et al*. Lipids Health Dis. 2004;3:2.
81. Ganoderic acid and its derivatives as cholesterol synthesis inhibitors. Komoda Y, Shimizu M, Sonoda Y, Sato Y. Chem Pharm Bull (Tokyo). 1989;37(2):531-3.
82. Anti-atherosclerotic properties of higher mushrooms (a clinico-experimental investigation). Li KR, Vasil'ev AV, Orekhov AN, Tertov VV, Tutel'ian VA. Vopr Pitan. 1989;(1):16-9.
83. Effective dose of ganoderma in humans. Chang. In Proceedings of the 5th Int Mycol Congr, Vanvouver. 1994;117-121.
84. Chinese Medical Herbology and Pharmacology. Chen JK, Chen TT. 2004 Art of Medicine Press, City of Industry. p.770.
85. Materia Medica. Bensky D, Cavey S, Stoger E. Eastland Press, Seattle. 3rd edition 2004. p.933.
86. Experimental and clinical studies on inhibitory effect of *Ganoderma lucidum* on platelet aggregation. Tao J, Feng KY. J Tongji Med Univ. 1990;10(4):240-3.
87. A prospective, randomized, double-blind, placebo-controlled study of the platelet and global hemostatic effects of *Ganoderma lucidum* (LingZhi) in healthy volunteers. Kwok Y, Ng KF, Li CC, Lam CC, Man RY. Anesth Analg. 2005 Aug;101(2):423-6.

Grifola frondosa

Japanese name
Maitake

Chinese name
Hui Shu Hua

English name
Hen of the Woods

A popular gourmet mushroom, *G. frondosa* is also a highly regarded clinically, especially in cancer therapy.

As with other major anti-cancer mushrooms such as *Lentinula edodes* (Shiitake) and *Trametes versicolor* (Coriolus), polysaccharides have been shown to be the major active components of *G. frondosa* and several beta-glucan, heteropolysaccharide and proteoglycan fractions have been isolated with potent immunomodulatory action, including D-fraction and MD-fraction[1-5].

Most of the clinical research has been carried out by one group of

researchers in Japan, initially using D-fraction together with powdered fruiting body, later switching to the more bioactive MD-fraction, again in combination with powdered whole fruiting body.

CANCER - A 1997 paper by Nanba reported benefits from D-fraction taken together with whole fruiting body in a range of stage III-IV cancers with *G. frondosa* increasing the benefit of chemotherapy by an additional 12-28%[6]. The paper further reports synergistic benefits from combining D-fraction and Mitomycin C (MMC) in an animal tumour model with D-fraction (1mg/day) showing superior tumour inhibition to MMC (0.5mg/day) on its own.

A subsequent paper by Nanba et al reported impressive results for MD-fraction and whole *G. frondosa* fruiting body powder in cancer patients who had discontinued chemotherapy because of side effects with improvement in 7 of 12 liver cancer patients, 11 of 16 breast cancer patients and 5 of 8 lung cancer patients, together with increases in IL-2 (a major Th1 cytokine) and CD4+[7].

Further studies confirmed alleviation of side effects from chemotherapy, including loss of appetite, vomiting, nausea, hair loss and leukopaenia, as well as synergy between D-fraction and vitamin C[2,7].

DIABETES - Various animal studies indicate benefit from *G. frondosa* in diabetes models but at high doses, in one case giving 1g/day *G. frondosa* powder to genetically diabetic mice and in another a purified alpha-glucan at a dose of 150-450mg/kg[8,9].

In small scale clinical studies *G. frondosa* polysaccharide extract (dose unknown) was reported to control blood sugar levels in one patient and produce a 30% reduction in blood sugar levels in 4 other patients while inclusion of *G. frondosa* beta-glucans (150mg/day) in

yoghurt produced significant improvement in blood glucose levels in 20 type II diabetes patients[3, 10].

POLYCYSTIC OVARY SYNDROME (PCOS) - In the majority of cases, PCOS is associated with some level of insulin resistance and *G. frondosa* polysaccharide extracts also show promise as agents for helping address this condition[11].

In one Japanese study, ovulation was observed in 20 of the 26 women given a *G. frondosa* polysaccharide extract and 6 of 8 women who failed to ovulate after being treated with clomiphene citrate did so after being given the polysaccharide extract. In addition, all 3 women who expressed an interest in becoming pregnant were able to do so[12].

CHOLESTEROL - Inclusion of *G. frondosa* in the diet of experimental animals at 5-20% of feed produces reductions in cholesterol consistent with the results seen in other mushrooms[13].

HYPERTENSION - A number of studies report short-lived hypotensive action for *G. frondosa* included in the diet of hypertensive animals (typically 5% of feed)[14]-[16].

CLINICAL SUMMARY

Main Therapeutic Application - *Cancer, PCOS.*

Key Component - *Polysaccharides.*

Dose - *The optimum dose of D-fraction/MD-fraction in animal studies is reported to be 1mg/kg i.p. with human trials using D-fraction/MD-fraction at oral doses of 35-150mg/day in combination with 4-6g/day G. frondosa fruiting body.*

REFERENCES

1. A polysaccharide extracted from *Grifola frondosa* enhances the anti-tumour activity of bone marrow-derived dendritic cell-based immunotherapy against murine colon cancer. Masuda Y, Ito K, Konishi M, Nanba H. Cancer Immunol Immunother. 2010.
2. Maitake extracts and their therapeutic potential - A review. Mayell M. Alt Med Rev, 2001;6(1).
3. *Grifola frondosa* (Dicks.: Fr.) S.F. Gray (Maitake Mushroom): medicinal properties, active compounds, and biotechnological cultivation. Boh B, Berovic M.M. Int J Med Mushr. 2007;9(2):10.
4. Anti tumour activity of orally administered d-fraction from Maitake (*Grifola frondosa*). Nanba H. J Naturopathic Medicine. 1993;1:10-15.
5. Oral administration of soluble β-glucans extracted from *Grifolafrondosa* induces systemic antitumor immune response and decreases immunosuppression in tumor-bearing mice. Masuda Y, Inoue H, Ohta H, Miyake A, Konishi M, Nanba H. Int J Cancer. 2013 Jul;133(1):108-19.
6. Maitake D-fraction: healing and preventive potential for cancer. Nanba H. J Orthomolecular Med. 1997;12:43-49.
7. Can Maitake MD-fraction aid cancer patients? Kodama N, Komuta K, Nanba H. Alt Med Rev. 2002;(7)3:236-9.
8. Anti-diabetic activity present in the fruit body of *Grifola frondosa* (Maitake). Kubo K, Aoki H, Nanba H. Biol Pharm Bull. 1994;17: 1106-1110.
9. Anti-diabetic effect of an alpha-glucan from fruit body of maitake (*Grifola frondosa*) on KK-Ay mice. Hong L, Xun M, Wutong W. J Pharm Pharmacol. 2007;59(4):575-82.
10. Anti-cancer and hypoglycemic effects of Polysaccharides in edible and medicinal Maitake mushroom [*Grifola frondosa*(Dicks.: Fr.) S. F. Gray] Konno S *et al*. Int J Med Mushr 4(3).
11. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. Teede H, Deeks A and Moran L. BMC Medicine, 2010;8:41.

12. Maitake Mushroom (*Grifola frondosa*) Extract Induces Ovulation in Patients with Polycystic Ovary Syndrome: A Possible Monotherapy and a Combination Therapy After Failure with First-Line Clomiphene Citrate. Chen J *et al*. J Alt Comp Med, 2010;16(12):1295-1299.
13. Anti-hyperliposis effect of Maitake fruit body (*Grifola frondosa*) Kubo K, Nanba H. Biol Pharm Bull. 1997;20:781-785
14. Blood pressure lowering activity present in the fruit body of *Grifola frondosa* (maitake). Adachi K, Nanba H, Otsuka M, Kuroda H. Chen Pharm Bull. 1988;36:1000-1006.
15. Effect of shiitake (*Lentinus edodes*) and maitake (*Grifolafrondosa*) mushrooms on blood pressure and plasma lipids in spontaneously hypertensive rats. Kabir Y, Yamaguchi M, Kimua S. J Nutr Sci Vitaminol. 1987;33:341-346.
16. Dietary mushrooms reduce blood pressure in spontaneously hypertensive rats (SHR). Kabir Y, Kimura S. J Nutr Sci Vitaminol. 1989;35:91-94.

Hericium erinaceus

Japanese Name
Yamabushitake

Chinese Name
Hou Tou Gu (Monkey Head Mushroom)

English Name
Lion's Mane Mushroom/Hedgehog Mushroom

This delicious mushroom has been referred to as 'Nature's Nutrient for the Neurons' on account of its ability to stimulate the production of nerve growth factor (NGF)[1],[2].

NGF plays an essential role in the differentiation and survival of several cell populations in the central and peripheral nervous system and lower than normal levels of NGF have been linked to early stages of both Alzheimer's disease and dementia[3]-[8].

Although therapeutic interest has largely focussed on its importance for neurological function, NGF plays a much wider role in

maintaining homoeostasis in the body[9,10]. It is known to have insulinotropic, angiogenic, and antioxidant properties and reduced plasma levels of NGF have been associated with cardiovascular diseases and metabolic syndromes, including type 2 diabetes[11,12]. It has been shown to accelerate wound healing and there is evidence that it could be useful in the treatment of skin and corneal ulcers[13]. Animal studies have shown NGF to have a profound effect on airway inflammation and asthma-related symptoms with increased NGF levels observed in bronchoalveolar lavage fluid and serum from patients with asthma[14].

NGF also has a dynamic relationship with the immune system. Generation of NGF is increased after brain injury, in part due to cytokines produced by immune cells. At the same time immune cells express receptors for NGF, which is involved in immune modulation[15].

Two families of compounds from *H. erinaceus* have been identified as being active in the stimulation of NGF production: the aromatic hericenones (isolated from the fruiting body) and the diterpenoid erinacines (isolated from the mycelium). Critically these molecules are small enough to pass through the blood-brain barrier. There is also evidence that they can increase myelination[1,16-18].

In China the mycelium is used to make *H. erinaceus* pills to treat gastric and duodenal ulcers, chronic gastritis, gastric and oesophageal cancer.

DEMENTIA - In controlled studies *H. erinaceus* supplementation showed beneficial effects in patients with mild dementia. In one study six out of seven patients showed improvement in functional capacity (understanding, communication, memory etc.) while all seven showed improved Functional Independence Scores (eating, dressing, walking etc.), after consuming 5g *H. erinaceus* fruiting body daily in soup for

six months[1].

In another study, 30 patients aged 50-80 with mild dementia were randomised into treatment and control groups. *H. erinaceus* was given as tablets at 3g/day for 16 weeks and produced significant increases in cognitive function in the treatment group. However, four weeks after the conclusion of the trial, cognitive function scores decreased indicating a need for continued supplementation[17].

MS - *H. erinaceus* fruiting body extract has been shown to improve the myelination process in mature myelinating fibres with possible benefits for MS patients[18,19]. NGF has also been shown to have a protective effect on axons and myelin by suppressing the immune-mediated inflammatory processes responsible for chronic brain destruction in neurodegenerative disorders such as MS by switching the immune response to an anti-inflammatory, suppressive mode in a brain-specific environment[13].

NEUROPATHY - NGF plays a role in pain sensitivity and low NGF levels have been linked to sensory neuropathy in both *in vivo* and *in vitro* studies[10]. Enhanced NGF production has been shown to protect sensory function in diabetic rats and NGF reduction has been shown to cause cardiac sensory neuropathy[21,22].

Clinical studies with recombinant human NGF indicate benefit in patients with diabetic polyneuropathy[23] and NGF has also been reported to reduce pain in patients with HIV associated sensory neuropathy[24,25]. However, ability to promote regeneration of sensory neurons has yet to be demonstrated[26,27].

NERVE DAMAGE - Rats given aqueous extract of *H. erinaceus* fruiting bodies showed faster recovery from nerve injury, suggesting

potential for application of *H. erinaceus* in the early stages of nerve regeneration[28]-[31].

ANXIETY / DEPRESSION - One study reports reduction in anxiety and depression from consumption of 2g/day (taken in cookies) and patients often report increased feelings of wellbeing when taking *H. erinaceus*, possibly due to the kappa opiod receptor agonist activity of the erinacines[32],[33].

MENOPAUSAL SYNDROME - Many patients report reduction in symptoms related to menopause and perimenopause, including sleep disturbance, anxiety and hot flushes (hot flashes) from consumption of *H. erinaceus* 3-5g/day d.w. although this is as yet unsupported by clinical research.

MRSA - Extracts of both fruiting body and mycelium exhibit anti-MRSA activity with erinacines identified as active compounds. In clinical tests in Japan MRSA is reported to have been cleared in a number of patients whose diet was supplemented with *H. erinaceus*[34].

GASTRIC ULCERS - One of the traditional indications for *H. erinaceus*, it appears likely that the antibacterial action of the erinacines and hericenones contribute to its benefit in this regard, with *Helicobacter pylori* now known to be a major cause of gastric ulcers and chronic gastritis[35]-[37].

A rat study on the effects of *H. erinaceus* aqueous extract on alcohol-induced ulcers showed a significant reduction of the ulcer area, as well as protection against gastric mucosa injury, while an *in vitro* study found that *H. erinaceus* extract was active against nine clinical strains of *H. pylori* with a 0.02% concentration having a 50%

bactericidal activity[38],[39].

CLINICAL SUMMARY

Main Therapeutic Application - *Dementia, Alzheimer's disease, MS, nerve damage, menopausal synrome.*

Key Component - *Hericenones and erinacines.*

Dose - *Clinical trials support the use of dried fruiting body at a dose of 3-5g/day for increasing NGF production while animal studies on the use of H. erinaceus for gastric ulcers produced the best results with a daily intake of 500mg/kg, which equates to the dosage prescribed in the Chinese Phamacopoeia of 25-50g/day[40]. It is likely that similar doses would be required in cases of MRSA.*

High in vitro NGF promoting activity of mycelial extracts and the fermentation broth also indicates potential for the use of mycelial biomass products[41],[42].

Caution - *Asthma and other allergic conditions. Erinacine E is a potent agonist of the kappa opioid receptor with potential hallucinogenic properties[33].*

REFERENCES

1. The anti-Dementia effect of Lion's Mane mushroom and its clinical application. Kawagishi H, Zhuang C, Shnidman E. Townsend Letter for Doctors and Patients, 2004.
2. Erinacines E, F, and G, stimulators of nerve growth factor (NGF)-synthesis, from the mycelia of *Hericium erinaceum*. Kawagishi H *et al*. Tetra Lett. 1996 37(41):7399-402.
3. Erinacine A increases catecholamine and nerve growth factor content in the central nervous system of rats. M. Shimbo M, Kawagishi H, Yokogoshi H. Nutrition Research. ;25(6):617-623.
4. NGF and BDNF: from nerves to adipose tissue, from neurokines to metabokines. Chaldakov G.N, Tonchev A.B, Aloe L. Riv Psichiatr. 2009;44(2):79-87.
5. Development of a non invasive NGF-based therapy for Alzheimer's disease. Covaceuszach S, Capsoni S, Ugolini G, Spirito F, Vignone D, Cattaneo A. Curr Alzheimer Res. 2009;6(2):158-70.
6. Neurotrophins: from pathophysiology to treatment in Alzheimer's disease. Schulte-Herbrüggen O, Jockers-Scherübl MC, Hellweg R. Curr Alzheimer Res. 2008;5(1):38-44.
7. One hundred years after the discovery of Alzheimer's disease. A turning point for therapy? Giacobini E, Becker RE. J Alzheimers Dis. 2007;12(1):37-52.
8. Neurotrophic factors—a tool for therapeutic strategies in neurological, neuropsychiatric and neuroimmunological diseases? Schulte-Herbrüggen O, Braun A, Rochlitzer S, Jockers-Scherübl MC, Hellweg R. Curr Med Chem. 2007;14(22):2318-29.
9. The nerve growth factor and the neuroscience chess board. Levi-Montalcini R. Prog. Brain Res. 2004, 146: 525–7.
10. Neurotrophin presence in human coronary atherosclerosis and metabolic syndrome: a role for NGF and BDNF in cardiovascular disease? Chaldakov GN *et al*. Prog Brain Res.2004;146:279–89.

11. Reduced plasma levels of NGF and BDNF in patients with acute coronary syndromes. Int J Cardiol. Manni L, Nikolova V, Vyagova D, Chaldakov GN, Aloe L. 2005;102(1):169–71.
12. Homo obesus: a metabotrophin-deficient species. Pharmacology and nutrition insight. Curr Pharm Des. Chaldakov GN, Fiore M, Tonchev AB, Dimitrov D, Pancheva R, Rancic G, Aloe L. 2007; 13(21):2176–9.
13. Nerve growth factor and wound healing. Prog Brain Res. Kawamoto K, Matsuda H. 2004;146:369–84.
14. Expression of nerve growth factor in the airways and its possible role in asthma. Freund V, Frossard N. Prog Brain Res. 2004;146: 335–46.
15. Role of nerve growth factor and other trophic factors in brain inflammation. Villoslada P, Genain CP. Prog Brain Res. 2004; 146:403–14.
16. Nerve growth factor-inducing activity of *Hericium erinaceus* in 1321N1 human astrocytoma cells. Mori K, Obara Y, Hirota M, Azumi Y, Kinugasa S, Inatomi S, Nakahata N. Biol Pharm Bull. 2008;31(9):1727-32.
17. Improving effects of the mushroom Yamabushitake (*Hericium erinaceus*) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. Mori K, Inatomi S, Ouchi K, Azumi Y, Tuchida T. Phytother Res. 2009;23(3):367-72.
18. The influence of *Hericium erinaceus* extract on myelination process *in vitro*. Kolotushkina EV, Moldavan MG, Voronin KY, Skibo GG. Fiziol ZH. 2003;49(1):38-45.
19. *Hericium erinaceus* (Bull.: Fr.) Pers. extract effect on nerve cells. Grygansky AP, Moldavan MG, Kolotushkina OV, Skibo GG. Int J Med Mushr. 2001;3(2-3):152.
20. Haploinsufficiency of the nerve growth factor beta gene in a 1p13 deleted female child with an insensitivity to pain. Fitzgibbon GJ, Kingston H, Needham M, Gaunt L. Dev Med Child Neurol. 2009;51(10):833-7.
21. Protection of sensory function in diabetic rats by Neotrofin. Calcutt NA, Freshwater JD, Hauptmann N, Taylor EM, Mizisin AP. Eur J Pharmacol. 2006;534(1-3):187-93.
22. Nerve growth factor is critical for cardiac sensory innervation and rescues neuropathy in diabetic hearts. Ieda M, Kanazawa H, Ieda Y, Kimura K, Matsumura K, Tomita Y, Yagi T, Onizuka T, Shimoji K, Ogawa S, Makino

S, Sano M, Fukuda K. Circulation. 2006;114(22): 2351-63.

23. Recombinant human nerve growth factor in the treatment of diabetic polyneuropathy. SC. Apfel *et al*. Neurology. 1998;51:695-702.
24. Long-term treatment with recombinant nerve growth factor for HIV-associated sensory neuropathy. G. Schifitto *et al*. Neurology. 2001; 57:1313-1316.
25. A phase II trial of nerve growth factor for sensory neuropathy associated with HIV infection. J. C. McArthur *et al*. Neurology. 2000;54: 1080-1088.
26. Regeneration of primary sensory neurons. Donnerer J. Pharmacology. 2003;67(4):169-81.
27. Nerve growth factor and diabetic neuropathy. Pittenger G, Vinik A. Exp Diabesity Res. 2003;4(4):271-85.
28. Functional recovery enhancement following injury to rodent peroneal nerve by Lion's Mane mushroom, *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae). Wong KH, Naidu M, David RP, Abdulla MA, Abdullah N, Kuppusamy UR, Sabaratnam V. Int J Med Mushr.11(3):20.
29. Potential activity of aqueous extract of culinary-medicinal Lion's Mane mushroom, *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae) in accelerating wound healing in rats. Abdulla MA, Fard AA, Sabaratnam V, Wong KH, Kuppusamy UR, Abdullah N, Ismail S. Int J Med Mushr. 2011;13(1):33-9.
30. Neuroregenerative Potential of Lion's Mane Mushroom, *Hericium erinaceus* (Bull. Fr.) Pers. (Higher Basidiomycetes), in the Treatment of Peripheral Nerve Injury (Review). Wong KH, Naidu M, David RP, Bakar R, Sabaratnam V. Int J Med Mushr, 2012; 14(5):427-446.
31. Neurotrophic Properties of the Lion's Mane Medicinal Mushroom, *Hericium erinaceus* (Higher Basidiomycetes) from Malaysia. Lai PL *et al*. Int J Med Mushr. 2013;15(6):539-554
32. Reduction of depression and anxiety by 4 weeks *Hericium erinaceus* intake. Nagano M, Shimizu K, Kondo R, Hayashi C, Sato D, Kitagawa K, Ohnuki K. Biomed Res. 2010 Aug;31(4):231-7.
33. Erinacine E as a kappa opioid receptor agonist and its new analogs from a basidiomycete, *Hericium ramosum*. Saito T *et al*. J Antibiot (Tokyo). 1998 Nov;51(11):983-90.

34. Anti-MRSA compounds of *Hericium erinaceus*. Kawagishi H *et al*. Int J Med Mushr. 2005;7(3):350.
35. A double-blind study of effectiveness of *Hericium erinaceus* pers therapy on chronic atrophic gastritis. A preliminary report. Xu CP, Liu WW, Liu FX, Chen SS, Liao FQ, Xu Z, Jiang LG, Wang CA, Lu XH. Chin Med J (Engl). 1985;98(6):455-6.
36. Cytoprotective effects of *Hericium erinaceus* on gastric mucosa in rats. Yu CG, Xu ZM, Zhu QK *et al*. Chinese J Gastrent. 1999-02.
37. Effect of culinary-medicinal Lion's Mane mushroom, *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae), on Ethanol-induced gastric ulcers in rats. Abdulla MA, Noor S, Sabaratnam V, Abdullah N, Wong KH, Ali H.M. Int J Med Mush. 2008;10(4):325-330.
38. Gastroprotective effects of Lion's Mane mushroom *Hericium erinaceus* (Bull.:Fr.) Pers. (Aphyllophoromycetideae) extract against ethanol-induced ulcer in rats. JY Wong *et al*. Evid Based Complement Alternat Med. Epub 2013 Nov 5.
39. *In Vitro* Anti-Helicobacter pylori Effects of Medicinal Mushroom Extracts, with Special Emphasis on the Lion's Mane Mushroom, *Hericium erinaceus* (Higher Basidiomycetes). Shang X, Tan Q, Liu R, Yu K, Li P, Zhao GP. Int J Med Mushr. 2013;15(2):165-174.
40. Chinese Pharmacopoeia, 2010. Beijing:Chinese Medicine Science and Technology Publishing House
41. Activity of aqueous extracts of Lion's Mane mushroom *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae) on the neural cell line NG108-15. Wong KH, Vikineswary S, Abdullah N, Naidu M, Keynes R. Int J Med Mushr. 2007;9(1): 57-65.
42. Neurotropic and trophic action of Lion's Mane mushroom *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae) extracts on nerve cells *in vitro*. Moldavan MG, Grygansky AP, Kolotushkina OV, Kirchhoff B, Skibo GG, Pedarzani P. Int J Med Mush. 2007;9(1).

Inonotus obliquus

Japanese name
Kabanoanatake

Chinese name
Bai Hua Rong /Hua Jie Kong Jun

English name
Chaga

I. obliquus grows widely in the forests of Eastern Europe and Russia on several trees, including birch, alder and spruce, where it appears as a sterile growth or conk on the trunk of the tree. The fruiting body is reported to be found growing nearby but is extremely rare in nature.

Traditionally only *I. obliquus* growing on birch trees was used as a tea in the treatment of cancers including inoperable breast cancer, hip, gastric, parotid, pulmonary, stomach, skin, rectal and Hodgkin lymphoma and *I. obliquus* is recorded as a miraculous cure for cancer in Solzhenitsyn's semi-autobiographical 1967 novel, the 'Cancer

Ward'[1].

The wisdom of using birch grown *I. obliquus* is supported by the finding that some of its key components are the triterpenoids betulin and betulinic acid, which occur naturally in a number of plants but primarily in the bark of the white birch (*Betula pubescens* - seen as the tree of life and fertility in many Eastern European and Siberian myths) from which it gets its name. Although it has been assumed that *I. obliquus* derives betulinic acid exclusively from the bark of host birch trees a recent study reported a small amount of betulin (0.12%) in *I. obliquus* mycelial biomass grown on rice indicating that some may also be generated by the mushroom itself[2].

Betulinic acid has been shown to induce mitochondrial apoptosis in different cancer cell lines and inhibit the enzyme topoisomerase[3], which is essential for the unwinding and winding of the DNA strands in cell replication. In addition it possesses anti-retroviral, anti-parasitic and anti-inflammatory properties[4]. It is currently being developed as an anti-cancer agent through the Rapid Access to Intervention Development program of the US National Cancer Institute and is also a major contributor to the anti-cancer action of mistletoe[5].

Other important components of *I. obliquus* include polysaccharides and sterols. Its high phenolic content gives it exceptional antioxidant properties and a melanin complex has also been identified as having significant antioxidant and genoprotective properties[6]-[8].

CANCER - Widely used in Poland and Russia as a folk remedy against cancer[9], *I. obliquus* is now attracting increasing interest among practitioners with its combination of immune supporting polysaccharides and triterpenoid components with direct anti-cancer activity, especially betulinic acid derivatives[10]-[14].

In vitro studies on betulinic acid have shown it to be highly effective against a wide variety of cancer cells: human melanoma,

neuroectodermal (neuroblastoma, medulloblastoma, Ewing's sarcoma) and malignant brain tumours, ovarian cancer, human leukaemia HL-60 cells and malignant head and neck squamous cell cancers, including those derived from therapy-resistant and refractory tumours[15,17]. However, it was found to have no effect on epithelial tumours, such as breast cancer, colon cancer, small cell lung cancer and renal cell cancer as well as T-cell leukaemia cells. Its anti-tumour activity has been related to its direct effects on mitochondria and induction of apoptosis, irrespective of cells p53 status[18].

Both betulinic acid and polysaccharides from *I. obliquus* have significant *in vitro* activity against brain cancer cells with one study showing that betulinic acid exerted cytotoxic activity against primary tumour cells cultured from patients in 4 of 4 medulloblastoma-tumour samples tested and in 20 of 24 glioblastoma-tumour samples[19,20]. It also shows great promise in combination with radiotherapy, exhibiting a strictly additive mode of growth inhibition in combination with radiation in human melanoma cells in one study and acting as a radiosensitizer in head and neck squamous cell cancers in another[21,22].

In vivo studies confirm its anti-cancer action as well as a complete absence of systemic toxicity in rodents[8].

DIGESTIVE DISORDERS - Melano-glucan complexes have wide antimicrobial activity and *I. obliquus* has traditionally been used as an internal cleanser with Befungin, an alcohol extract of *I. obliquus*, licensed in Russia for the treatment of stomach and intestinal disorders[9,23].

PSORIASIS - Several anecdotal reports indicate benefit of *I. obliquus* for psoriasis and this is supported by a Russian study on 50 psoriasis patients, which reported a 76% cure rate, with improvement in a further 16% of cases. The same study reported that it typically took 9-

12 weeks for improvement to become apparent[24].

ANTI-VIRAL - *I. obliquus* has traditionally been used to treat a number of viral conditions and aqueous extracts of *I. obliquus* prevented *Herpes simplex* virus entry through inhibition of viral-induced membrane fusion with a 50% inhibitory concentration of 3.82 µg/ml[25]. Betulinic acid analogs have also been shown to disrupt assembly and budding of the HIV-1 virus and viral fusion to the cell membrane.

CLINICAL SUMMARY

Main Therapeutic Applications - *Cancer, anti-viral, antioxidant.*

Key Component - *Polysaccharides, betulin and betulinic acid derivatives.*

Dose - *It is reported that only aqueous extracts prepared by boiling, as done traditionally, show anti-tumour activity*[26]*. However, the level of triterpenes in pure aqueous extracts is low and many practitioners prefer to combine aqueous and ethanolic extracts. Average dosage for aqueous extracts as powder is 1-3g/day.*

Safety - *I. obliquus contains high oxalate concentrations and there is one report of a 72-year-old Japanese woman diagnosed with liver cancer who developed oxalate nephropathy after consuming 4-5 teaspoons a day of I. obliquus powder for 6 months*[27].

REFERENCES

1. Plants used against cancer. Hartwell JL. 1982. Quartermain Pubs: Lawrence, Mass. p.694.
2. Quality characteristics of rice inoculated with *Inonotus obliquus* mycelia and incubated under different cultivating conditions. Afr J Biotech. 2013;12(33):5131-5139.
3. Betulinic acid, a potent inhibitor of eukaryotic topoisomerase I: identification of the inhibitory step, the major functional group responsible and development of more potent derivatives. Chowdhury AR, Mandal S, Mittra B, Sharma S, Mukhopadhyay S, Majumder HK. Medical Science Monitor. 2002;8(7):254–65
4. Antimalarial activity of betulinic acid and derivatives *in vitro* against *Plasmodium falciparum* and *in vivo* in P. berghei-infected mice. de Sá MS, Costa JF, Krettli AU, Zalis MG, Maia GL, Sette IM, Câmara Cde A, Filho JM, Giulietti-Harley AM, Ribeiro Dos Santos R, Soares MB. Parasitol Res. 2009;105(1): 275-9
5. Solubility studies of oleanolic acid and betulinic acid in aqueous solutions and plant extracts of *Viscum album* L. Jäger S, Winkler K, Pfüller U, Scheffler A. Planta Med. 2007;73(2):157-62.
6. Antioxidant small phenolic ingredients in *Inonotus obliquus* (persoon) Pilat (Chaga). Nakajima Y, Sato Y, Konishi T. Chem Pharm Bull (Tokyo). 2007;55(8):1222-6.
7. Melanin complex from medicinal mushroom *Inonotus obliquus* (Pers.: Fr.) Pilat (Chaga) (Aphyllophoromycetideae). Bisko NA, Mitropolskaya NY, Ikonnikova NV. Int J Med Mushr. 2002;4(2):139-145.
8. Anti-inflammatory and anticancer activities of extracts and compounds from the mushroom *Inonotus obliquus*. Ma L, Chen H, Dong P, Lu X. Food Chem. 2013 Aug 15;139(1-4):503-8.
9. The Chaga Storey. Spinosa R. 2006. The Mycophile, 47:1.
10. *In vitro* antitumor activity and structure characterization of ethanol extracts from wild and cultivated Chaga medicinal mushroom, *Inonotus obliquus*

(Pers.:Fr.) Pilát (Aphyllophoromycetideae). Sun Y, Yin T, Chen XH, Zhang G, Curtis RB, Lu ZH, Jiang JH. Int J Med Mushr. 2011;13(2):121-30.

11. Immunostimulating activity by polysaccharides isolated from fruiting body of *Inonotus obliquus*. Won DP, Lee JS, Kwon DS, Lee KE, Shin WC, Hong EK. Mol Cells. 2011 Feb;31(2):165-73.
12. Anticancer Effects of Fraction Isolated from Fruiting Bodies of Chaga Medicinal Mushroom, *Inonotus obliquus* (Pers.:Fr.) Pilát (Aphyllophoromycetideae): *In Vitro* Studies. Lemieszek MK, Langner E, Kaczor J, Kandefer-Szerszen M, Sanecka B, Mazurkiewicz W, Rzeski W. Int J Med Mushr. 2011;13(2):131-143
13. Antitumor and immunomodulatory activity of water-soluble polysaccharide from *Inonotus obliquus*. Fan L, Ding S, Ai L, Deng K. Carbohydr Polym. 2012 Oct 1;90(2):870-4.
14. Progress on understanding the anticancer mechanisms of medicinal mushroom: *Inonotus obliquus*. Song FQ, Liu Y, Kong XS, Chang W, Song G. Asian Pac J Cancer Prev. 2013;14(3): 1571-8.
15. Betulinic acid, a natural compound with potent anticancer effects. Mullauer FB, Kessler JH, Medema JP. Anticancer Drugs. 2010;21(3):215-27. 2010;24(1):90-114.
16. Betulinic Acid as a potent and complex antitumor phytochemical: a minireview. Gheorgheosu D, Duicu O, Dehelean C, Soica C, Muntean D. Anticancer Agents Med Chem. 2014;14(7):936-45.
17. Betulinic acid induces apoptosis in human neuroblastoma cell lines. Schmidt ML, Kuzmanoff KL, Ling-Indeck L, Pezzuto JM. European Journal of Cancer. 1997;33(12):2007–10.
18. Chemistry, biological activity, and chemotherapeutic potential of betulinic acid for the prevention and treatment of cancer and HIV infection. Cichewicz RH, Kouzi SA. Med Res Rev. 2004; 24(1):90-114.
19. Betulinic acid: a new cytotoxic agent against malignant brain-tumour cells. Fulda S, Jeremias I, Steiner HH, Pietsch T, Debatin KM. Int J Cancer. 1999;82(3):435-41.
20. Inhibitory Effects of a Polysaccharide Extract from the Chaga Medicinal Mushroom, *Inonotus obliquus* (Higher Basidiomycetes), on the Proliferation of Human Neurogliocytoma Cells. Ning XB, Qi Luo Q, Li C, Ding ZY, Pang J, Zhao C. Int J Med Mushr. 2014;16(1):29-36.

21. Effects of betulinic acid alone and in combination with irradiation in human melanoma cells. Selzer E, Pimentel E, Wacheck V, *et al*. The Journal of Investigative Dermatology. 2000;114(5):935–40.
22. Betulinic acid - a radiosensitizer in head and neck Squamous cell carcinoma cell lines. Eder-Czembirek C, Erovic BM, Czembirek C, Brunner M, Selzer E, Pötter R, Thurnher D. Strahlenther Onkol. 2010.
23. Medicinal plants of the Russian Pharmacopoeia; their history and applications. Shikov AN, Pozharitskaya ON, Makarov VG, Wagner H, Verpoorte R, Heinrich M. J Ethnopharmacol. 2014 Jul 3;154(3):481-536.
24. Treatment of Psoriasis with Using Chaga Mushroom Preparations. Dosychev EA, Bystrova VN. 1973. Vestn Dermatol Venerol. May;47(5):79-83.
25. Aqueous extract from a Chaga medicinal mushroom, *Inonotus obliquus* (higher Basidiomycetes), prevents herpes simplex virus entry through inhibition of viral-induced membrane fusion. Pan HH *et al.* Int J Med Mushr. 2013;15(1):29-38.
26. Medicinal Mushrooms. An exploration of tradition, healing and culture. Hobbs C. 1986. Pub Botanica Press, Williams.
27. Chaga mushroom-induced oxalate nephropathy. Kikuchi Y, Seta K, Ogawa Y, Takayama T, Nagata M, Taguchi T, Yahata K. Clin Nephrol. 2014 Jun;81(6):440-4.

Lentinula edodes

(Lentinus edodes)

Japanese name
Shiitake

Chinese name
Xiang Gu (Fragrant Mushroom)

L. edodes is an important ingredient in Asian cuisine and its annual production (2 million tonnes) is second only to the common button mushroom (*Agaricus bisporus*). As well as being delicious, it has an excellent nutritional profile with high levels of B vitamins and pro-vitamin D2 (ergosterol)[1].

Lentinan, a highly purified polysaccharide from *L. edodes*, is licensed in Japan for the treatment of gastric cancer and *L. edodes* is also one of the main species from which the popular mushroom α-glucan extract AHCC (Active Hexose Correlated Compound - reported to be the second most widely used supplement by cancer

patients in Japan, after *Agaricus subrufescens*[2]) is derived. *L. edodes* is also the source of LEM, a crude mycelial extract containing glycoproteins, nucleic acid derivatives, vitamin B compounds and ergosterol with proven immuno-modulating properties.

Other bioactive compounds from *L. edodes* include eritadenine, which shows promise for lowering cholesterol levels, and Lentin, an anti-fungal protein, which also inhibits HIV-1 reverse transcriptase activity and proliferation of leukaemia cells[3].

CANCER - Analysis of 5 clinical trials with a total of 650 participants shows that the addition of Lentinan at 2mg/week to standard chemotherapy offers a significant advantage over chemotherapy alone in terms of survival for patients with advanced gastric cancer, patients with lymph node metastasis having slightly better results than patients without[4].

Additional trials confirm increased survival, reduced side effects from chemotherapy and improved quality of life in patients with colorectal, hepatocelluar, oesophagel, breast cancer and metastatic prostate cancer[5,6]. In a trial with 69 metastatic prostate cancer patients the 50% survival length of treated and control patients was 48 and 35 months respectively, while the five-year survival rate of treated patients was 43% against 29% in the control group[7].

Although usually delivered by injection, Lentinan is also orally bioavailable although the clinical dosage is likely to be significantly higher[8,9].

Clinical trials using AHCC, a polysaccharide extract from multiple mushroom species including *L. edodes*, have shown positive effects in a number of cancers including breast, prostate and liver with reduction in side-effects from conventional treatment and improvement in haematopoetic parameters and cancer markers at a dose of 3g/day[10-16].

CHOLESTEROL CONTROL - Eritadenine has been shown to be a potent inhibitor of S-adenosylhomocysteine hydrolase and to accelerate excretion of ingested cholesterol and its metabolic decomposition. When added to the diet of rats (0.005%), eritadenine caused a 25% decrease in total cholesterol in one week[1].

Early studies indicated that levels found in whole shiitake mushrooms were too small to have a significant effect but recent research has shown the presence of eritadenine at levels 10 times higher than originally thought, indicating therapeutic possibilities for shiitake, particularly in cases where patients have shown statin intolerance[17],[18].

In clinical trials dried *L. edodes* (9g/day) decreased serum cholesterol 7-10% in patients suffering from hypercholesterolemia and 90g/day fresh *L. edodes* (equivalent to 9g/day dried mushroom) led to a decrease in total cholesterol of 9-12% and triglycerides of 6-7%[1].

HEPATITIS B - Polysaccharide extracts from *L. edodes* have been shown to have broad anti-viral and hepatoprotective properties[19]. In a study of 40 patients with chronic hepatitis B, LEM at 6g/day for 4 months led to improved liver function and resulted in 17 patients becoming seronegative for Hbe antigen (HbeAg)[20].

HIV - LEM increased the T-cell count in HIV patients with AIDS symptoms from 1250/mm^{3}to 2550/mm^3 after 60 days[1].

CANDIDA - *In vitro* studies show *L. edodes* to have consistently high levels of anti-microbial activity, including the highest anti-candidal action among several mushroom species (for further discussion see section on Candidiasis).

CLINICAL SUMMARY

Main Therapeutic Application - *Cancer, cholesterol control, especially as an adjunct to statins.*

Key Components - *Polysaccharides and eritadenine.*

Dose - *2-6g/day polysaccharide extract for immune support. 9g/day dried fruit body for cholesterol control.*

Because eritadenine's cholesterol-lowering action differs from that of prescription statins or natural sources of statins such as Pleurotus ostreatus or Monascus purpureus, it can usefully be combined with them in cholesterol control protocols.

Safety - *Although there have been a number of reports of dermatitis (Shiitake Dermatitis) developing following consumption of L. edodes these have been related to consumption of the raw mushroom and no cases have been reported for the use of L. edodes in supplement form*[21]-[26].

REFERENCES

1. Shiitake (*Lentinus edodes*) Wasser SP. Encyclopedia of Dietary Supplements. 2005.
2. Nationwide survey on complementary and alternative medicine in cancer patients in Japan. Hyodo I, Amano N, Eguchi K. Journal of Clinical Oncology 23(12): 2645–54.
3. Lentin, a novel and potent antifungal protein from shitake mushroom with inhibitory effects on activity of human immuno-deficiency virus-1 reverse transcriptase and proliferation of leukaemia cells. Ngai P.H, Ng T.B. Life Sci. 2003;73(26):3363-74.
4. Individual patient based meta-analysis of lentinan for unresectable/recurrent gastric cancer. Oba K, Kobayashi M, Matsui T, Kodera Y, Sakamoto J. Anticancer Res. 2009;29(7):2739-45.
5. Effects of lentinan in advanced or recurrent cases of gastric, colorectal, and breast cancer. Taguchi T. Gan To Kagaku Ryoho. 1983;10(2 Pt 2): 387-93.
6. Combination therapy with lentinan improves outcomes in patients with esophageal carcinoma. Wang JL, Bi Z, Zou JW, Gu XM. Mol Med Rep. 2012 Mar;5(3):745-8.
7. Effect of lentinan for advanced prostate carcinoma. Tari K, Satake I, Nakagomi K, Ozawa K, Oowada F, Higashi Y, Negishi T, Yamada T, Saito H, Yoshida K. Hinyokika Kiyo. 1994;40(2):119-23.
8. Inhibition of human colon carcinoma development by lentinan from shiitake mushrooms (*Lentinus edodes*). Ng ML, Yap AT. J Altern Complement Med. 2002;8(5):581-9.
9. The medicinal benefits of Lentinan (ß-1, 3-D glucan) from *Lentinus edodes* (Berk.) singer (Shiitake Mushroom) through oral administration. Yap AT, Ng MH. Int J Med Mushr. 2005;7(12):170.
10. Immunomodulatory and Anticancer Effects of Active Hemicellulose Compound (AHCC). Ghoneum M. Wimbley M, Salem F. McKlain A, Atallah N, Gill G. Int J Immunotherapy, 1995;11(1):23-28
11. Prognostic improvement of patients with advanced liver cancer after active

hexose correlated compound (AHCC) treatment. Cowawintaweewat S, Manoromana S, Sriplung H, Khuhaprema T, Tongtawe P, Tapchaisri P, Chaicumpa W. Asian Pac J Allergy Immunol. 2006 Mar;24(1):33-45.

12. Active hexose correlated compound enhances tumor surveillance through regulating both innate and adaptive immune responses. Gao Y, Zhang D, Sun B, Fujii H, Kosuna K, Yin Z. Cancer Immunol Immunother. 2006 Oct;55(10):1258-66.
13. Dramatic prostate-specific antigen response with activated hemicellulose compound in metastatic castration-resistant prostate cancer. Turner J, Chaudhary U. Anticancer Drugs. 2009 Mar;20(3):215-6.
14. An evidence-based review of a *Lentinula edodes* mushroom extract as complementary therapy in the surgical oncology patient. Shah SK, Walker PA, Moore-Olufemi SD, Sundaresan A, Kulkarni AD, Andrassy RJ. JPEN J Parenter Enteral Nutr. 2011 Jul;35(4):449-58.
15. Effect of active hexose-correlated compound in women receiving adjuvant chemotherapy for breast cancer: a retrospective study. Hangai S *et al.* J Altern Complement Med. 2013 Nov;19(11):905-10.
16. Reduction of adverse effects by a mushroom product, active hexose correlated compound (AHCC) in patients with advanced cancer during chemotherapy - the significance of the levels of HHV-6 DNA in saliva as a surrogate biomarker during chemotherapy. Ito T *et al*. Nutr Cancer. 2014;66(3):377-82.
17. Production of the bioactive compound eritadenine by submerged cultivation of shiitake (*Lentinus edodes*) mycelia. Enman J, Hodge D, Berglund KA, Rova U.J Agric Food Chem. 2008;56(8):2609-12.
18. Quantification of the bioactive compound eritadenine in selected strains of shiitake mushroom (*Lentinus edodes*). Enman J, Rova U, Berglund KA. J Agric Food Chem. 2007;55(4):1177-80.
19. Polysaccharide and extracts from *Lentinula edodes*: structural features and antiviral activity. Rincão VP, Yamamoto KA, Ricardo NM, Soares SA, Meirelles LD, Nozawa C, Linhares RE. Virol J. 2012 Feb 15;9:37.
20. Shiitake, *Lentinus edodes*: Functional properties for medicinal and food purposes Mizuno T. Food Reviews International, 1995;1(1): 109-128.
21. Shiitake dermatitis: flagellate dermatitis after eating mushrooms. Hautarzt. Haas N, Vogt R, Sterry W. 2001;52(2):132-5.

22. Systemic allergic contact dermatitis due to consumption of raw shiitake mushroom. Kopp T, Mastan P, Mothes N, Tzaneva S, Stingl G, Tanew A. Clin Exp Dermatol. 2009 Dec;34(8):e910-3.
23. Shiitake dermatitis now occurs in France. Hérault M, Waton J, Bursztejn AC, Schmutz JL, Barbaud A. Ann Dermatol Venereol. 2010;137(4): 290-3.
24. Shiitake dermatitis: a report of 3 cases and review of the literature. Chu EY, Anand D, Dawn A, Elenitsas R, Adler DJ. Cutis. 2013 Jun;91(6): 287-90.
25. Shiitake Dermatitis - Now Also in Poland. Baran W, Batycka-Baran A, Maj J, Szepietowski JC. Acta Derm Venereol. 2014 Apr 7.
26. Shiitake dermatitis: toxic or allergic reaction? Corazza M, Zauli S, Ricci M, Borghi A, Pedriali M, Mantovani L, Virgili A. J Eur Acad Dermatol Venereol. 2014 Apr 8.

Phellinus linteus

Japanese name
Meshimakobu

Chinese name
Sang Huang
(Mulberry Yellow)

P. linteus is a basidiomycete fungus, popular in China, Korea and Japan and reported to work as a ‘miracle medicine’, prolonging longevity. Identified by Ikekawa as having the highest anti-tumour activity of the Hymenomycetes[1] (a fungal grouping containing the major medicinal mushrooms), and by Stamets as having the greatest macrophage activation of 7 species surveyed[2], it has been heavily researched in the last decade, especially in Korea, showing broad immunostimulant activity, strong anti-cancer properties and the ability to enhance the efficacy of existing chemotherapeutic drugs[3].

Uniquely among the medicinal mushrooms, the Chinese Pharmacopoeia describes the energy of *P. linteus* as Cold (see section on Medicinal Mushrooms According to Traditional Chinese Medicine) and ascribes to it an extensive range of indications, including: cancer, diabetes, HIV, angina, leucorrhoea, diarrhoea and accelerated wound healing.

Research has focussed on *P. linteus*' polysaccharide and proteoglycan components although it also contains a number of flavonoid-like polyphenol pigments with antioxidant, anti-inflammatory, cytotoxic and anti-viral effects[4].

CANCER - Interest in the potential of *P. linteus* in cancer therapy has been stimulated by recent reports of remarkable effects in a number of cancer patients taking it. One case reported dramatic remission in a hormone refractory prostate cancer with rapidly progressive bone metastasis[5], while in a second a 65 year old man with a large hepatocellular cancer and metastasis in the skull, sternum and ribs, who declined all treatment except radiation for the painful frontal bone mass in favour of *P. linteus*, experienced spontaneous regression of the tumours[6]. In a third case spontaneous regression of hepatocellular cancer with multiple lung metastasis was linked to consumption of *P. linteus* mycelium (no conventional therapy undertaken)[7].

In vitro studies show that low levels of *P. linteus* polysaccharides induce cell cycle arrest in lung cancer cells[8] and exhibit synergistic action with chemotherapeutic drugs such as doxorubicin, inducing apoptosis at a sub-therapeutic dose in prostate and lung cancer cells[9], while at high doses activating apoptosis in lung cancer cells, hormone sensitive and, to a lesser degree, refractory prostate cancer cells, as well as suppressing growth, angiogenesis and invasive behaviour of breast cancer cells[10],[11]. Modes of action identified include inhibition of Akt signalling and caspase induction.

In vitro studies also show significant inhibition of bladder cancer cell growth with enhanced cytotoxic activity in combination with vitamin C[12].

In vivo studies show significantly prolonged survival, reduced tumour growth and reduced frequency of lung metastasis in mice transplanted with melanoma cells after administration of polysaccharide extract[13],[14].

RHEUMATOID ARTHRITIS - In a murine rheumatoid arthritis model polysaccharide extract from *P. linteus* fruiting bodies reduced expression of pro-inflammatory Th2 cytokines (such as TNF-α and IFN-γ) and increased expression of anti-inflammatory Th1 cytokines, including IL-10 and TGF-ß, resulting in the subsidence of the autoimmune response in the joints of the mice. Similar results were seen with polysaccharides from the related species *Phellinus rimosus*[15],[16]

P. linteus polysaccharides have also been shown to reduce expression of TNF-α and major histocompatability complex II expression in lipopolysaccharide induced septic shock, supporting their use as anti-inflammatory agents[17].

ALLERGIES - Several studies show strong effect of *P. linteus* polysaccharides in suppressing production of Th2 cytkines and promoting secretion of Th1 cytokines, thereby addressing the immune imbalance involved in allergic responses[18]-[20]. At the same time it is reported that aqueous extract of *P. linteus* fruiting body prevented histamine release in response to allergenic stimuli and inhibited mast cell mediated anaphylaxis-like reactions[21].

Other atopic conditions have also shown benefit from *P. linteus* in animal models including asthma and dermatitis[22],[23].

INFERTILITY - *P. linteus* shows considerable promise in cases where infertility is associated with elevated cytokine and NK cell levels, with 23 of 26 women in one study showing improvement in immune parameters from supplementation with mycelial biomass at 3g/day[24].

CLINICAL SUMMARY

Therapeutic Application - *Cancer, rheumatoid arthritis, allergies.*

Key Component - *Polysaccharides.*

Dose - *The Chinese Pharmacopoeia prescribes a daily dose of 10-30g for the dried mushroom, while for polysaccharide extract 2-3g/day is usual*[25].

REFERENCES

1. Antitumour activity of some basidiomycetes, especially *Phellinus linteus*. Ikekawa *et al*. Jpn J Cancer Res. 1968;59:155-157.
2. Potentiation of cell-mediated host defense using fruitbodies and mycelia of medicinal mushrooms. Stamets P. Int J Med Mushr. 2003;5:179-191.
3. A medicinal mushroom: *Phellinus linteus*. Zhu T, Kim SH, Chen CY. Curr Med Chem. 2008;15(13):1330-5.
4. Styrylpyrone-class compounds from medicinal fungi Phellinus and Inonotus spp., and their medicinal importance. Lee IK, Yun BS. J Antibiot (Tokyo). 2011 May;64(5):349-59.
5. Dramatic remission of hormone refractory prostate cancer achieved with extract of the mushroom, *Phellinus linteus*. Shibata Y, Kurita S, Okugi H, Yamanaka H. Urol Int. 2004;73(2):188-90.
6. Spontaneous regression of a large hepatocellular carcinoma with skull metastasis. Nam SW *et al*. J Gastroenterol Hepatol. 2005; 20(3):488-92.
7. A case of spontaneous regression of hepatocellular carcinoma with multiple lung metastases. Kojima H, Tanigawa N, Kariya S, Komemushi A, Shomura Y, Sawada S, Arai E, Yokota Y. Radiat Med. 2006;24(2):139-42.
8. Modulation of lung cancer growth arrest and apoptosis by *Phellinus Linteus*. Guo J, Zhu T, Collins L, Xiao ZX, Kim SH, Chen CY. Mol Carcinog. 2007;46(2):144-54.
9. *Phellinus linteus* sensitises apoptosis induced by doxorubicin in prostate cancer. Collins L, Zhu T, Guo J, Xiao ZJ, Chen CY. Br J Cancer. 2006;95(3):282-8.
10. *Phellinus linteus* activates different pathways to induce apoptosis in prostate cancer cells. Zhu T, Guo J, Collins L, Kelly J, Xiao ZJ, Kim SH, Chen CY. Br J Cancer. 2007;96(4):583-90.
11. *Phellinus linteus* suppresses growth, angiogenesis and invasive behaviour of breast cancer cells through the inhibition of AKT signalling. Sliva D, Jedinak A, Kawasaki J, Harvey K, Slivova V. Br J Cancer. 2008;98(8):1348-56.

12. Effect of various natural products on growth of bladder cancer cells: two promising mushroom extracts. Konno S, Alt Med Rev. 2007;12(1):63-68.
13. Acidic polysaccharide from *Phellinus linteus* inhibits melanoma cell metastasis by blocking cell adhesion and invasion. Han SB, Lee CW, Kang JS, Yoon YD, Lee KH, Lee K, Park SK, Kim HM. Int Immunopharmacol. 2006;6(4):697-702.
14. The inhibitory effect of polysaccharide isolated from *Phellinus linteus* on tumour growth and metastasis. Han B, Lee CW, Jeon YJ, Hong ND, Yoo ID, Yang KH, Kim HM. Immuno-pharmacology. 1999;41:157-164.
15. Oral administration of proteoglycan isolated from *Phellinus linteus* in the prevention and treatment of collagen-induced arthritis in mice. Kim GY, Kim SH, Hwang SY, Kim HY, Park YM, Park SK, Lee MK, Lee SH, Lee TH, Lee JD. Biol Pharm Bull. 2003;26(6):823-31.
16. Antiarthritic activity of a Polysaccharide-protein complex isolated from *Phellinus rimosus* (Berk.) Pilát (Aphyllo-phoromycetideae) in Freund's complete adjuvant–induced arthritic rats. Meera CR, Smina TP, Nitha B, Mathew J, Janardhanan KK. Int J Med Mushr. 2009;11(1):21-28.
17. Alleviation of experimental septic shock in mice by acidic polysaccharide isolated from the medicinal mushroom *Phellinus linteus*. Kim GY, Roh SI, Park SK, Ahn SC, Oh YH, Lee JD, Park YM. Biol Pharm Bull. 2003;26(10):1418-23.
18. Stimulation of humoral and cell mediated immunity by polysaccharide from mushroom *Phellinus linteus*. Kim HM, Han SB, Oh GT, Kim YH, Hong DH, Hong ND, Yoo ID. Int J Immunopharmac. 1996;18(5):295-303.
19. *Phellinus linteus* extract augments the immune response in Mitomycin C-induced immunodeficient mice. Matsuba S, Matsuno H, Sakuma M, Komatsu Y. Evid Based Complement Alternat Med. 2008;5(1):85-90.
20. *Phellinus linteus* grown on germinated brown rice suppresses IgE production by the modulation of Th1/Th2 balance in murine mesenteric lymph node lymphocytes. Lim BO, Jeon TI, Hwang SG, Moon JH, Park K. Biotechnol Lett. 2005;27(9):613-7.
21. Inhibition of anaphylaxis-like reaction and mast cell activation by water extract from the fruiting body of *Phellinus linteus*. Choi YH *et al*. Biol Pharm Bull. 2006;29(7):1360-5.
22. Immunomodulatory effect of water soluble extract separated from mycelium

of *Phellinus linteus* on experimental atopic dermatitis. Hwang JS, Kwon HK, Kim JE, Rho J, Im SH. BMC Complement Altern Med. 2012 Sep 18;12:159.

23. *Phellinus linteus* Extract Exerts Anti-asthmatic Effects by Suppressing NF-κB and p38 MAPK Activity in an OVA-induced Mouse Model of Asthma. Yan GH, Choi YH. Immune Netw. 2014 Apr;14(2):107-15.
24. Immune Related Female Infertility. Wing T. TCM Kongress Rothenburg 2012.
25. Chinese Pharmacopoeia, 2010. Beijing:Chinese Medicine Science and Technology Publishing House.

Pleurotus ostreatus

Japanese name
Hiratake

English name
Oyster Mushroom

Chinese name
Ping Gu

One of the principal culinary mushrooms, *P. ostreatus* fruiting bodies contain lovastatin in concentrations ranging from 0.7-2.8% dried weight depending on the strain.

P. ostreatus has also been commercialized as a source of polysaccharide extracts for immune support and shows promise for general health maintenance[1,2].

Related species including *Pleurotus eryngii*, *Pleurotus tuber-regium* and *Pleurotus citronopileatus* show similar immune-modulating and cholesterol-lowering activity[3-7].

CHOLESTEROL CONTROL - Dried *P. ostreatus* fed to hamsters at 2% of a high fat diet for six months is reported to have lowered VLDL by 65-80% and total serum lipid levels by 40% and to totally negate increases in triglyceride and liver cholesterol levels associated with chronic alcohol intake[8]-[10]. Multiple animal studies show *P. ostreatus* to produce improvements in blood lipid levels at 5% of diet[11]-[17]. Intake of more than 5% was seen to suppress appetite[18].

Bobek *et al* reported reductions in cholesterol in humans from intake of 15-20g/day[11] and Khatun *et al* reported *P. ostreatus* to reduce cholesterol levels in diabetic patients[19]. However, in a small clinical study on HIV patients with elevated non-HDL cholesterol (>160mg/dl) who were taking protease inhibitors no significant change was seen from supplementation with 15g/day freeze-dried *P. ostreatus* for 8 weeks (abnormalities in lipid metabolism are a common side effect of anti-retroviral treatment)[20],[21].

ANTI-AGEING - As well as having immunomodulatory, anti-cancer and hepatoprotective properties in common with those from other mushrooms, polysaccharides from *P. ostreatus* have been shown to increase activity of catalase, superoxide dismutase and glutathione peroxidase, as well as counter age-related reductions in levels of vitamins C and E[22]-[27].

CLINICAL SUMMARY

Therapeutic Application - *General health maintenance, especially in the elderly. Can be prescribed for cholesterol control, although Monascus purpureus products (Hong Qu Mi - Red Yeast Rice) usually give a more controlled dose of lovastatin.*

Key Components - *Lovastatin, polysaccharides.*

Dose - *1-2g/day polysaccharide extract or 2-3g/day mycelial biomass for general health maintenance. 10-15g/day dried fruit body for cholesterol*

control.

Caution - *Patients taking protease inhibitors such as ritonavir, indinavir etc., which have been shown to raise statin levels significantly through common use of the CYP3A4 enzyme system.*

REFERENCES

1. Immunomodulatory effect of pleuran (β-glucan from *Pleurotus ostreatus*) in children with recurrent respiratory tract infections. Jesenak M, Majtan J, Rennerova Z, Kyselovic J, Banovcin P, Hrubisko M. Int Immunopharmacol. 2013 Feb;15(2):395-9.
2. Anti-allergic effect of Pleuran (β-glucan from *Pleurotus ostreatus*) in children with recurrent respiratory tract infections. Jesenak M, Hrubisko M, Majtan J, Rennerova Z, Banovcin P. Phytother Res. 2014 Mar;28(3):471-4.
3. Evaluation of mushroom dietary fiber (nonstarch polysaccharides) from sclerotia of Pleurotustuber-regium (Fries) singer as a potential antitumor agent. Zhang M, Cheung PC, Zhang LJ Agric Food Chem. 2001 Oct;49(10):5059-62.
4. Optimization for the production of water-soluble polysaccharide from *Pleurotus citrinopileatus* in submerged culture and its antitumor effect. Wang JC, Hu SH, Liang ZC, Yeh CJ. Appl Microbiol Biotechnol. 2005 Jun;67(6):759-66.
5. Hypolipidemic effect of *Pleurotus eryngii* extract in fat-loaded mice. Mizutani T, Inatomi S, Inazu A, Kawahara E. J Nutr Sci Vitaminol (Tokyo). 2010;56(1):48-53.
6. Dietary effect of *Pleurotus eryngii* on biochemical function and histology in hypercholesterolemic rats. Alam N, Yoon KN, Lee JS, Cho HJ, Shim MJ, Lee TS. Saudi J Biol Sci. 2011 Oct;18(4):403-9.
7. Antitumor activity of a polysaccharide from *Pleurotus eryngii* on mice bearing renal cancer. Yang Z, Xu J, Fu Q, Fu X, Shu T, Bi Y, Song B. Carbohydr Polym. 2013 Jun 20;95(2):615-20.
8. Effect of mushroom *Pleurotus ostreatus* and isolated fungal polysaccharide on serum and liver lipids in Syrian hamsters with hyperlipoproteinemia. Bobek P, Ginter E, Kuniak L, Babala J, Jurcovicova M, Ozdín L, Cerven J. Nutrition. 1991;7(2):105-8.
9. Cholesterol-lowering effect of the mushroom *Pleurotus ostreatus* in hereditary hypercholesterolemic rats. Bobek P, Ginter E, Jurcovicová M,

Kuniak L. Ann Nutr Metab. 1991;35(4):191-5.

10. Effect of oyster fungus (*Pleurotus ostreatus*) on serum and liver lipids of Syrian hamsters with a chronic alcohol intake. Bobek P, Ginter E, Jurcovicová M, Ozdín L, Mekinová D. Physiol Res. 1991;40(3):327-32.
11. Dose-dependent hypocholesterolaemic effect of oyster mushroom *(Pleurotus ostreatus*) in rats. Bobek P, Ozdín L, Kajaba I. Physiol Res. 1997;46(4):327-9.
12. Dose-and time-dependent hypocholesterolemic effect of oyster mushroom (*Pleurotus ostreatus*) in rats. Bobek P, Ozdín L, Galbavý S. Nutrition. 1998;14(3):282-6.
13. Hypocholesterolemic activity of the genus Pleurotus (Jacq.: Fr.) P. Kumm. (Agaricales s. I., Basidiomycetes). Gunde-Cimerman N et al, Int J Med Mushr 2001;3(4).
14. Evidence for the anti-hyperlipidaemic activity of the edible fungus *Pleurotus ostreatus*. Opletal L, Jahodár L, Chobot V, Zdanský P, Lukes J, Brátová M, Solichová D, Blunden G, Dacke CG, Patel AV. Br J Biomed Sci. 1997;54(4):240-3.
15. Dietary mushroom (*Pleurotus ostreatus*) ameliorates atherogenic lipid in hypercholesterolaemic rats. Hossain S, Hashimoto M, Choudhury EK, Alam N, Hussain S, Hasan M, Choudhury SK, Mahmud I. Clin Exp Pharmacol Physiol. 2003;30(7):470-5.
16. Role of oyster mushroom (*Pleurotus florida*) as hypocholesterolemic/antiatherogenic agent. Bajaj M, Vadhera S, Brar AP, Soni G.L. Indian J Exp Biol. 1997;35(10):1070-5.
17. Cholesterol-lowering effect of Pleurotus species (Agarico-mycetideae) (Abstracts of papers published in 1991-1999) Bobek P. Int J Med Mushr. 1999;1(4):371-380.
18. A lectin from the edible and medicinal mushroom *Pleurotus ostreatus* (Jacq.: Fr.) Kumm. as a food intake suppressing substance. Yokoyama S, Nakamura H, Tokuyama S. Int J Med Mush. 2001;3(2-3).
19. Oyster mushroom reduced blood glucose and cholesterol in diabetic subjects. Khatun K, *et al* Mymensingh Med J. 2007;16(1):94-9.
20. Antihyperlipidemic effect of *Pleurotus ostreatus* in HIV: results of a pilot proof-of-principle clinical trial. Abrams DI, Couey P, Shade SB, Kelly ME,

Kamanu-Elias N, Stamets PE. Int J Med Mushr. 2007;9(3):204.

21. Antihyperlipidemic effects of *Pleurotus ostreatus* (oyster mushrooms) in HIV-infected individuals taking antiretroviral therapy. Abrams DI, Couey P, Shade SB, Kelly ME, Kamanu-Elias N, Stamets P. BMC Complement Altern Med. 2011 Aug 10;11:60.
22. Effect of oyster mushroom (*Pleurotus ostreatus*) on pathological changes in dimethylhydrazine-induced rat colon cancer. Bobek P, Galbavy S, Ozdin L. Oncol Rep. 1998;5(3):727-30.
23. Cytotoxic effect of oyster mushroom *Pleurotus ostreatus* on human Androgen-independent prostate cancer PC-3 cell. Gu YH, Sivam G. J Med Food. 2006;9(2):196-204.
24. Effects of *Lentinus edodes*, *Grifola frondosa* and *Pleurotus ostreatus* administration on cancer outbreak and activities of macrophages and lymphocytes in mice treated with a carcinogen N-butyl-N-butnolnitrosamine. Kurashige S, Aleusawa Y, Endo F. Immunopharm. Immunodetox. 1997;19:175-183.
25. Antioxidant activity of the oyster mushroom, *Pleurotus ostreatus*, on CCl(4)-induced liver injury in rats. Jayakumar T, Ramesh E, Geraldine P. Food Chem Toxicol. 2006;44(12):1989-96.
26. Protective effect of an extract of the oyster mushroom, *Pleurotus ostreatus*, on antioxidants of major organs of aged rats. Jayakumar T *et al.* Exp Gerontol. 2007;42(3):183-91.
27. An extract of the oyster mushroom, *Pleurotus ostreatus*, increases catalase gene expression and reduces protein oxidation during aging in rats. Thanasekaran J, Aloysius P.T, Mathivanan I, Pitchairaj GJ. Chin Int Med. 2010;8(8):774-780.

Polyporus umbellatus

(Grifola umbellata)

Chinese Name
Zhu Ling
(sclerotium)

Japanese Name
Chorei Maitake
(fruiting body)

A close relative of *Grifola frondosa* (Maitake), *P. umbellatus* differs from most medicinal mushrooms in that traditionally it has been harvested as a hyphal mass, or sclerotium, which only forms when *P. umbellatus* is symbiotically associated with *Armillaria* species[1,2].

Li Shi Zhen, in his comprehensive materia medica the *Ben Cao Gang Mu* (1578), says of this mushroom's actions, quoting the earlier *Shen Nong Ben Cao*, 'dispersing invading vicious factors and facilitating urination. Long term use makes one feel happy and

vigorous and look younger'[3].

As well as its traditional use as a diuretic, polysaccharide extracts of *P. umbellatus* show promise as adjuvant nutrition alongside chemotherapy and are licensed in China for use in cancer therapy[4]. A number of steroids with cytotoxic activity against cancer cells have also been isolated from the fruiting body[5-7].

DIURETIC - *P. umbellatus* is a component of the classical diuretic herbal formula *Wu Ling San* and a number of compounds have been identified as contributing to its diuretic activity, including triterpenes, ergosterol and d-mannitol[8-11].

Comparison with other diuretics, including *Poria cocos* and caffeine, indicates that *P. umbellatus* has stronger action with oral administration of 8g aqueous decoction leading to a 62% increase in 6-hour urine output and a 54.5% increase in chloride excretion[4].

CANCER - Co-administration of *P. umbellatus* polysaccharide extracts with chemotherapy is reported to improve treatment outcomes and quality of life indicators in patients with a number of cancers including lung, liver, leukaemia, nose and throat[12-14].

In vivo studies confirm increases in survival when given with chemotherapy (119.9% compared to 70.1% for Mitomycin C on its own in experimental liver cancer[12]) and *in vitro* and *in vivo* studies show broad effects on the immune system, including TLR4 mediated macrophage activation and increased antibody production[12,15-17].

P. umbellatus aqueous extract significantly inhibited the development of bladder cancer in rats exposed to N-butyl-N-(4-hydroxybutyl) nitrosamine, with 61.1% of animals in the treatment group developing cancer compared to 100% in the control group, and it was also reported to be effective in reducing recurrence in 22 patients with recurrent bladder cancer[18-20].

In addition *P. umbellatus* polysaccharides prevented the development of toxohormone-L (a compound produced by cancer cells) induced cachexia (loss of weight, muscle atrophy, fatigue) in rats[21], while a number of steroids from *P. umbellatus* show promise as agents for promoting hair regrowth with low doses of extract (1.28 and 6.4 µg/ml) found to markedly enhance hair growth and lengthen the period of hair growth when applied topically[22].

CLINICAL SUMMARY

Therapeutic Application - *Cancer, fluid retention.*

Key Component - *Polysaccharides.*

Dose - *While the sclerotium has traditionally been prescribed as a diuretic in formulae at a dose of 6-15g/day, polysaccharide extracts are preferred for cancer care - 3-6g/day polysaccharide extract.*

Caution - *Patients on prescription diuretics.*

REFERENCES

1. Involvement of Ca2+ Channel Signalling in Sclerotial Formation of *Polyporus umbellatus*. Liu YY, Guo SX. Mycopathologia. 2009;169(2):139-150.
2. Identification of Armillaria species associated with *Polyporus umbellatus* using ITS sequences of nuclear ribosomal DNA. Gen Kikuchi and Hiroki Yamaji. Mycoscience. 2010;51(5):366-372.
3. Compendium of Materia Medica (Ben Cao Gang Mu). Li Shi Zhen. Tran. Luo Xiwen. 2003. Beijing:Foreign Languages Press.
4. Pharmacology and Applications of Chinese Materia Medica. Chang HM, But PPH. 1986. Singapore:World Scientific.
5. Studies on constituents of fruit body of *Polyporus umbellatus* and their cytotoxic activity. Ohsawa T, Yukawa M, Takao C, Murayama M, Bando H. Chem Pharm Bull (Tokyo). 1992;40(1): 143-7.
6. Cytotoxic steroids from *Polyporus umbellatus*. Zhao YY, Chao X, Zhang Y, Lin RC, Sun WJ. Planta Med. 2010.
7. Simultaneous determination of eight major steroids from *Polyporus umbellatus* by high-performance liquid chromatography coupled with mass spectrometry detections. Zhao YY, Cheng XL, Zhang Y, Zhao Y, Lin R.C, Sun WJ. Biomed Chromatogr. 2010;24(2):222-30.
8. Bioactivity-directed isolation, identification of diuretic compounds from *Polyporus umbellatus*. Zhao YY, Xie RM, Chao X, Zhang Y, Lin RC, Sun W.J. J Ethnopharmacol. 2009;126(1):184-7.
9. An anti-aldosteronic diuretic component (drain dampness) in *Polyporus sclerotium*. Yuan D, *et al*. Biol Pharm Bull. 2004;27(6): 867-70.
10. Diuretic activity and kidney medulla AQP1, AQP2, AQP3, V(2)R expression of the aqueous extract of sclerotia of *Polyporus umbellatus* FRIES in normal rats. Zhang G, Zeng X, Han L, Wei JA, Huang H. J Ethnopharmacol. 2010.
11. Traditional uses, phytochemistry, pharmacology, pharmacokinetics and quality control of *Polyporus umbellatus* (Pers.) Fries: a review. Zhao YY. J

Ethnopharmacol. 2013 Aug 26;149(1):35-48.

12. Recent advances on the active components in Chinese medicine. Zhu D. Abstracts of Chinese Medicines. 1987;1:251-286
13. Review on the studies of antineoplastic fungal polysaccharides. Li M. Jiangxi Zhongyiyao. 1985;63:59-61.
14. Chinese Medical Herbology and Pharmacology. Chen JK, Chen TT. Pub. Art of Medicine Press, City of Industry2001:386.
15. Combined effects of chuling (*Polyporus umbellatus*) extract and mitomycin C on experimental liver cancer. You JS, Hau DM, Chen K.T, Huang HF. Am J Chin Med. 1994;22(1):19-28.
16. TLR4-mediated activation of macrophages by the polysaccharide fraction from *Polyporus umbellatus* (pers.) Fries. Li X, Xu W. J Ethnopharmacol. 2010.
17. Polysaccharide purified from *Polyporus umbellatus* (Per) Fr induces the activation and maturation of murine bone-derived dendritic cells via toll-like receptor 4. Li X, Xu W, Chen J. Cell Immunol. 2010;265(1):50-6.
18. Inhibitory effect of Chinese herb medicine zhuling on urinary bladder cancer. An experimental and clinical study. Yang D.A. Zhonghua Wai Ke Za Zhi. 1991;29(6):393-5,399.
19. Prevention of postoperative recurrence of bladder cancer: a clinical study. Yang D, Li S, Wang H, Li X, Liu S, Han W, Hao J, Zhang H. Zhonghua Wai Ke Za Zhi. 1999;37(8):464-5.
20. Inhibition of urinary bladder carcinogenesis by aqueous extract of sclerotia of Polyporusumbellatus fries and polyporus polysaccharide. Zhang G, Zeng X, Li C, Li J, Huang Y, Han L, Wei JA, Huang H. Am J Chin Med. 2011;39(1):135-44.
21. Inhibitive effect of umbellatus polyporus polysaccharide on cachexic manifestation induced by toxohormone-L in rats. Wu GS, Zhang L.Y, Okuda H. Zhongguo Zhong Xi Yi Jie He Za Zhi. 1997;17(4):232-3.
22. Studies of the active substances in herbs used for hair treatment. II. Isolation of hair regrowth substances, acetosyringone and polyporusterone A and B, from *Polyporus umbellatus* Fries. Ishida H, Inaoka Y, Shibatani J, Fukushima M, Tsuji K. Biol Pharm Bull. 1999;22(11):1189-92.

Poria cocos

English Name
Hoelen

Chinese name
Fu Ling

Japanese name
Bukuryo

P. cocos is a component in many traditional Chinese herbal formulae, with functions described as diuretic, tonic and sedative but is almost never used singly. As the fruiting body is rarely seen, *P. cocos*, like *Polyporus umbellatus*, is traditionally harvested as the sclerotium from the roots of the pine trees on which it grows.

Research has focused on two fractions: polysaccharides and triterpenes, with the triterpenes showing wider activity. Although the majority of the the sclerotium (91-98%) is composed of polysaccharides the vast majority are insoluble and most evidence suggests that, unlike in mushrooms such as *P. umbellatus* and *Grifola*

frondosa, the soluble polysaccharides have low immunological activity.

Traditionally four parts of *P. cocos* are recognised in Chinese medicine: *Fu Ling* - the main body of the sclerotium, *Fu Shen* - the central portion considered be mildly sedative, *Fu Ling Pi* - the outer skin with the strongest diuretic action and *Chi Fu Ling* - the reddish part just under the skin with heat-clearing (anti-inflammatory) properties[1].

DIURETIC - Triterpenes are the key components in the diuretic activity of *P. cocos* and in accordance with traditional use are principally found in the outer layer of the sclerotium (*Fu Ling Pi*) with triterpene-rich extracts showing significant increases in urine output in rats at doses of 25 and 50mg/kg[2, 3].

CANCER - Triterpenes and heteropolysaccharides from *P. cocos* both show anti-tumour activity including inhibition of skin tumours in mice by triterpenes isolated from the sclerotium[4-9].

ANTI-INFLAMMATORY - Triterpene fractions from *P. cocos* show strong anti-inflammatory activity in animal models of dermatitis, suppressing carrageenan, arachidonic acid, tetradecanoyl phorbol acetate (TPA) acute oedemas, TPA chronic inflammation and oxazolone delayed hypersensitivity in mice. The fact that triterpenes are found primarily in the outer portion of *P. cocos* supports the traditional use of this part for treating inflammatory conditions[10-13].

CLINICAL SUMMARY

Main Therapeutic Application - *Mainly used in Chinese herbal formulae to reinforce/balance the effects of other herbs.*

Key Components - *Triterpenes, polysaccharides.*

Dose - *9-15g/day dried herb is used traditionally in aqueous decoctions. However, for single use the tincture is preferred in order to enhance extraction of the triterpenes.*

REFERENCES

1. Contents of Some Metabolites in the Peel and Flesh of the Medicinal Mushroom *Wolfiporia cocos* (F.A. Wolf) Ryvarden et Gilb. (Higher Basidiomycetes). Yuanzhong Wang, Tao Li, Yanli Zhao, Ji Zhang, Honggao Liu. Int J Med Mushr. 2012;14(1):79-83
2. Diuretic activity of some fractions of the epidermis of *Poria cocos*. Feng YL, Lei P, Tian T, Yin L, Chen DQ, Chen H, Mei Q, Zhao YY, Lin RC. J Ethnopharmacol. 2013 Dec 12;150(3):1114-8.
3. Diuretic activity of the ethanol and aqueous extracts of the surface layer of *Poria cocos* in rat. Zhao YY, Feng YL, Du X, Xi ZH, Cheng XL, Wei F. J Ethnopharmacol. 2012 Dec 18;144(3):775-8.
4. Antitumour activities of heteropolysaccharides of *Poria cocos* mycelia from different strains. Jin Y, Zhang L, Zhang M, Chen L, Keung PC, Cheung, Oi VEC, Lin Y. Carbohydrate Research. 2003;338(14):1517-1521.
5. Biological activities and potential health benefits of polysaccharides from *Poria cocos* and their derivatives. Sun Y. Int J Biol Macromol. 2014 Jul;68:131-4.
6. Chemical constituents and pharmacological properties of *Poria cocos*. Ríos JL. Planta Med. 2011 May;77(7):681-91.
7. Triterpene acids from *Poria cocos* and their anti-tumour-promoting effects. Akihisa T, *et al* J Nat Prod. 2007;70(6):948-53.
8. Antitumour-promoting effects of 25-methoxyporicoic acid A and other triterpene acids from *Poria cocos*. Akihisa T, Uchiyama E, Kikuchi T, Tokuda H, Suzuki T, Kimura Y. J Nat Prod. 2009;72(10):1786-92.
9. Inhibition of tumour-promoting effects by poricoic acids G and H and other lanostane-type triterpenes and cytotoxic activity of poricoic acids A and G from *Poria cocos*. Ukiya M, Akihisa T, Tokuda H, Hirano M, Oshikubo M, Nobukuni Y, Kimura Y, Tai T, Kondo S, Nishino H. J Nat Prod. 2002;65(4):462-5.
10. Isolation of inhibitors of TPA-induced mouse ear edema from Hoelen, *Poria cocos*. Nukaya H, Yamashiro H, Fukazawa H, Ishida H, Tsuji K. Chem

Pharm Bull (Tokyo). 1996;44(4):847-9.

11. Effect of the basidiomycete Poria cocos on experimental dermatitis and other inflammatory conditions. Cuellar MJ, Giner RM, Recio MC, Just M.J, Mañez S, Rios J.L.Chem Pharm Bull (Tokyo). 1997;45(3):492-4.
12. 3β-p-Hydroxybenzoyldehydrotumulosic acid from *Poria cocos*, and its anti-inflammatory effect. Yasukawa K, Kaminaga T, Kitanaka S, Tai T, Nunoura Y, Natori A, Takido M. Phyto-chemistry. 1998;48(8):1357-1360.
13. Antioxidant activity of anti-inflammatory plant extracts. Schinella GR, Tournier HA, Prieto JM, Mordujovich de Buschiazzo P, Ríos JL. Life Sciences. 2002;70(9):1023-1033.

Sparassis crispa

Japanese name
Hanabiratake

Chinese name
Xiu Qiu Jun

English Name
Cauliflower Mushroom

S. crispa is a popular culinary mushroom throughout its range in the northern temperate zone where it grows primarily on conifers, especially pines[1].

It has recently gained popularity as a medicinal mushroom because of its exceptional beta-glucan content, which has been reported to be as high as 43%[2]. In addition it contains multiple anti-microbial agents as well as active terpenoid compounds and phthalides that have been implicated in its anti-cancer activity[3-6].

CANCER - *In-vitro* and *in-vivo* tests have shown a high level of immunomodulatory and anti-tumour activity with both the dectin-1 and TLR-4 receptors and NF-kB and MAPK signalling pathways involved leading to significant increases in IFN-γ, TNF-a and IL-12 as well as enhancement of the haematopoietic response, macrophage and dendritic cell activation together with inhibition of angiogenesis and metastasis[6-12].

In one human study healthy men given 300mg *S. crispa* powder per day for 8 weeks showed significantly enhanced NK cell cytotoxicity compared to preadministration and in another the same dose produced increased quality of life scores in a small group of cancer patients (lung, stomach, colon, breast, ovarian, uterine, prostate, pancreatic and liver) over extended follow-up (mean: 15 months) when given after one course of lymphocyte transfer immunotherapy[13,14].

ANTI-MICROBIAL - One of the earliest reports of the separation and isolation of a microbial antibiotic was of Sparassol from *S. crispa* in 1923 and more recent studies have confirmed the prescence of multiple anti-bacterial compounds, including those with inhibition against MRSA, as well as anti-fungal agents[5,15,16]. A hot-water extract of *S. crispa* also showed a high level of HIV-1 reverse transcriptase activity with 70.3% inhibition at a concentration of 1mg/ml[17].

SKIN REPAIR - Daily supplementation with 70mg/kg *S. crispa* powder significantly increased the level of newly synthesized collagen in the skin of rats fed a protein deficient diet and *S. crispa* has also been reported to enhance wound healing in diabetic rats at 1g/kg[18,19].

In a controlled human study daily consumption of 320mg/day *S. crispa* fruiting body by healthy volunteers over a period of 28 days dramatically reduced transepidermal water loss in the treatment group with no change in the control group indicating enhanced skin

integrity[20].

Oral *S. crispa* supplementation also reduced inflammation, blood IgE level and scratching index in a mouse dermatitis model while anti-microbial compounds from *S. crispa* were found to inhibit melanin synthesis at a significantly lower concentrations than arbutin, a commonly used skin-whitening agent[16,21].

STROKE PREVENTION - In stroke-prone spontaneously hypertensive rats dietary supplementation with 1.5% *S. crispa* in feed delayed incidence of stroke and death with significantly decreased blood pressure and amelioration of cerebrovascular endothelial dysfunction[22].

CLINICAL SUMMARY

Main Therapeutic Application - *Skin repair, immune support, stroke prevention.*

Key Components - *Polysaccharides.*

Dose - *While benefit was seen both for immune and skin health from supplementation with the comparatively low dose of 0.3g/day S. crispa fruiting body, more acute cases will benefit from higher levels of supplementation (3-5g/day).*

REFERENCES

1. Properties and Potential Applications of the Culinary-Medicinal Cauliflower Mushroom, *Sparassis crispa* Wulf.:Fr. (Aphyllophoromycetideae): A Review. Gayathri Chandrasekaran, Deuk-Sil Oh, Hyun-Jae Shin. Int J Med Mushr. 2011;13(2):177-183.
2. IFN-gamma induction by SCG, 1,3-beta-D-glucan from *Sparassi scrispa*, in DBA/2 mice in vitro. Harada T *et al*. J Interferon Cytokine Res. 2002 Dec;22(12):1227-39.
3. New sesquiterpenoid from the mushroom *Sparassis crispa*. Kodani S *et al*. Biosci Biotechnol Biochem. 2009 Jan;73(1):228-9.
4. Novel phthalide compounds from *Sparassis crispa* (Hanabiratake), Hanabiratakelide A-C, exhibiting anti-cancer related activity. Yoshikawa K, Kokudo N, Hashimoto T, Yamamoto K, Inose T, Kimura T. Biol Pharm Bull. 2010;33(8): 1355-9.
5. Natural products and biological activity of the pharmacologically active cauliflower mushroom *Sparassis crispa*. Kimura T. Biomed Res Int. Epub 2013 Mar 18.
6. Antitumor 1,3-beta-glucan from cultured fruit body of *Sparassis crispa*. Ohno N, Miura NN, Nakajima M, Yadomae T. Biol Pharm Bull. 2000 Jul;23(7):866-72.
7. Effect of SCG, 1,3-beta-D-glucan from *Sparassis crispa* on the hematopoietic response in cyclophosphamide induced leukopenic mice. Harada T, Miura N, Adachi Y, Nakajima M, Yadomae T, Ohn N. Biol Pharm Bull. 2002 Jul;25(7):931-9.
8. Enhanced cytokine synthesis of leukocytes by a beta-glucan preparation, SCG, extracted from a medicinal mushroom, *Sparassis crispa*. Nameda S, Harada T, Miura NN, Adachi Y, Yadomae T, Nakajima M, Ohno N. Immunopharmacol Immunotoxicol. 2003 Aug;25(3):321-35.
9. Anti-angiogenic and anti-metastatic effects of beta-1,3-D-glucan purified from Hanabiratake, *Sparassis crispa*. Yamamoto K, Kimura T, Sugitachi A, Matsuura N. Biol Pharm Bull. 2009 Feb;32(2):259-63.

10. Induction of dendritic cell maturation by β-glucan isolated from *Sparassis crispa*. Kim HS. Int Immunopharmacol. 2010 Oct;10(10): 1284-94.
11. Mitogen activated protein kinases are prime signalling enzymes in nitric oxide production induced by soluble β-glucan from *Sparassis crispa*. Lee SY *et al*. Arch Pharm Res. 2010 Nov;33(11): 1753-60.
12. Oral Administration of Soluble β-Glucan Preparation from the Cauliflower Mushroom, *Sparassis crispa* (Higher Basidiomycetes) Modulated Cytokine Production in Mice. Hida TH *et al*. Int J Med Mushr. 2013;15(6):525-538
13. *Sparassis crispa* as biological response modifier. Hasegawa A *et al*. Gan To Kagaku Ryoho. 2004 Oct;31(11):1761-3.
14. Immunomodulating Activity of a b-Glucan Preparation, SCG, Extracted from a Culinary–Medicinal Mushroom, *Sparassis crispa* Wulf.:Fr. (Aphyllophoromycetideae), and Application to Cancer Patients. Ohno N *et al*. Int J Med Mushr. 2003;5(4): 15. Two New Antifungal Metabolites produced by *Sparassis crispa* in culture and in decayed trees. Woodward S, Sultan HY, Barrett DK, Pearce RB. J. Gen. Microbiol. 1993;139(1):153-159.
16. Novel bioactive compound from the *Sparassis crispa* mushroom. Kawagishi H *et al*. Biosci Biotechnol Biochem. 2007 Jul;71(7): 1804-6.
17. A peptide with HIV-1 reverse transcriptase inhibitory activity from the medicinal mushroom *Russula paludosa*. Wang J, Wang HX, Ng TB. Peptides. 2007 Mar;28(3):560-5.
18. Effects of medicinal mushroom (*Sparassis crispa*) on wound healing in streptozotocin-induced diabetic rats. Kwon AH, Qiu Z, Hashimoto M, Yamamoto K, Kimura T. Am J Surg. 2009 Apr;197(4):503-9.
19. Orally and topically administered *Sparassis crispa* (Hanabiratake) improved healing of skin wounds in mice with streptozotocin-induced diabetes. Yamamoto K, Kimura T. Biosci Biotechnol Biochem. 2013;77(6):1303-5.
20. *Sparassis crispa* (Hanabiratake) ameliorates skin conditions in rats and humans. Kimura T, Hashimoto M, Yamada M, Nishikawa Y. Biosci Biotechnol Biochem. 2013;77(9):1961-3.
21. *Sparassis crispa* suppresses mast cell-mediated allergic inflammation: Role of calcium, mitogen-activated protein kinase and nuclear factor-κB. Kim HH, Lee S, Singh TS, Choi JK, Shin TY, Kim SH. Int J Mol Med. 2012 Aug;30(2):344-50.

22. Beneficial effect of *Sparassis crispa* on stroke through activation of Akt/eNOS pathway in brain of SHRSP. Yoshitomi H, Iwaoka E, Kubo M, Shibata M, Gao M. J Nat Med. 2011 Jan;65(1):135-41.

Trametes versicolor

(Coriolus versicolor)

Japanese name
Kawaratake

Chinese name
Yun Zhi

English name
Turkey Tail

T. versicolor is the most extensively researched of all medicinal mushrooms with large scale clinical trials on the extracts PSK (‘Krestin’) and PSP showing impressive results in a variety of cancers including gastric, oesophageal, lung, breast and colorectal[1-8].

PSK and PSP are both polysaccharide-protein complexes that are soluble in water but insoluble in ethanol[9]. PSK contains 34-35% polysaccharide (~92% glucan) and 28-35% protein[10].

PSK has been shown to boost immune cell production, ameliorate chemotherapy and radiotherapy side effects, enhance immune status and tumour infiltration by dendritic and cytotoxic cells and significantly extend survival in cancers of the stomach, colon-rectum, oesophagus, nasopharynx, uterus and lung (non-small cell types), and in an HLA B40-positive breast cancer subset in combination with conventional treatment[1]. In addition to its immune related effects, PSK has shown an ability to enhance superoxide dismutase and glutathione peroxidase activity[11,12].

PSP has been shown to significantly enhance immune status in 70-97% of patients with cancers of the stomach, oesophagus, lung, ovary and cervix[8].

Although most clinical trials have been conducted with the above proteoglycan extracts, there is also evidence of immunomodulatory action for *T. versicolor* mycelial biomass, with improvements of immune status in patients with chronic fatigue syndrome and enhanced clearance of low grade squamous intraepithelial lesions (LSIL) from the cervix.

CANCER - The use of *T. versicolor* extracts in cancer treatment is supported by a significant number of clinical trials[8,13,14].

STOMACH CANCER - Multiple clinical trials of PSK given alongside surgery and chemotherapy at 3-6g/day significantly extended survival times in stomach cancer at all stages. Even in patients with advanced stomach cancer with metastasis PSK doubled 2-year and 5-year survival and extended 15-year survival[15-20].

COLORECTAL - In different clinical trials PSK extended 5-year and 8-year survival after surgery and chemotherapy and after surgery, chemotherapy and radiotherapy[21-23].

LUNG CANCER (NSCLC**) STAGES I-III** - PSK extended 5-year survival 2-4x for all cancer stages with stage III cancer patients taking PSK having a better prognosis than stage II patients without PSK[24].

OESOPHAGEAL - PSK extended 5-year survival after surgery, radiotherapy and chemotherapy while in double-blind trials PSP significantly extended 5-year survival in oesophageal cancer as well as improving quality of life, providing substantial pain relief and enhancing immune status in 70-97% of patients with cancers of the stomach, oesophagus, lung, ovary and cervix at a dose of 3g/day[25].

NASOPHARYNGEAL - PSK extended 5-year survival after radiotherapy and chemotherapy (28% vs, 15%)[26].

BREAST CANCER - Evidence from clinical trials (given alongside chemotherapy) is mixed. In one trial PSK was shown to extend survival in patients with oestrogen receptor negative, non-metastasised, stage II cancer but no benefit was shown in another. In a third trial significant benefit was seen in patients positive for HLA B40 with 100% survival after 10 years[27-29].

CERVICAL/UTERINE CANCER - In combination with radiotherapy PSK (3-6g/day) given to patients with stage III uterine and cervical cancer enhanced survival and increased sensitivity of the cancers to radiotherapy[30]. In another trial cervical cancer patients given the same dose together with radiotherapy showed clearance of cancer cells in 36% of patients versus 11% of controls and improved 5-year survival from 48% to 79%[9]. In a recent study using *T. versicolor* biomass, supplementation with 3g/day produced a 72.5% regression rate in LSIL lesions, compared to 47.5% without supplementation, and also increased the clearance of high risk HPV strains from 8.5% to 91.5%[31-33].

HIV - In several *in vitro* experiments PSK was found to exhibit anti-HIV activity through multiple routes[34-35]:

- Inhibition of HIV reverse transcriptase
- Inhibition of viral binding to lymphocytes
- Inhibition of cell-to-cell infection of HIV-1 and HIV-2

Use of *T. versicolor* supplementation (3.0g/day *T. versicolor* biomass) has been reported to improve HIV patients' immune status and produce improvement in HIV related Kaposi's sarcoma[36,37].

HERPES - Clinically *T. versicolor* supplementation is seen to reduce the frequency of *Herpes simplex* virus (HSV) outbreaks and it has also been shown to inactivate HSV in a dose-dependent manner[38].

CHRONIC FATIGUE SYNDROME (ME) - *T. versicolor* biomass has shown promise in the treatment of Chronic Fatigue Syndrome with immune system activation and increased NK cell activity reported in patients at 1.5g/day (3.0/day for the first 2 weeks) over a 2 month period[39].

HEPATOPROTECTIVE - *T. versicolor* polysaccharide extracts demonstrate hepato-protective properties[40,41].

CLINICAL SUMMARY

Main Therapeutic Application - *Cancer.*

Key Component - *Polysaccharides.*

Dose - *Commercial polysaccharide extracts are commonly prescribed at 3g/day and for long term use may be given in cycles of two weeks on, two weeks off. Dosage for crude polysaccharide extracts is typically 3-6g/day for cancer and 1-2g/day for immune support. For chronic immune deficient*

conditions the biomass also shows promise at 3g/day.

REFERENCES

1. Krestin (PSK). Tsukagoshi S, Hashimoto Y, Fujii G, Kobayashi H, Nomoto K, Orita K. Cancer Treat Rev. 1984;11(2):131-55.
2. Anticancer effects and mechanisms of polysaccharide-K (PSK): Implications of cancer immunotherapy. Fisher M, Yang LX. Anticancer Res. 2002;22:1737-1754.
3. A review of research on the protein-bound polysaccharide (polysaccharopeptide, PSP) from the mushroom *Coriolus versicolor* (Basidiomycetes: Polyporaceae). Ng TB. Gen Pharmacol. 1998; 30(1):1-4.
4. Polysaccharopeptides of *Coriolus versicolor*: physiological activity, uses, and production. Cui J, Chisti Y. Biotechnol Adv. 2003;21(2):109-22.
5. Effects of PSK on T and dendritic cells differentiation in gastric or colorectal cancer patients. Kanazawa M, Yoshihara K, Abe H, Iwadate M, Watanabe K, Suzuki S, Endoh Y, Takita K, Sekikawa K, Takenoshita S, Ogata T, Ohto H. Anticancer Res. 2005;25(1B):443-9.
6. The immunomodulator PSK induces *in vitro* cytotoxic activity in tumour cell lines via arrest of cell cycle and induction of apoptosis. Jiménez-Medina E, Berruguilla E, Romero I, Algarra I, Collado A, Garrido F, Garcia-Lora A. BMC Cancer. 2008;8:78.
7. *Trametes versicolor* mushroom immune therapy in breast cancer. Standish LJ, Wenner CA, Sweet ES, Bridge C, Nelson A, Martzen M, Novack J, Torkelson C. J Soc Integr Oncol. 2008; 6(3):122-8.
8. The use of mushroom glucans and proteoglycans in cancer treatment. Parris K. Alternative Medicine Rev. 2000:5(1).
9. Medicinal value of turkey tail fungus *Trametes versicolor* (L.:Fr.) Pilát (Aphyllophoromycetideae). A Literature Review. Christopher Hobbs. Int J Med Mushr 2004;6(3).
10. Method of producing nitrogen-containing polysaccharides. Ueno S, Yoshikumi C, Hirose F, Omura Y, Wada T, Fujii T *et al.* 1980. US Patent 4,202,969.
11. Polysaccharide Krestin enhances manganese superoxide dismutase activity

and mRNA expression in mouse peritoneal macrophages. Pang ZJ, Chen Y, Zhou M. Am J Chin Med. 2000;28:331-341.

12. Effect of polysaccharide krestin on glutathione peroxidase gene expression in mouse peritoneal macrophages. Pang Z.J, Chen Y, Zhou M. Brit J Biomed. 2000;57:130-16.
13. Efficacy of Yun Zhi (*Coriolus versicolor*) on survival in cancer patients: systematic review and meta-analysis. Eliza WL, Fai CK, Chung LP. Recent Pat Inflamm Allergy Drug Discov. 2012 Jan;6(1):78-87.
14. PSP in clinical cancer therapy – a review. In: Yang Q, ed. Advanced Research in PSP, 1999. Liu T. Hong Kong: Hong Kong Association for Health Care Ltd; 1999:68-75.
15. Postoperative long-term chemotherapy for advanced gastric cancer. Kaibara N, Soejima K, Nakamura T, *et al.* Jpn J Surg. 1976;6:54-59.
16. Combined effect of prophylactic lymphadenectomy and long-term combination chemotherapy for curatively resected carcinoma of the stomach. Kodama Y, Kano T, Tamada R, *et al.* Jpn J Surg. 1982;12:244-248.
17. Clinical study of PSK as an adjuvant immunochemotherapeutic agent against gastric cancer. Mitomi T, Ogoshi K. Jpn J Cancer Chemother. 1986;13:2532-2537.
18. Postoperative adjuvant immunochemotherapy with mitomycin C, futraful and PSK for gastric cancer. An analysis of data on 579 patients followed for five years. Niimoto M, Hattori T, Tamada R, *et al.* Jpn J Surg. 1988;18:681-686.
19. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. Nakazato H, Koike A, Saji S, *et al.* Lancet 1994;343:1122-1126.
20. Immunotherapy as adjuvant treatment after curative resection of gastric cancer. Kondo M. Lancet 1994;344:274.
21. Significant prolongation of disease-free period gained by oral polysaccharide K (PSK) administration after curative surgical operation of colorectal cancer. Torisu M, Hayashi Y, Ishimitsu T, et al.Cancer Immunol Immunother. 1990;31:261-268.
22. Randomized, controlled study on adjuvant immunochemotherapy with PSK in curatively resected colorectal cancer. Mitomi T, Tsuchiya S, Iijima N, *et*

al. Dis Colon Rectum 1992;35:123-130.

23. Adjuvant immunochemotherapy with oral Tegafur/Uracil plus PSK in patients with stage II or III colorectal cancer: a randomised controlled study. Ohwada S *et al*. Br J Cancer. 2004 Mar 8;90(5): 1003-10.
24. Effect of Krestin (PSK) as adjuvant treatment on the prognosis after radiotherapy in patients with non-small cell lung cancer. Hayakawa K, Mitsuhashi N, Saito Y, *et al*. Anticancer Res 1993;13:1815-1820.
25. Postoperative long-term immunochemotherapy for esophageal carcinoma. Okudaira Y, Sugimachi K, Inokuchi K, *et al*. Jpn J Surg. 1982;12:249-256.
26. Adjuvant PSK immunotherapy in patients with carcinoma of the nasopharynx. Go P, Chung CH. J Int Med Res. 1989;17:141-149.
27. Randomized adjuvant trial to evaluate the addition of tamoxifen and PSK to chemotherapy in patients with primary breast cancer. Toi M, Hattori T, Akagi M, *et al*. Cancer 1992;70:2475-2483.
28. Immunochemotherapies versus chemotherapy as adjuvant treatment after curative resection of operable breast cancer. Iino Y, Yokoe T, Maemura M, *et al* .Anticancer Res 1995;15:2907-2912.
29. Yokoe T, Iino Y, Takei H, *et al*. HLA antigen as predictive index for the outcome of breast cancer patients with adjuvant immunochemotherapy with PSK. Anticancer Res. 1997;17:2815-2818.
30. Enhancing effect of irradiation on carcinoma of the uterine cervix by administering the protein-bound polysaccharide kureha (PSK)--quantitative nuclear DNA analysis following irradiation. Hayashi Y. Nihon Sanka Fujinka Gakkai Zasshi. 1988 Feb;40(2):179-86.
31. *Coriolus versicolor* - innovation in prevention of oncogyneco-logical diseases, especially HPV. Bogdanova J. Akush Ginekol (Sofia). 2008;47 Suppl 3:51-3.
32. *Coriolus versicolor* supplementation in HPV patients. Couto S., da Silva D.P. 20th European Congress of Obstetrics and Gynaecology, 2008.
33. Coriolus – Assessment of the effect on patients infected with low and high-risk types of HPV. Borisov S. 2012. Clin J Mycol. Vol.3, Ed.2, 2-3.
34. A biological response modifier, PSK, inhibits reverse transcriptase in vitro. Hirose K, Hakozaki M, Kakuchi J, Matsunaga K, Yoshikumi C, Takahashi M, Tochikura T.S, Yamamoto N. Biochem Biophys Res Commun.

1987;149(2): 562-7.

35. Polysaccharopeptide from the turkey tail fungus *Trametes versicolor* (L.:Fr.) Pilát inhibits human immunodeficiency virus type 1 reverse Transciptase and Protease. Ng TB, Wang H, Wan DCC. Int J Med Mushr. 2006;8(1):39-43.
36. The clinical use of *Coriolus versicolor* supplementation in HIV+ patients and the impact on CD4 count and viral load. Pfeiffer M. 3rd International Symposium on Mushroom Nutrition, 2001.
37. The effectiveness of *Coriolus versicolor* supplementation in the treatment of Kaposi sarcoma in HIV+Patients. Tindall J, Clegg E. 10th International Congress of Mucosal Immunology, 1999.
38. *In vitro* inactivation of herpes simplex virus by a biological response modifier, PSK. Monma Y, Kawana T, Shimizu F. Antiviral Res. 1997;35:131-138.
39. Coriolus. Jean Munroe. J Integrative Medicine. 2004;8:101-108.
40. Effects of a hot water extract of *Trametes versicolor* on the recovery of rat liver function. Kim BK *et al.* Int J Med Mushr. 2000;2(1):35-42.
41. Pharmacological studies on certain mushrooms from china. Ooi VEC. Int J Med Mushr. 2001;3(4):341-354.

Tremella fuciformis

English name
Snow Fungus

Japanese name
Shirokikurage/
Hakumokuji

Chinese name
Bai Mu Er/Yin Er

As well as being a popular culinary mushroom in oriental cuisine, *T. fuciformis* has a long history of medicinal use and was one of the mushrooms included in the *Shen Nong Ben Cao* (c.200AD). Its traditional indications include clearing Heat and Dryness, nourishing the brain and enhancing beauty.

Like other jelly fungi, *T. fuciformis* is rich in polysaccharides and these are the main bioactive component[1]. The principal polysaccharide is a glucoronoxylomannan with a linear backbone of 1,3 linked α-D-mannan residues with side chains consisting mainly of xylose and

glucoronic acid[2,3]. The glucuronic acid side chains in *Auricularia auricula* have been found to be essential for its anti-coagulant action and they are likely to contribute to *T. fuciformis*'s action in this regard.

Research in China has focused on its use to alleviate the side effects of radiotherapy and as an anti-ageing supplement with over 40 Chinese patents citing it during the 1990s alone[4,5].

RADIOTHERAPY - As well as demonstrating broad immuno-modulatory activity and *in vitro* anti-cancer activity[6-8], *T. fuciformis* polysaccharides have been shown to protect against the consequences of acute radiation exposure, restoring the blood-producing mechanism of the bone marrow[9]. When administered at a dose of 54mg/kg i.p. for 3 days before γ-irradiation they resulted in 50% 30-day survival in mice exposed to whole body lethal γ-irradiation compared to 100% mortality without and when administered at a dose of 200mg/kg for 3-5 days prior to γ-irradiation they exerted a protective effect on bone marrow with myeloid granulocytes reduced to 60% of normal compared to 20% of normal without[10]. They also significantly increased 30-day survival rates in mice, dogs and monkeys exposed to γ-irradiation[11].

CIRCULATORY DISORDERS - *T. fuciformis* polysaccharides have been shown to stimulate DNA synthesis in vascular endothelial cells, the dysfunction of which is a major factor in the pathogenesis of atherosclerosis, hypertension and thrombophlebitis, with therapeutic implications for these conditions. They have also been shown to protect endothelium cells from histamine damage, increase clotting time, reduce platelet adherence and blood viscosity[9].

NEUROLOGICAL DAMAGE - The water extract of *T. fuciformis* (0.01-1 microg/ml) promoted neurite outgrowth of PC12 cells in a

dose dependent manner, indicating potential for application of *T. fuciformis* polysaccharides in the treatment of neurological damage[12].

Experiments with mice also showed the ability of *T. fuciformis* polysaccharides to exert an anti-ageing effect by increasing the superoxide dismutase activity of the brain and liver[9].

MEMORY IMPAIRMENT - Traditionally considered to nourish the brain, supplementation with *T. fuciformis* polysaccharide extract (100 or 400 mg/kg) for 14 days significantly reversed the scopolamine-induced deficit in learning and memory in rats and alleviated decrease in cholinergic immuno-reactivity induced by scopolamine in the medial septum and hippocampus[13,14].

COSMETIC APPLICATION - *T. fuciformis* has traditionally been used to benefit the skin and 'enhance beauty' and *T. fuciformis* polysaccharides have been developed for use in cosmetics on account of their excellent skin moisture retention, skin protection, flexibility and flattening effects, as well as anti-inflammatory and anti-allergenic properties. Their ability to prevent senile degeneration of micro-vessels helps maintain blood perfusion to the skin and they have also been shown to promote wound healing[15,16].

CLINICAL SUMMARY

Main Therapeutic Application - *Immune support, anti-ageing, radiotherapy.*

Key Component - *Polysaccharides.*

Dose - *1-3g/day polysaccharide extract for health maintenance, 3-6g/day for radiotherapy support.*

T. fuciformis polysaccharides are beneficial for counteracting the harmful effects of radiotherapy and also possess excellent anti-ageing activity with a combination of neurological, circulatory and immune-

modulating benefits. In addition they are an ideal supplement for those who smoke because of their moistening and nourishing properties, as well as beneficial effects on the skin and immune system.

Safety - *Although a widely consumed culinary mushroom with no reported side-effects, T. fuciformis' mild anti-coagulant activity indicates a need for caution when using alongside anti-coagulant medication.*

REFERENCES

1. Research advances in primary biological effects of Tremella polysaccharides. Chen FF, Cai DL. Zhong Xi Yi Jie He Xue Bao. 2008;6(8):862-6.
2. Characterisation of acidic heteroglycans from *Tremella fuciformis* Berk with cytokine stimulating activity. Gao Q, Seljelid R, Chen H, Jiang R. Carbohydrate Research. 1996;288:135-142.
3. Antioxidation activities of polysaccharides extracted from *Tremella fuciformis* Berk. Liu P, Gao X, Xu W, Zhou Z, Shen X. Chinese Journal of Biochemical Pharmaceutics. 2005;03.
4. Effect of polysaccharides from Auricularia auricula underw, *Tremella fuciformis* Berk and spores of Tremella fuciformis Berk on aging. Chen Yi-jun *et al*. Chinese Journal of Modern Applied Pharmacy. 1989-02.
5. Effect of Tremella polysaccharides on the immune function of experimental aging model mice. La Y, Liu X, Pei S, Shi Y, Cai D. Chinese Journal of Clinical Nutrition. 2005-04.
6. Effect of Tremella polysaccharide on IL-2 production by mouse splenocytes. Ma L, Lin ZB. Yao Xue Xue Bao. 1992;27(1):1-4.
7. Effects of Tremella polysaccharides on immune function in mice. Xia D, Lin ZB. Zhongguo Yao Li Xue Bao. 1989;10(5): 453-7.
8. Antitumour activity on sarcoma 180 of the polysaccharides from *Tremella fuciformis* Berk. Ukai S, Hirose K, Kiho T, Hara C, Irikura T. Chem Pharm Bull (Tokyo). 1972;20(10):2293-4.
9. Medicinal value of the genus Tremella Pers. (Hetero-basidiomycetes) (Review). Reshetnikov SV, Wasser SP, Duckman I, and Tsukor K. 2000. Int J Med Mushr. 2000;2:345-367.
10. Effect of nourishing Yin and antitoxic capsule II on oxidative injury by X-ray irradiation in rats. Chen R, Shi HJ, Hou Y. Journal of Hebei Medical University. 2006-05.
11. Effect of *Tremella fuciformis* Berk on acute radiation sickness in dogs. Zhao TF *et al*. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 1982;4(1):20-3.

12. Long-Term Regeneration and Functional Recovery of a 15mm Critical Nerve Gap Bridged by *Tremella fuciformis* Polysaccharide-Immobilized Polylactide Conduits. Hsu SH, Chan SH, Weng CT, Yang SH, Jiang CF. Evid Based Complement Alternat Med. Epub 2013 Aug 21.
13. Effect of *Tremella fuciformis* on the neurite outgrowth of PC12h cells and the improvement of memory in rats. Kim JH, Ha HC, Lee MS, Kang JI, Kim HS, Lee SY, Pyun KH, Shim I. Biol Pharm Bull. 2007;30(4):708-14.
14. *Tremella fuciformis* enhances the neurite outgrowth of PC12 cells and restores trimethyltin-induced impairment of memory in rats via activation of CREB transcription and cholinergic systems. Park HJ *et al*. Behav Brain Res. 2012 Apr 1;229(1):82-90.
15. *Tremella fuciformis* (Shirokikurage) polysaccharide. Ahashi Y, Yamamoto Y. Fragrance Journal. 2005;33,3:45-50.
16. Skin Wound Healing Promoting Effect of Polysaccharides Extracts from *Tremella fuciformis* and Auricularia auricula on the *ex-vivo* Porcine Skin Wound Healing Model. 2012 4th International Conference on Chemical, Biological and Environmental Engineering, vol.43. IACSIT Press, Singapore.

Medicinal Mushrooms in Cancer Therapy

Cancer has traditionally been one of the main conditions for which medicinal mushrooms have been used and in the Far East several mushroom extracts are licensed as adjuvant nutrition for cancer therapy, including:

- PSK and PSP - Proteoglycan extracts from *Trametes versicolor* mycelium
- Lentinan - Polysaccharide extract from *Lentinula edodes* fruit body
- Schizophyllan - Polysaccharide extract from *Schizophyllan commune* culture broth

These extracts have impressive risk/benefit profiles with large scale clinical trials demonstrating extended survival times in a range of cancers and an absence of serious side effects[1]. Use of these mushroom polysaccharide extracts has been shown to promote[2]:

- Anti-inflammatory Activity
- Inhibition of cell proliferation
- Induction of cell-cycle arrest
- Induction of apoptosis
- Inhibition of angiogenesis and tumour invasiveness
- Cell-signalling pathway interference
- Reduction in side-effects from chemotherapy and radiotherapy

As well as polysaccharides several other categories of compound produced by mushrooms for their antimicrobial properties have also been shown to have anti-cancer activity, including:

- Statins - Lovastatin is found in a number of mushroom species and exhibits several beneficial antineoplastic properties, including decreased tumour growth and inhibition of angiogenesis and metastasis[3].
- Sterols - Ergosterol (pro-vitamin D2) and other sterols with anti-cancer activity are present to varying degrees in all mushrooms[4].
- Triterpenes - produced in significant quantities by some mushrooms, especially *Antrodia camphorata*, *Ganoderma lucidum* and *Inonotus obliquus*[5-7].
- Nucleoside Derivatives - found primarily in *Cordyceps* species with cordycepin from *Cordyceps militaris* having been shown to inhibit metastasis, induce apoptosis, provoke RNA chain termination and interfere with mTOR signal transduction[8].

Medicinal Mushrooms and Chemotherapy

Mushroom extracts are routinely prescribed in Japan and China alongside a range of chemotherapeutic agents with multiple clinical trials confirming enhanced treatment outcomes as well as reduction in side effects including nausea, hair loss and lowered immune status, as well as improved appetite, general condition and haematopoietic parameters[9-17].

Chemotherapy regimes for which adjuvant mushroom nutrition has been reported to be beneficial include:

- Lentinan extended survival in inoperable or recurrent gastric cancer in conjunction the tegafur - 50% survival time 173 days compared to 92 days with tegafur alone[18].

- Lentinan prolonged survival and reduced the incidence of adverse effects in patients with gastric cancer receiving S-1-based chemotherapy (tegafur, gimeracil, oteracil)[19].
- Five-year disease free survival in colorectal cancer cases was significantly higher with PSK and oral Tegafur/Uracil (UFT) than with UFT alone (73% vs. 58.8%, p=.016)[20].
- PSK increased five-year disease-free period (70.7% vs. 59.4%, p<0.05) and five-year survival (73.0% vs. 60.0%, p=0.04) when given together with mitomycin and fluorouracil[21].
- *Agaricus subrufescens* polysaccharide extract reduced chemotherapy related side effects (appetite, alopecia, emotional stability, and general weakness) in one hundred cervical, ovarian, and endometrial cancer patients treated either with carboplatin plus VP16 (etoposide) or with carboplatin plus taxol[22].
- *Grifola frondosa* polysaccharide fractions potentiated the action of carmustine and increased efficacy when given in combination with chemotherapy across a range of cancers, as well as reducing cisplatin-induced nephrotoxicity[23].

In addition to supporting the immune system and ameliorating chemotherapy-induced immune suppression there is some evidence that mushroom polysaccharide extracts contribute to the efficacy of the chemotherapeutic drugs themselves through enhanced production of reactive oxygen species (ROS). Liu *et al* reported an increase in ROS and reactive nitrogen intermediates in peritoneal macrophages of mice given PSP, an extract of *A. subrufescens* was shown to induce apoptosis through an ROS-dependent pathway and Grifron-D, a polysaccharide extract from *G. frondosa*, has been shown to have a direct cytotoxic effect on cancer cells through oxidative membrane damage leading to apoptosis[24-26].

Although antioxidant activity of mushroom extracts has been demonsrated *in vitro* this was shown to be strongly correlated with pro-oxidant activity in a study of 39 commercial mushroom extracts

(7 species) and 12 fruiting body extracts (11 species) as well as with their respective polysaccharide and polyphenol content, indicating that possible excess cell defense−related intracellular ROS generated by mushroom extracts may be downregulated by the antioxidant components present in the same extracts[27].

CLINICAL NOTE

Medicinal mushrooms may also offer some protection against venous thromboembolism (VTE), which some chemotherapy drugs are known to increase the risk of (the annual incidence of VTE in patients receiving chemotherapy is estimated at 11% and this can climb to 20% or higher depending on the type of drug(s) being administered)[28].

Elderly patients are especially at risk and mushrooms with anti-coagulant properties (such as Ganoderma lucidum and Tremella fuciformis) can be beneficial in such cases.

Caution - *Because of medicinal mushrooms' ability to support immune function in patients receiving chemotherapy, they are not considered suitable for use alongside immuno-suppressive agents such as methotrexate.*

Mushrooms and Radiotherapy

As with chemotherapy, there is evidence for benefit from medicinal mushroom use alongside radiotherapy including:

- Reduction in radiation-induced leukopaenia - in a trial with 136 patients undergoing radiotherapy, oral consumption of *T. fuciformis* polysaccharide extract (3g/day) resulted in a 13.2% reduction in WBC compared to a 35.2% reduction in the control group and *T. versicolor* mycelial biomass (6g/day) prevented decreases in red and white blood cells in lung cancer patients undergoing radiotherapy[29],[30].

- Enhanced treatment efficacy - oral administration of *T. versicolor* extract PSP with radiotherapy significantly increased the percentage of apoptotic cells at 24hr compared to radiation alone and reduced radiotherapy induced reduction in white blood cell count[31].

Mushrooms and Surgery

Mushroom extracts such as PSK and Lentinan are routinely used alongside surgical excision of tumours with no contraindication. In addition, two double-blind placebo-controlled studies at Harvard Medical School showed fungal beta-glucan (2g/day) to be effective at protecting patients from infection after undergoing major surgery, indicating their role in enhancing host immunity[32],[33].

CLINICAL NOTE

Mushrooms with anti-coagulant properties are best avoided immediately before surgery. The main mushrooms in this category are Antrodia camphorata, Auricularia auricula, Ganoderma lucidum and Tremella fuciformis.

Cancer Prevention

There is growing evidence linking increased mushroom consumption with reduced risk of developing cancer and some that regular consumption of both mushrooms and green tea provides even greater levels of protection[34].

An epidemiological study of 2,000 Chinese women, half with breast cancer and half without, found a reduction in risk of breast cancer in those women who regularly consumed mushrooms (10g/day fresh or 4g/day dried) and drank green tea (1.05g/day dried green tea

leaves) with an increased reduction in women who did both[35].

Two Korean studies of women with histologically confirmed breast cancer, one with 362 women and the other with 358, also found a strong inverse correlation between mushroom consumption and breast cancer risk with the strongest association in women with oestrogen receptor (ER)+/progesterone receptor (PR) + tumours (OR = 0.30)[36,37].

In studies on the population in the Nagano area of Japan, mushroom farmers had a much lower rate of death from cancer than the general population (97.1/100,000cf. 160.1/100,000) with *Flammulina velutipes* and *Hypzisygus marmoreus* farmers showing the greatest reduction in risk of developing cancer[38,39].

Bladder Cancer

Clinical studies in China showed polysaccharide extracts of *Polyporus umbellatus* to be as effective in preventing post-operative recurrence of bladder cancer as BCG (Bacillus Calmette-Guérin) and greater than Mitomycin C (MMC)[40,41]. One study of 313 patients after TURBT (transurethral resection of bladder tumour) or partial cystectomy who were followed up for 2 to 15 years (average 7.6 years) reported recurrence rates of 34.9% in the group receiving *P. umbellatus* polysaccharide extract, compared with 35.1% in the BCG group, 41.7% in the MMC group and 64.7% in the control group[42].

In animal experiments *P. umbellatus* also inhibited the development of bladder cancer in rats exposed to N-butyl-N-(4-hydroxybutyl) nitrosamine with 11 of 18 animals staying cancer free. Polysaccharide extracts of *Lentinula edodes, Grifola frondosa* and *Pleurotus ostreatus* showed similar increases in host resistance with 9 of 17, 13 of 20 and 7 of 15 animals staying cancer free[43].

In vitro studies with *G. frondosa* and *Phellinus linteus* extracts showed synergistic action with vitamin C against bladder cancer cell

lines with non-cytotoxic doses of polysaccharide extracts becoming highly cytotoxic in combination with non-toxic levels of vitamin C[44].

Brain Cancer

Betulinic acid, a major component of extracts from *Inonotus obliquus* grown on birch trees, exerted cytotoxic activity against primary tumour cells cultured from patients in 4 of 4 medulloblastoma-tumour samples and in 20 of 24 glioblastoma-tumour samples with induction of apoptosis, while being non-toxic against mouse nerve cells[45-47].

Maitake D-fraction in combination with Maitake (*Grifola frondosa*) fruiting body was reported by Nanba to produce tumour regression or significant symptom improvement in 37% of brain cancer patients[48].

Breast Cancer

Polysaccharide extracts from *Lentinula edodes*, *Grifola frondosa* and *Trametes versicolor* have all been reported to be beneficial for breast cancer[49].

Long term immunotherapy with PSK has been shown to significantly improve the survival rate of patients with breast cancer[50-51], while a separate study in breast cancer patients with vascular invasion linked the effect of PSK supplementation to B40 antigen status (a known indicator of breast cancer survival) with 100% of B40-positive patients treated with PSK as well as chemotherapy surviving beyond 10 years, while for B40-negative patients the 10-year survival rate was approximately 50%[52].

Symptomatic improvement or regression was also reported by Nanba for 11 out of 15 breast cancer patients treated with a combination of Maitake D-fraction and Maitake *(G. frondosa*) fruiting

body[48]. Mizuno reported recovery in a breast cancer patient with lung metastases using *Agaricus subrufescens* polysaccharide extract[53], while *Phellinus linteus* has traditionally been used to treat breast cancer in Korea and polysaccharide extracts show strong *in vitro* activity[54].

Breast Cancer - Oestrogen independent

The transcription factor NF-kB has been identified as a key component in the ability of breast cancer cells to multiply independently of oestrogen while resisting chemotherapy and avoiding apoptosis[49].

Ganoderma lucidum has shown the most significant inhibitory effect on NF-kB in highly invasive breast cancer cells with the triterpenes particularly active. Triterpenes from *G. lucidum* have also been shown to inhibit aromatase activity, as well as the transcription factor AP1 (characteristic of highly metastatic breast cancer cells), while the clinical role of a triterpene-enriched *G. lucidum* extract in inhibiting NF-kB in a case of breast cancer is also reported in one paper[55].

Other mushrooms which have demonstrated NF-kB inhibition *in vitro* include *Phellinus linteus* and *Lentinula edodes*.

Cervical Cancer

Schizophyllan (Sizofiran), a polysaccharide extract from *Schizophyllan commune*, is licensed in Japan for the treatment of cervical cancer and, in a 5-year multi-centre study, has been shown to significantly extend time to recurrence and improve survival rates in patients with stage II cervical cancer but not in those with stage III cancer[56],[57]. A polysaccharide extract of *Agaricus subrufescens* was

shown to enhance NK cell activity in patients with gynaecological cancers (cervical, uterine and endometrial) undergoing chemotherapy (either carboplatin plus etoposide or carboplatin plus taxol) and reduce side effects from the chemotherapy (appetite suppression, alopecia, emotional stability and general weakness)[58].

Fve, a protein from *Flammulina velutipes*, enhanced immune response to vaccination against HPV in an animal model and, in early stage cervical dysplasia (LSIL), *Trametes versicolor* mycelial biomass (3g/day) significantly increased the percentage of women showing normal cytology after 1 year (72.5% compared to 47.5% in the control group) and increased clearance of associated high risk HPV strains (91.5% vs. 8.5%)[58,60].

Colorectal Cancer

A recent meta-analysis of 3 clinical trials in Japan with 1,094 patients showed clear benefit from PSK supplementation (3.0g/day) in improving both survival and disease-free survival in cases of curatively resected colorectal cancer[61,62]. Chihara *et al* also report excellent results from a 4 year follow-up of Lentinan in phase III patients with colorectal cancer[63].

In a study on patients with advanced colorectal cancer, a polysaccharide extract from *Ganoderma lucidum* (5.4g/day) produced improvements in immune parameters with increases in mitogenic reactivity to phytohemagglutinin, counts of CD3, CD4, CD8 and CD56 lymphocytes, plasma concentrations of interleukin (IL)-2, IL-6 and IFN-γ, and NK-cell activity, and decreases in plasma concentrations of IL-1 and tumour necrosis factor-alpha[64].

It is also likely that dietary consumption of mushrooms might be beneficial in reducing incidences of colon cancer due to their high dietary fibre content and immune modulating activity, with *Pleurotus*

ostreatus given at 5% of feed showing a protective effect on the development of dimethylhydrazine-induced colon cancer in rats[65,66]. Extracts from *G. lucidum* and *Lentinula edodes* also show protective effects against colon cancer development[67,68].

Endometrial Cancer

Agaricus subrufescens polysaccharide extract enhanced NK cell activity in gynaecological cancer patients (including endometrial) undergoing chemotherapy (either carboplatin plus etoposide or carboplatin plus taxol) and reduced side effects from the chemotherapy[59].

Gastric Cancer (Stomach cancer)

Previously the most common cancer in Japan[69], mushroom polysaccharide extracts form part of mainstream treatment and their effects have been evaluated in several large scale clinical trials with very positive results.

A recent meta-analysis of trials with PSK including 8,009 patients confirmed improved survival of patients after curative gastric cancer resection and an individual patient data meta-analysis of 690 patients from 5 trials with Lentinan showed it to offer a significant advantage over chemotherapy alone in terms of survival for patients with advanced gastric cancer[70,71].

Leukaemia

PSK increased median duration for complete remission and survival when given alongside mercaptopurine chemotherapy after remission had been induced by combination therapy without side effects in one

trial and there was a trend to longer survival in a second[72,73]. Nanba *et al* also reported reductions in CD4+ (26%) and IL-2 (17%) in 3 leukaemia cases with a combination of Maitake (*Grifola frondosa*) D-fraction and *G. frondosa* fruiting body[74].

In vitro experiments with polysaccharide extracts from several mushrooms, including *Agaricus subrufescens*, *Ganoderma lucidum*, *Poria cocos*, *Trametes versicolor* and *Ophiocordyceps sinensis* show activity against human leukaemia cell lines through induction of apoptosis, as do triterpenes from *G. lucidum* and *Antrodia camphorata*[75-85], while *in vivo* and *in vitro* studies with *Agaricus subrufescens* polysaccharide extracts showed tumour-selective growth inhibitory activity against human leukaemia cells[86].

Liver Cancer

Nanba *et al* reported that 7 of 12 patients with liver cancer responded to a combination of *Grifola frondosa* fruiting body (4-6g/day) and purified polysaccharide extract (MD fraction - 40-150mg/day)[45].

Studies using implanted sarcoma 180 as a model for liver cancer have shown rates of tumour inhibition of 52.8%, 56.6% and 51.9% when given polysaccharide extracts of *Flammulina velutipes*, *Lentinula edodes* and *Agaricus subrufescens* respectively[87] and a 71.6% increase in lifespan of tumour-bearing mice with *Polyporus umbellatus* polysaccharide extract (i.p.) on its own and a 119.9% increase when given in conjunction with mitomycin C[88].

Several *in vitro* studies using *Ganoderma lucidum* and *G. lucidum* triterpenes have demonstrated cell growth inhibition and anti-invasive effects by multiple mechanisms including suppression of protein kinase C, activation of protein kinases, G2-phase cell cycle arrest, inactivation of MAPK/ERK signal transduction pathway and inhibition of the binding activities of NF-kB and AP-1[89-94]. In a human

tumour xenograft model, a doseresponse inhibition was also observed in the average size, volume, and weight of tumours upon oral administration of *G. lucidum* extract[95].

Antrodia camphorata has traditionally been used in the treatment of liver cancer in Taiwan. *In vitro* studies confirm its apoptotic effects on human liver cancer cell lines and a number of promising cases have been reported combining it with conventional treatment in cases of advanced liver cancer[96,97].

Ophiocordyceps sinensis, *Pleurotus ostreatus* and *Inonotus obliquus* have all shown *in vitro* efficacy against liver cancer cell lines[98-100].

Lung Cancer

Trametes versicolor polysaccharide extracts show impressive benefits in cases of lung cancer.

In a 1993 study on patients with stage I-III non-small cell lung cancer treated with radiotherapy and PSK, PSK extended 5-yr survival 2-4x for all stages with maximum benefit in patients over the age of 70 and for tumours less than 5cm in diameter. In a 2003 study with non-small-cell lung cancer patients post-radiotherapy, those patients who received 3g PSK daily in 2 week cycles (2 weeks on, 2 weeks off) were almost 4 times more likely to be alive after 5 years than those without PSK (27% vs. 7%), with stage III patients who received PSK having a better prognosis than stage I/II patients who did not[101].

Grifola frondosa polysaccharide extract/fruiting body combination has also been reported to produce improvement in 65% of lung cancer patients[48].

Lymphoma

A number of papers report beneficial immunological effects from extracts of *Trametes versicolor* and *Ganoderma lucidum* in human lymphoma cell lines[102-106]. PSK was also reported to inhibit lymphoma development in a mouse model and a case of regression of gastric large B-Cell lymphoma following high *G. lucidum* intake has been reported[107,108].

Ovarian Cancer

PSK has been shown to reduce chemotherapy-induced IL2 suppression in ovarian cancer patients and to increase the survival rate of mice with human ovarian cancer[109-111]. PSK also showed combined benefit with cisplatin, a finding confirmed by *in vitro* studies[112].

A polysaccharide extract of *Agaricus subrufescens* was reported to increase NK cell activity and improve quality of life in patients with ovarian cancer, as well as other gynaecological cancers[58].

Pancreatic Cancer

There have been two reports of unresectable pancreatic cancer responding to combined chemotherapy and PSK/Lentinan and one *in vitro* study showing PSK enhancing docetaxel induced apoptosis through NF-kB inhibition[113-115].

Clinically triterpene-rich *Ganoderma lucidum* products are often used in China and there is *in vitro* evidence of benefit for triterpenes from *Poria cocos* as well as a natural ubiquinone derivative from *Antrodia camphorata*[116,117].

Prostate Cancer

Ganoderma lucidum has been identified as a promising agent for

prostate cancer with *in vitro* evidence showing inhibition of hormone dependent and independent prostate cancer cells through multiple pathways, including binding to androgen receptor, inhibition of the active transcription factors: NF-kB and AP-1, inhibition of urokinase-type plasminogen activator (uPA) and its receptor uPAR, as well as cell adhesion and cell migration of highly invasive breast and prostate cancer cells[118-130].

Ganodermic triterpenes have also been shown to suppress steroid 5α-reductase, which converts testosterone to dihydrotestosterone (DHT) and has been shown to play an important role in the development of prostate cancer and benign prostatic hyperplasia (BPH). The use of other steroid 5α-reductase inhibitors has been found to decrease the incidence of prostate cancer and *G. lucidum* would appear to be a promising candidate for further research in this regard.

Several *in vitro* studies using mushroom polysaccharides have also shown suppression of both androgen-dependent and -independent cell growth with a comparative study of aqueous extracts from 23 mushroom species, including *G. lucidum*, *Trametes versicolor*, *Grifola frondosa*, *Ophiocordyceps sinensis*, *Agaricus subrufescens*, *Lentinula edodes* and *Hericium erinaceus*, on androgen-independent PC-3 cells showing *Pleurotus ostreatus* and *Flammulina velutipes* to have the greatest cytotoxicity, significantly increasing cancer cell apoptosis[131,132]. *Coprinus comatus* has also been shown to reduce androgen and glucocorticoid receptor transcriptional activity in a dose dependent manner[133].

In addition, an *in vivo* study using severely immunodeficient mice found *A. subrufescens* polysaccharides to directly inhibit the growth of prostate cancer cells via an apoptotic pathway and suppress prostate tumour growth via antiproliferative and antiangiogenic mechanisms[134].

A 2002 clinical study of an *L. edodes* polysaccharide extract

however, showed it to be ineffective in stopping the disease with no instances of regression and progression in 23 of 61 men over a 6 month period[135].

Skin Cancer (Melanoma)

In one *in vivo* study, injection of Maitake D-fraction produced 27% inhibition of a melanoma cell line in mice at a dose of 1mg/kg[136], while in others an ethanol extract of *Ophiocordyceps sinensis* was effective at inhibiting growth of melanoma in the lungs of mice[137,138] and PSK at suppressing lung metastases of mouse melanoma[139].

Extracts of *Inonotus obliquus* and *Lentinula edodes* have also shown *in vitro* activity against melanoma cells lines[140,141], while triterpenes from *Poria cocos* have demonstrated anti-inflammatory activity and inhibition of the development of skin cancer in a mouse model[142,143].

CLINICAL NOTES

Oral dosage of polysaccharide/proteoglycan extracts such as PSK is typically 3-6g/day, although for long term supplementation this is sometimes reduced to every other day or given in weekly or fortnightly cycles (1-2 weeks on, 1-2 weeks off).

Dosages of dried herb material or mycelial biomass products can be considerably higher with doses of 15-50g/day reported for supplementation with mushroom mycelial biomass products in cancer cases.

As mushroom polysaccharide extracts not only strengthen immune response but also enhance the efficacy of conventional treatment, while at the same time reducing its side effects, it is beneficial to start supplementation as soon as cancer is diagnosed or suspected, continuing during any conventional treatment and for 3-6 months after. It can then be appropriate to continue with low dose supplementation to support immune health and help prevent recurrence, either daily or on alternate days or

weeks (epidemiological studies show benefits from consuming mushrooms three or more times a week).

There is some in vitro evidence to suggest that co-administration of vitamin C can increase effectiveness of mushroom polysaccharide supplementation in cancer therapy, with non-toxic doses of polysaccharide extracts from both Grifola frondosa and Phellinus linteus found to be strongly cytotoxic to bladder cancer cells when combined with a non-toxic dose of vitamin C, producing over 90% cell death[44, 131].

In vitro studies with extracts of Ganoderma lucidum and green tea showed a synergistic enhancement of their independent abilities to inhibit adhesion, migration and invasion of oestrogen-independent and highly metastatic human breast cancer cells supporting the epidemiological observation of reduced risk of developing breast cancer from regular consumption of both green tea and mushrooms and it is likely that combined consumption of mushrooms and green tea will have similar benefits in other cancers[144].

Transfer factors have also been suggested as beneficial adjuvants to mushroom nutrition supplementation[145].

REFERENCES

1. The use of mushroom glucans and proteoglycans in cancer treatment. Kidd PM. Altern Med Rev. 2000;5(1):4-27.
2. Antitumor activity of mushroom polysaccharides: a review. Ren L, Perera C, Hemar Y. Food Funct. 2012 Nov;3(11):1118-30.
3. Effects of statins in cancer. Cuello FM, Kato CS, Díaz SD, Owen G. Rev Med Chil. 2013 Feb;141(2):227-36.
4. Terpenoids and sterols from some Japanese mushrooms. Yaoita Y, Kikuchi M, Machida K. Nat Prod Commun. 2014 Mar;9(3): 419-26
5. *Ganoderma lucidum* and its pharmaceutically active compounds. Boh B, Berovic M, Zhang J, Zhi-Bin L. Biotechnol Annu Rev. 2007;13:265-301.
6. Recent research and development of *Antrodia cinnamomea*. Lu MC, El-Shazly M, Wu TY, Du YC, Chang TT, Chen CF, Hsu YM *et al*. Pharmacol Ther. 2013 Aug;139(2):124-56.
7. Progress on understanding the anticancer mechanisms of medicinal mushroom: *Inonotus obliquus*. Song FQ, Liu Y, Kong XS, Chang W, Song G. Asian Pac J Cancer Prev. 2013;14(3):1571-8.
8. Cordycepin: a bioactive metabolite with therapeutic potential. Tuli HS, Sharma AK, Sandhu SS, Kashyap D. Life Sci. 2013 Nov 26;93(23):863-9.
9. Advances in immunomodulating studies of PSP. Li KY. Hong Kong Assoc. for Health Care Ltd. 1999;Advanced Research in PSP:39-46.
10. Polysaccharide peptide (PSP) restores immunosuppression induced by cyclophosphamide in rats. Qian ZM, Xu MF, Tang PL. Am J Chin Med. 1997;25(1):27-35.
11. Krestin (PSK). Tsukagoshi SY, Hashimoto G, Fujii H, Kobayashi K, Nomoto, Orita K. Cancer Treatment Review. 1984;11:131-155.
12. Polysaccharopeptides derived from *Coriolus versicolor* potentiate the S-phase specific cytotoxicity of Camptothecin (CPT) on human leukaemia HL-60 cells. Wan JM, Sit WH, Yang X, Jiang P, Wong LL. Chin Med. 2010;5:16.

13. Polysaccharopeptide enhances the anticancer activity of doxorubicin and etoposide on human breast cancer cells ZR-75-30. Wan JM, Sit WH, Louie JC. Int J Oncol. 2008; 32(3):689-99.
14. Enhancement of anticancer activity of cisdiaminedichloroplatinum by the protein-bound polysaccharide of *Coriolus versicolor* QUEL (PS-K) *in vitro*. Kobayashi Y, Kariya K, Saigenji K, Nakamura K. Cancer Biother. 1994;9(4):351-8.
15. Antitumour effect of PSK and its combined effect with CDDP on ovarian serous adenocarcinoma-bearing nude mice. Ishii K, Kita T, Hirata J, Tode T, Kikuchi Y, Nagata I. Nippon Sanka Fujinka Gakkai Zasshi. 1993;45(4):333-9.
16. Effects of PSK on interleukin-2 production by peripheral lymphocytes of patients with advanced ovarian carcinoma during chemotherapy. Kikuchi Y, Kizawa I, Oomori K, Iwano I, Kita T, Kato K. Jpn J Cancer Res. 1988;79(1):125-30.
17. The effect of lentinan combination therapy for unresectable advanced gastric cancer. Higashi D *et al.* Anticancer Res. 2012 Jun;32(6):2365-8.
18. End-point result of a randomised controlled study on the treatment of gastrointestinal cancer with a combination of Lentinan and chemotherapeutic agents. Taguchi T, Furue H *etal*. Excerpta Medica. 1985:151-165.
19. Lentinan prolonged survival in patients with gastric cancer receiving S-1-based chemotherapy. Ina K *et al*. World J Clin Oncol. 2011 Oct 10;2(10):339-43.
20. Adjuvant immunochemotherapy with oral Tegafur/Uracil plus PSK in patients with stage II or III colorectal cancer: a randomised controlled study. Ohwada S, Ikeya T, Yokomori T, Kusaba T, Roppongi T, Takahashi T, *et al*. Br J Cancer 2004 Mar;90(5):1003-10.
21. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. Nakazato H, Koike A, Saji S, Ogawa N, Sakamoto J. The Lancet 1994;343:1122-6.
22. Natural killer cell activity and quality of life were improved by consumption of a mushroom extract, *Agaricus blazei* Murill Kyowa, in gynecological cancer patients undergoing chemotherapy. Ahn W.S, *et al*. Int J Gynecol Cancer 2004; 14(4):589-594.
23. Maitake beta-glucan enhances therapeutic effect and reduces myelo-

supression and nephrotoxicity of cisplatin in mice. Masuda Y, Inoue M, Miyata A, Mizuno S, Nanba H. Int Immunopharmacol. 2009;9(5):620-6.

24. Induction of apoptosis in human prostatic cancer cells with beta-glucan (Maitake mushroom polysaccharide). Fullerton SA, Samadi AA, Tortorelis DG, Choudhury MS, Mallouh C, Tazaki H, Konno S. Mol Urol. 2000;4(1):7-13.
25. *Agaricus blazei* Extract Induces Apoptosis through ROS-Dependent JNK Activation Involving the Mitochondrial Pathway and Suppression of Constitutive NF-κB in THP-1 Cells. Kim MO, Moon DO, Jung JM, Lee WS, Choi YH, Kim GY. Evid Based Complement Alternat Med. Epub 2011 Feb 20.
26. Mechanism of Nitric Oxide Production in Macrophages Treated with Medicinal Mushroom Extracts (Review). Huang M, Mei XD, Zhang S. Int J Med Mushr. 2011;13(1):1-6.
27. Pro-and antioxidative properties of medicinal mushroom extracts. Wei S, Griensven LJLD. Int J Med Mushr. 2008;10(4):30.
28. Chemotherapy-induced thrombosis. Haddad TC, Greeno EW. Thromb Res. 2006;118(5):555-68.
29. The effect of Tremella polysaccharides on leukopoenia following radiotherapy. Dai H. Chinese Pharmaceutical Journal 2006;41(13)p:1033-4.
30. The use of Coriolus-MRL supplementation in lung cancer patients undergoing radiotherapy. Catita J. Mycology News. 2000;1(4):3-4.
31. The ameliorative effect of PSP on the toxic and side effect reactions of chemo-and radiotherapy of cancers. Advanced research in PSP. Sun Z *et al*. Hong Kong Association for Health Care Ltd. 1999:304-307.
32. A phase II multicenter, double-blind, randomized, placebo-controlled study of three dosages of an immunomodulator (PGG-glucan) in high-risk surgical patients. Babineau TJ, Hackford A, Kenler A, Bistrian B, Forse RA, Fairchild PG, Heard S *et al.* Arch Surg. 1994;129(11):1204-10.
33. Effect of PGG-glucan on the rate of serious postoperative infection or death observed after high-risk gastrointestinal operations. Betafectin Gastrointestinal Study Group. Dellinger EP, Babineau TJ, Bleicher P, Kaiser AB, Seibert GB, Postier RG, Vogel SB *et al*. Arch Surg. 1999;134(9):977-83.

34. The cancer preventive effects of edible mushrooms. Xu T, Beelman RB, Lambert JD. Anticancer Agents Med Chem. 2012 Dec;12(10):1255-63.
35. Dietary intakes of mushrooms and green tea combine to reduce the risk of breast cancer in Chinese women. Zhang M, Huang J, Xie X, Holman CD. Int J Cancer. 2009;124(6):1404-8.
36. A case-control study on the dietary intake of mushrooms and breast cancer risk among Korean women. Hong SA, Kim K, Nam SJ, Kong G, Kim MK. Int J Cancer. 2008; 122(4):919– 23.36. A case-control study on the dietary intake of mushrooms and breast cancer risk among Korean women. Hong SA, Kim K, Nam SJ, Kong G, Kim MK. Int J Cancer. 2008; 122(4):919–23.
37. Dietary mushroom intake and the risk of breast cancer based on hormone receptor status. Shin A, Kim J, Lim SY, Kim G, Sung MK, Lee ES, Ro J. Nutr Cancer. 2010;62(4):476-83.
38. Beneficial Effects of Edible and Medicinal Mushrooms on Health Care. Ikekawa Int J Med Mushr. 2001;3(4).
39. Cancer Risk Reduction by Intake of Mushrooms and Clinical Studies on EEM. Ikekawa Int J Med Mushr. 2005;7(3).
40. Inhibitory effect of Chinese herb medicine zhuling on urinary bladder cancer. An experimental and clinical study. Yang DA. Zhonghua Wai Ke Za Zhi. 1991;29(6):393-5,399.
41. Prophylactic effects of zhuling and BCG on postoperative recurrence of bladder cancer. Zhonghua Wai Ke Za Zhi. Yang DA, Li SQ, Li XT. 1994;32(7):433-4.
42. Prevention of postoperative recurrence of bladder cancer: a clinical study. Yang D, Li S, Wang H, Li X, Liu S, Han W, Hao J, Zhang H. Zhonghua Wai Ke Za Zhi. 1999;37(8):464-5.
43. Effects of *Lentinus edodes*, *Grifola frondosa* and *Pleurotusostreatus* administration on cancer outbreak, and activities of macrophages and lymphocytes in mice treated with a carcinogen, N-butyl-N-butanol-nitrosoamine. Kurashige S, Akuzawa Y, Endo F. Immunopharmacol Immunotoxicol. 1997;19(2):175-83.
44. Effect of various natural products on growth of bladder cancer cells: two promising mushroom extracts. Konno S. Altern Med Rev. 2007;12(1):63-8.
45. Betulinic acid: a new cytotoxic agent against malignant brain-tumour cells.

Fulda S, Jeremias I, Steiner HH, Pietsch T, Debatin KM. Int J Cancer. 1999;82(3):435-41.

46. Chemistry, biological activity, and chemotherapeutic potential of betulinic acid for the prevention and treatment of cancer and HIV infection. Cichewicz RH, Kouzi SA. Med Res Rev. 2004;24(1):90-114.
47. Betulinic acid, a natural compound with potent anticancer effects. Mullauer FB, Kessler JH, Medema JP. Anticancer Drugs. 2010;21(3):215-27.
48. Maitake D-fraction: healing and preventive potential for cancer. Nanba H. J Orthomolecular Med. 1997;12:43-49.
49. Potential Role of Medicinal Mushrooms in Breast Cancer Treatment: Current Knowledge and Future Perspectives. Petrova RD, Wasser SP; Mahajna JA, Denchev CM, Neva E. Intl J Med Mush. 2005;7(1-2):141-153.
50. Hormone conditioned cancer chemotherapy for recurrent breast cancer prolongs survival. Sugimachi K, Inokuchi K, Matsuura H, Ueo H, Kumashiro R. Jpn J Surg. 1984 May;14(3):217-21.
51. Immunochemotherapies versus chemotherapy as adjuvant treatment after curative resection of operable breast cancer. Iino Y, Yokoe T, Maemura M, Horiguchi J, Takei H, Ohwada S, Morishita Y. Anticancer Res. 1995 Nov-Dec;15(6B):2907-11.
52. HLA antigen as predictive index for the outcome of breast cancer patients with adjuvant immunochemotherapy with PSK. Yokoe T, Iino Y, Takei H, Horiguchi J, Koibuchi Y, Maemura M, Ohwada S, Morishita Y. Anticancer Res. 1997 Jul-Aug;17(4A):2815-8.
53. Medicinal properties and clinical effects of culinary-medicinal mushroom *Agaricus blazei* Murrill (Agaricomycetideae) (Review). Mizuno T. Int J Med Mushr. 2002;4:299–312.
54. *Phellinus linteus* suppresses growth, angiogenesis and invasive behaviour of breast cancer cells through the inhibition of AKT signalling. Sliva D, Jedinak A, Kawasaki J, Harvey K, Slivova V. Br J Cancer. 2008;98(8): 1348-56.
55. Potential Benefits of Ling Zhi or Reishi Mushroom *Ganodermalucidum* (W. Curt.: Fr.) P. Karst. (Aphyllophoromycetideae) to Breast Cancer Patients. Chen AW, Seleen J. Int J Med Mushr. 2007;9(1):29-38.
56. Clinical evaluation of schizophyllan combined with irradiation in patients

with cervical cancer. A randomized controlled study. Okamura K, Suzuki M, Chihara T, Fujiwara A, Fukuda T, Goto S *et al.* Cancer. 1986;58(4):865-72.

57. Clinical evaluation of sizofiran combined with irradiation in patients with cervical cancer. A randomized controlled study; a five-year survival rate. Okamura K, Suzuki M, Chihara T, Fujiwara A, Fukuda T, Goto S *et al.* Biotherapy. 1989;1(2):103-7.
58. Natural killer cell activity and quality of life were improved by consumption of a mushroom extract, *Agaricus blazei* Murill Kyowa, in gynecological cancer patients undergoing chemotherapy. Ahn WS, Kim DJ, Chae DJ, Lee JM, Bae SM, Sin JI *et al*. International Journal of Gynecological Cancer: 2004;14(4):589-594.
59. Coadministration of the fungal immunomodulatory protein FIP-Fve and a tumour-associated antigen enhanced antitumour immunity. Ding Y, Seow SV, Huang CH, Liew LM, Lim YC, Kuo IC, Chua KY. Immunology. 2009;128(1 Sup):e881-94.
60. *Coriolus versicolor* supplementation in HPV patients. Couto S. 20th European Congress of Obstetrics and Gynaecology, 2008.
61. Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curatively resected colorectal cancer: a meta-analysis of centrally randomized controlled clinical trials. Sakamoto J, Morita S, Oba K, Matsui T, Kobayashi M, Nakazato H, Ohashi Y. Cancer Immunol Immunother. 2006;55(4):404-11.
62. Monitoring of immune responses to a herbal immunomodulator in patients with advanced colorectal cancer. Chen X, Hu ZP, Yang XX, Huang M, Gao Y, Tang W *et al*. Int Immunopharmacol. 2006;6(3):499-508.
63. Antitumour and metastasis-inhibitory activities of lentinan as an immunomodulator: an overview. Chihara G, Hamuro J, Maeda Y.Y, Shiio T, Suga T, Takasuka N, Sasaki T. Cancer Detect Prev Suppl. 1987;1:423-43.
64. Immune responses to water-soluble ling zhi mushroom *Ganoderma lucidum* (W.Curt.:Fr.) P. Karst. Polysaccharides in patients with advanced colorectal cancer. Huang M; Gao YH; Tang W; Dai X; Gao H; Chen GL *et al*. Int J Med Mushr. 2006;7(4):525-538.
65. Effect of oyster mushroom (*Pleurotus ostreatus*) on pathological changes in dimethylhydrazine-induced rat colon cancer. Bobek P, Galbavy S, Ozdin L. Oncol Rep. 1998;5(3):727-30.

66. An aqueous polysaccharide extract from the edible mushroom *Pleurotus ostreatus* induces anti-proliferative and pro-apoptotic effects on HT-29 colon cancer cells. Lavi I, Friesem D, Geresh S, Hadar Y, Schwartz B. Cancer Lett. 2006;244(1):61-70.

67. A water-soluble extract from cultured medium of *Ganodermalucidum* (Rei-shi) mycelia suppresses azoxymethane-induction of colon cancers in male F344 rats. Lu H, Kyo E, Uesaka T, Katoh O, Watanabe H. Oncol Rep. 2003;10(2):375-9.

68. Inhibition of human colon carcinoma development by lentinan from shiitake mushrooms (*Lentinus edodes*). Ng ML, Yap AT. J Altern Complement Med. 2002;8(5):581-9.

69. Epidemiology of gastric cancer in Japan. Inoue M, Tsugane S. Postgrad Med J. 2005;81:419-424.

70. Efficacy of adjuvant immunochemotherapy with polysaccharide K for patients with curative resections of gastric cancer. Oba K, Teramukai S, Kobayashi M, Matsui T, Kodera Y, Sakamoto J. Cancer Immunol Immunother. 2007;56(6):905-11.

71. Individual patient based meta-analysis of lentinan for unresectable/recurrent gastric cancer. Oba K, Kobayashi M, Matsui T, Kodera Y, Sakamoto J. Anticancer Res. 2009;29(7): 2739-45.

72. Chemoimmunotherapy with Krestin in acute leukemia. Nagao T, Komatsuda M, Yamauchi K, Nozaki H, Watanabe K, Arimori S. Tokai Journal of Experimental and Clinical Medicine 1981; 6(2):141-6.

73. A randomized trial of chemoimmunotherapy of acute nonlymphocytic leukemia in adults using a protein-bound polysaccharide preparation. Ohno R, Yamada K, Masaoka T, Ohshima T, Amaki I, Hirota Y, *et al*. Cancer Immunology, Immunotherapy 1984;18:149-54.

74. Can Maitake MD-fraction aid cancer patients? Kodama N, Komuta K, Nanba H. Alt Med Rev. 2002;7(3):236.

75. *Ganoderma lucidum* causes apoptosis in leukaemia, lymphoma and multiple myeloma cells. Müller CI, Kumagai T, O'Kelly J, Seeram NP, Heber D, Koeffler HP. Leuk Res. 2006;30(7):841-8.

76. *Ganoderma lucidum* polysaccharides can induce human monocytic leukaemia cells into dendritic cells with immuno-stimulatory function. Chan WK, Cheung CC, Law HK, Lau YL, Chan GC. J Hematol Oncol. 2008;1:9.

77. Antiproliferative and differentiating effects of polysaccharide fraction from fu-ling (*Poria cocos*) on human leukemic U937 and HL-60 cells. Chen YY, Chang HM. Food Chem Toxicol. 2004;42(5):759-69.

78. *Coriolus versicolor* (Yunzhi) extract attenuates growth of human leukaemia xenografts and induces apoptosis through the mitochondrial pathway. Ho CY, Kim CF, Leung KN, Fung KP, Tse TF, Chan H, Lau CB. Oncol Rep. 2006;16(3):609-16.

79. Cytotoxic activities of *Coriolus versicolor*(Yunzhi) extract on human leukaemia and lymphoma cells by induction of apoptosis. Lau CB, Ho CY, Kim CF, Leung KN, Fung KP, Tse TF, Chan HH, Chow MS. Life Sci. 2004;75(7):797-808.

80. Primary mechanism of apoptosis induction in a leukaemia cell line by fraction FA-2-b-ss prepared from the mushroom *Agaricus blazei* Murill. Gao L, Sun Y, Chen C, Xi Y, Wang J, Wang Z. Braz J Med Biol Res. 2007;40(11):1545-55.

81. *Cordyceps sinensis* mycelium extract induces human premyelocytic leukaemia cell apoptosis through mitochondrion pathway. Zhang QX, Wu JY. Exp Biol Med (Maywood). 2007;232(1):52-7.

82. Effect of *Cordyceps sinensis* on the proliferation and differentiation of human leukemic U937 cells. Chen YJ, Shiao MS, Lee SS, Wang SY. Life Sci. 1997;60(25):2349-59.

83. *Ganoderma lucidum* causes apoptosis in leukaemia, lymphoma and multiple myeloma cells. Müller CI, Kumagai T, O'Kelly J, Seeram NP, Heber D, Koeffler HP. Leuk Res. 2006;30(7):841-8.

84. Lucidenic acid B induces apoptosis in human leukaemia cells via a mitochondria-mediated pathway. Hsu CL, Yu YS, Yen GC. J Agric Food Chem. 2008;56(11):3973-80.

85. Compound MMH01 possesses toxicity against human leukaemia and pancreatic cancer cells. Chen YJ, Chou CJ, Chang TT. Toxicol *in vitro*. 2009;23(3):418-24.

86. Inhibitory effects of *Agaricus blazei* extracts on human myeloid leukaemia cells. Kim CF, Jiang JJ, Leung KN, Fung KP, Lau CB. J Ethnopharmacol. 2009;122(2):320-6.

87. Inhibitory activity of polysaccharide extracts from three kinds of edible

fungi on proliferation of human hepatoma SMMC-7721 cell and mouse implanted S180 tumour. Jiang SM, Xiao ZM, Xu ZH. World J Gastroenterol. 1999;5(5):404-407.

88. Combined effects of chuling (*Polyporus umbellatus*) extract and mitomycin C on experimental liver cancer. You JS, Hau DM, Chen KT, Huang HF. Am J Chin Med. 1994;22(1):19-28.
89. Triterpene-enriched extracts from *Ganoderma lucidum* inhibit growth of hepatoma cells via suppressing protein kinase C, activating mitogen-activated protein kinases and G2-phase cell cycle arrest. Lin SB, Li CH, Lee SS, Kan LS. Life Sci. 2003;72(21):2381-90.
90. Ganoderic acid produced from submerged culture of *Ganoderma lucidum* induces cell cycle arrest and cytotoxicity in human hepatoma cell line BEL7402. Yang HL. Biotechnol Lett. 2005;27(12):835-8.
91. Antitumour activity of the sporoderm-broken germinating spores of *Ganoderma lucidum*. Liu X, Yuan JP, Chung CK, Chen XJ. Cancer Lett. 2002;182(2):155-61.
92. Ganoderiol F, a ganoderma triterpene, induces senescence in hepatoma HepG2 cells. Chang UM, Li CH, Lin LI, Huang CP, Kan LS, Lin SB. Life Sci. 2006;79(12):1129-39.
93. The anti-invasive effect of lucidenic acids isolated from a new *Ganoderma lucidum* strain. Weng CJ, Chau CF, Chen KD, Chen DH, Yen GC. Mol Nutr Food Res. 2007;51(12):1472-7.
94. Lucidenic acid inhibits PMA-induced invasion of human hepatoma cells through inactivating MAPK/ERK signal transduction pathway and reducing binding activities of NF-kappaB and AP-1. Weng CJ, Chau CF, Hsieh YS, Yang SF, Yen GC. Carcinogenesis. 2008;29(1): 147-56.
95. Inhibitory effects of *Ganoderma lucidum* on tumourigenesis and metastasis of human hepatoma cells in cells and animal models. Weng .J, Chau CF, Yen GC, Liao JW, Chen DH, Chen KD. J Agric Food Chem. 2009;57(11):5049-57.
96. Apoptotic effects of extract from *Antrodia camphorata* fruiting bodies in human hepatocellular carcinoma cell lines. Hsu YL, Kuo YC, Kuo PL, Ng LT, Kuo YH, Lin .C. Cancer Lett. 2005;221(1):77-89.
97. Niuchangchih (*Antrodia camphorata*) and its potential in treating liver diseases. Ao ZH, Xu ZH, Lu ZM, Xu HY, Zhang XM, Dou WF. J

Ethnopharmacol. 2009;121(2):194-212.

98. *Cordyceps sinensis* increases the expression of major histo-compatibility complex class II antigens on human hepatoma cell line HA22T/VGH cells. Chiu JH, Ju CH, Wu LH, Lui WY, Wu CW, Shiao MS, Hong CY. Am J Chin Med. 1998; 26(2):159-70.

99. A new lectin with highly potent antihepatoma and antisarcoma activities from the oyster mushroom *Pleurotus ostreatus*. Wang H, Gao J, Ng TB. Biochem Biophys Res Commun. 2000;275(3): 810-6.

00. Chaga mushroom (*Inonotus obliquus*) induces G0/G1 arrest and apoptosis in human hepatoma HepG2 cells. Youn MJ, Kim JK, Park SY, Kim Y, Kim SJ, Lee JS *et al*. World J Gastroenterol. 2008;14(4):511-7.

01. *Coriolus versicolor* polysaccharide peptide slows progression of advanced non-small cell lung cancer. Tsang KW, Lam CL, Yan C, Mak JC, Ooi GC, Ho JC *et al*. Respir Med. 2003;97(6): 618-24.

02. Protein-bound polysaccharide-K (PSK) directly enhanced IgM production in the human B cell line BALL-1. Maruyama S, Akasaka T, Yamada K, Tachibana H. Biomed Pharmacother. 2009;63(6):409-12.

03. Protein-bound polysaccharide K induced apoptosis of the human Burkitt lymphoma cell line, Namalwa. Hattori TS, Komatsu N, Shichijo S, Itoh K.Biomed Pharmacother. 2004;58(4):226-30.

04. *Ganoderma lucidum* causes apoptosis in leukaemia, lymphoma and multiple myeloma cells. Müller CI, Kumagai T, O'Kelly J, Seeram NP, Heber D, Koeffler HP. Leuk Res. 2006;30(7):841-8.

05. Cytotoxic action of *Ganoderma lucidum* on interleukin-3 dependent lymphoma DA-1 cells: involvement of apoptosis proteins. Calviño E, Pajuelo L, de Eribe Casas JA, Manjón JL, Tejedor M.C, Herráez A *et al*. Phytother Res. 2010 Jun.

06. Potentiation of T cell immunity against radiation-leukaemia-virus-induced lymphoma by polysaccharide K. Yefenof E, Einat E, Klein E. Cancer Immunol Immunother. 1991;34(2):133-7.

07. Prophylactic intervention in radiation-leukaemia-virus-induced murine lymphoma by the biological response modifier polysaccharide K. Yefenof E, Gafanovitch I, Oron E, Bar M, Klein E. Cancer Immunol Immunother. 1995;41(6):389-96.

08. Regression of gastric large B-Cell lymphoma accompanied by a florid lymphoma-like T-cell reaction: immunomodulatory effect of *Ganoderma lucidum* (Lingzhi)? Cheuk W, Chan JK, Nuovo G, Chan MK, Fok M. Int J Surg Pathol. 2007;15(2):180-6.

09. Effects of cimetidine and PSK on interleukin-2 production by PBL in patients with advanced ovarian carcinoma during the course of chemotherapy. Kikuchi Y, Kizawa I, Oomori K, Iwano I, Kita T, Miyauchi M, Kato K. Nippon Sanka Fujinka Gakkai Zasshi. 1987;39(11):1987-92.

10. Effects of PSK on interleukin-2 production by peripheral lymphocytes of patients with advanced ovarian carcinoma during chemotherapy. Kikuchi Y, Kizawa I, Oomori K, Iwano I, Kita T, Kato K. Jpn J Cancer Res. 1988;79(1):125-30.

11. Antitumour effect of PSK and its combined effect with CDDP on ovarian serous adenocarcinoma-bearing nude mice. Ishii K, Kita T, Hirata J, Tode T, Kikuchi Y, Nagata I. Nippon Sanka Fujinka Gakkai Zasshi. 1993;45(4):333-9.

12. Enhancement of anticancer activity of cisdiaminedichloroplatinum by the protein-bound polysaccharide of *Coriolus versicolor* QUEL (PS-K) *in vitro*. Kobayashi Y, Kariya K, Saigenji K, Nakamura K. Cancer Biother. 1994;9(4):351-8.

13. Two cases of unresectable pancreatic cancer responding to combined chemotherapy with cisplatin, PSK and UFT. Sohma M, Kitagawa T, Okano S, Utsumi M, Mutoh E, Takeda S *et al*. Gan To Kagaku Ryoho. 1987;14(6 Pt 1):1926-9.

14. A case of unresectable pancreatic cancer that responded to UFT chemotherapy. Gan No Rinsho. Sato Y, Sakai T, Okada T, Sasano Y, Ando T, Haruta J *et al*. 1990;36(11):2073-8.

15. PSK-mediated NF-kappaB inhibition augments docetaxel-induced apoptosis in human pancreatic cancer cells NOR-P1. Zhang H, Morisaki T, Nakahara C, Matsunaga H, Sato N, Nagumo F *et al*. Oncogene. 2003;22(14):2088-96.

16. Antroquinonol, a natural ubiquinone derivative, induces a cross talk between apoptosis, autophagy and senescence in human pancreatic carcinoma cells. Yu CC1, Chiang PC, Lu PH, Kuo MT, Wen WC, Chen P, Guh JH. J Nutr Biochem. 2012 Aug;23(8):900-7.

17. Triterpenes from *Poria cocos* suppress growth and invasiveness of

pancreatic cancer cells through the downregulation of MMP-7. Cheng S, Eliaz I, Lin J, Thyagarajan-Sahu A, Sliva D. Int J Oncol. 2013 Jun;42(6):1869-74.

18. Pharmacological values of medicinal mushrooms for prostate cancer therapy: the case of *Ganoderma lucidum*. Mahajna J, Dotan N, Zaidman BZ, Petrova RD, Wasser SP. Nutr Cancer. 2009;61(1):16-26.
19. *Ganoderma lucidum* (Reishi) in cancer treatment. Sliva D. Integr Cancer Ther. 2003;2(4):358-64.
20. Androgen receptor-dependent and -independent mechanisms mediate *Ganoderma lucidum* activities in LNCaP prostate cancer cells. Zaidman BZ, Wasser SP, Nevo E, Mahajna J. Int J Oncol. 2007;31(4):959-67.
21. Anti-androgen effects of extracts and compounds from *Ganoderma lucidum*. Liu J, Tamura S, Kurashiki K, Shimizu K, Noda K, Konishi F, Kumamoto S, Kondo R. Chem Biodivers. 2009;6(2):231-43.
22. The anti-androgen effect of ganoderol B isolated from the fruiting body of *Ganoderma lucidum*. Liu J, Shimizu K, Konishi F, Kumamoto S, Kondo R. Bioorg Med Chem. 2007;15(14):4966-72.
23. Medicinal mushroom cuts off prostate cancer cells' blood supply. Johnston N. Drug Discov Today. 2005;10(23-24):1584.
24. *Ganoderma lucidum* suppresses angiogenesis through the inhibition of secretion of VEGF and TGF-beta1 from prostate cancer cells. Stanley G, Harvey K, Slivova V, Jiang J, Sliva D. Biochem Biophys Res Commun. 2005;330(1):46-52.
25. *Ganoderma lucidum* inhibits proliferation and induces apoptosis in human prostate cancer cells PC-3. Jiang J, Slivova V, Valachovicova T, Harvey K, Sliva D. Int J Oncol. 2004;24(5):1093-9.
26. Biologic activity of spores and dried powder from *Ganodermalucidum* for the inhibition of highly invasive human breast and prostate cancer cells. Sliva D, Sedlak M, Slivova V, Valachovicova T, Lloyd FP Jr, Ho NW. J Altern Complement Med. 2003;9(4):491-7.
27. Ganoderic acid DM: anti-androgenic osteoclastogenesis inhibitor. Liu J, Shiono J, Shimizu K, Kukita A, Kukita T, Kondo R. Bioorg Med Chem Lett. 2009;19(8):2154-7.
28. Anti-androgenic activities of *Ganoderma lucidum*. Fujita R, Liu J, Shimizu

K, Konishi F, Noda K, Kumamoto S *et al*. J Ethnopharmacol. 2005;102(1):107-12.

29. Androgen receptor-dependent and -independent mechanisms mediate *Ganoderma lucidum* activities in LNCaP prostate cancer cells. Zaidman BZ, Wasser SP, Nevo E, Mahajna J.Int J Oncol. 2007;31(4):959-67.
30. Mushroom substances as therapeutics for hormone refractory prostate cancer. Mahajna JA *et al*. Int J Med Mushr. 2007;9(3): 212.
31. Induction of apoptosis in human prostatic cancer cells with beta-glucan (Maitake mushroom polysaccharide). Fullerton SA, Samadi AA, Tortorelis DG, Choudhury MS, Mallouh C, Tazaki H, Konno S. Mol Urol. 2000;4(1):7-13.
32. Cytotoxic effect of oyster mushroom *Pleurotus ostreatus* on human androgen-independent prostate cancer PC-3 cells. Gu YH, Sivam G. J Med Food. 2006;9(2):196-204.
33. *Coprinus comatus* and *Ganoderma lucidum* interfere with androgen receptor function in LNCaP prostate cancer cells. Zaidman BZ, Wasser SP, Nevo E, Mahajna J. Mol Biol Rep. 2008;35(2):107-17.
34. Inhibitory mechanisms of *Agaricus blazei* Murill on the growth of prostate cancer *in vitro* and *in vivo*. Yu CH, Kan SF, Shu CH, Lu TJ, Sun-Hwang L, Wang *PS*. J Nutr Biochem. 2009;20(10):753-64.
35. Effects of a mushroom mycelium extract on the treatment of prostate cancer. deVere White RW, Hackman RM, Soares SE, Beckett LA, Sun B. Urology. 2002;60(4):640-4.
36. Maitake D-fraction. Apoptosis inducer and immune enhancer. Konno S. Comp and Alt Ther. 2001;Apr:102-107.
37. Effects of *Cordyceps sinensis* on natural killer activity and colony formation of B16 melanoma. Xu RH, Peng XE, Chen GZ, Chen GL. Chin Med J (Engl). 1992;105(2):97-101.
38. Inhibitory effects of ethyl acetate extract of *Cordyceps sinensis* mycelium on various cancer cells in culture and B16 melanoma in C57BL/6 mice. Wu JY, Zhang QX, Leung PH. Phytomedicine. 2007;14(1):43-9.
39. Antimetastatic effect of PSK, a protein-bound polysaccharide, against the B16-BL6 mouse melanoma. Matsunaga K, Ohhara M, Oguchi Y, Iijima H, Kobayashi H. Invasion Metastasis. 1996;16(1):27-38.

40. Selective induction of apoptosis in murine skin carcinoma cells (CH72) by an ethanol extract of *Lentinula edodes*. Gu Y.H, Belury M.A. Cancer Lett. 2005;220(1):21-8.
41. Potential anticancer properties of the water extract of *Inonotusobliquus* by induction of apoptosis in melanoma B16-F10 cells. Youn MJ, Kim JK, Park SY, Kim Y, Park C, Kim ES *et al*. J Ethnopharmacol. 2009;121(2):221-8.
42. Inhibitory effects of lanostane-type triterpene acids, the components of *Poria cocos*, on tumour promotion by 12-O-tetradecanoylphorbol-13-acetate in two-stage carcinogenesis in mouse skin. Kaminaga T, Yasukawa K, Kanno H, Tai T, Nunoura Y, Takido M. Oncology. 1996;53(5):382-5.
43. Triterpene acids from *Poria cocos* and their antitumour-promoting effects. Akihisa T, Nakamura Y, Tokuda H, Uchiyama E, Suzuki T, Kimura Y, Uchikura K, Nishino H. J Nat Prod. 2007;70(6):948-53.
44. Induction of apoptosis in human prostatic cancer cells with beta-glucan (Maitake mushroom polysaccharide). Fullerton SA, Samadi AA, Tortorelis DG, Choudhury MS, Mallouh C, Tazaki H, Konno S. Mol Urol. 2000 Spring;4(1):7-13.
45. Combined effect of green tea and *Ganoderma lucidum* on invasive behavior of breast cancer cells. Thyagarajan A, Zhu J, Sliva D. Int J Oncol. 2007;30(4):963-9.
46. Increased tumour necrosis factor alpha (TNF-alpha) and natural killer cell (NK) function using an integrative approach in late stage cancers. See D, Mason S, Roshan R. Immunol Invest. 2002;31(2):137-53.

Medicinal Mushrooms for other conditions

Allergic Rhinitis (Hayfever)

Ganoderma lucidum shows excellent results in the management of allergic rhinitis, its polysaccharides suppressing the pro-inflammatory, Th2-mediated immune state responsible for the hypersensitivity to the particular allergen(s) while several of its triterpenoid ganoderic and lucidenic acids have direct anti-inflammatory and anti-histamine action[1-6]. It thus addresses both the symptoms and the underlying imbalance of the condition and can be used in either a prophylactic or therapeutic mode.

CLINICAL NOTE

Biomass is often effective in mild cases while triterpene-rich extracts have stronger anti-histamine activity for more severe cases (1-3g/day).

Alzheimer's Disease (AD)

Low levels of nerve growth factor (NGF) are seen in AD with implications for the application of *Hericium erinaceus* in the management of this condition (see discussion on Dementia)[7]. In addition, synaptic degeneration, with loss of synaptic density proteins, has been shown to be a key mode of neurodegeneration in AD with beta-amyloid (Abeta) identified as a cause of synaptic dysfunction and

contributor to AD pathology. *Ganoderma lucidum* aqueous extract, which has traditionally been considered to have anti-ageing properties, has been shown to significantly inhibit Abeta-induced synaptotoxicity and also inhibit Abeta-triggered DEVD cleavage in a dose-dependent manner with potential clinical application in management of AD and *Auricularia polytricha*, another mushroom considered to have anti-ageing properties, has been shown to inhibit the enzyme associated with release of Abeta[8-10].

CLINICAL NOTE

H. erinaceus fruiting body and G. lucidum extract can be combined in the treatment of AD. 3g/day H. erinaceus fruiting body with 1-2g/day G. lucidum extract.

Asthma

Ophiocordyceps sinensis has traditionally been used to treat respiratory disorders including asthma and serum markers of airway inflammation were seen to be reduced in patients with mild asthma given *O. sinensis* capsules[11]. *O. sinensis* also improved lung function in sensitized guinea pigs and reduced airway inflammation in sensitized rats[12]. An *in vitro* study on human airway epithelial cells showed *O. sinensis* and its components to alter ion transport and regulate Th1/Th2 balance[13,14].

Ganoderma lucidum has also traditionally been used to treat asthma and its triterpenoid components are known to have strong anti-inflammatory and anti-histamine activity. Research on a closely related species, *Ganoderma tsugae*, in murine models of allergic asthma shows that triterpenoid extracts reduce bronchoalveolar inflammation and attenuate Th2 responses without overall immunosuppressive effects[15,17].

In addition, mushroom polysaccharide extracts are known to shift immune balance away from Th2 dominance and towards Th1 dominance and have been shown to help correct a skewed Th1/Th2 balance in an animal asthma model, indicating their potential in the management of this condition, as well as other allergic disorders[18].

CLINICAL NOTE

O. sinensis mycelial biomass combines well with triterpene-rich or triterpene/polysaccharide extracts from G. lucidum to treat a wide range of lung disorders. 3g/day O. sinensis mycelial biomass with 1-3g/day G. lucidum extract.

Bacterial Infections

Through their ability to strengthen the host immune response, fungal polysaccharides increase resistance and reduce incidences of post-surgical infection[19]. In addition, mushrooms have evolved a range of defences against other competing microorganisms and several show direct antimicrobial action.

When aqueous extracts of *Lentinula edodes* and *Pleurotus ostreatus* were tested against a panel of 29 bacterial and 10 fungal pathogens, *L. edodes* extract showed extensive antimicrobial activity against 85% of the organisms, including 50% of the yeast and mould species, while aqueous extracts of *P. ostreatus* showed 87.5% inhibition against E. coli and 57.5% against B. subtilis[20]. In a study of over 200 species of mushroom in Spain almost 50% had direct antibiotic activity against a range of test organisms[21].

Extracts of both *Hericium erinaceus* fruiting body and mycelium exhibited anti-MRSA activity with erinacines identified as active compounds. In clinical tests in Japan MRSA was seen to disappear in a number of patients given *H. erinaceus* [22]. Similar cyathane type

compounds from other mushroom species also show antibiotic potential[23], while the traditional use of *H. erinaceus* in the treatment of gastritis (now known to be caused in many cases by the bacteria *H. pylori*) supports its antibacterial action.

In vitro studies using organic *Ganoderma lucidum* extracts also showed anti-MRSA activity while the use of *G. lucidum* hot-water extracts together with conventional antibiotics (ampicillin, ciprofloxacin, streptomycin, kanamycin and cephotaxamine) enhanced antibacterial activity compared with the antibiotic alone[24,25].

CLINICAL NOTE

Traditionally H. erinaceus fruiting body has been used but the fact that mushroom antimicrobial compounds are predominantly secreted into the growth substrate supports clinical use of mycelial biomass. Dosage of fresh fruiting body prescribed in the Chinese Pharmacopoeia is 25-50g/day (equivalent to 2.5-5g dried).

Benign Prostatic Hyperplasia (BPH)

Triterpenoid compounds from *Ganoderma lucidum* have a marked anti-androgenic effect, inhibiting 5alpha-reductase and significantly reducing testosterone-induced growth of the ventral prostate in rats. In a randomized clinical trial 6mg daily dose of an ethanolic extract produced improvements in International Prostate Symptom Score in men over the age of 50[26-32].

An aqueous extract of *Phellinus linteus* has also been reported to inhibit testosterone-induced BPH *in vivo* at a dose of 1.725ml/kg[33].

CLINICAL NOTE

G. lucidum triterpene-rich extract (1-3g/day).

Candidiasis

Mushrooms exhibit both direct and indirect anti-fungal activity *in vitro* and *in vivo* [34].

The widely held belief that mushrooms somehow exacerbate candidal overgrowth runs contrary to scientific research, clinical experience and theoretical understanding. Not only do mushrooms stimulate the body's anti-fungal immune response but in nature they need to compete for resources with other fungi, as well as other microorganisms, and so have evolved a range of powerful anti-fungal defences.

Lentinula edodes extracts and juice show strong anti-fungal action, as do aqueous extracts of *Pleurotus ostreatus*, with 50% inhibition against *C. albicans*[35-39]. In addition, triterpenes from *Ganoderma* species show anti-fungal activity, while mice given a polysaccharide-rich extract of *A. subrufescens* showed enhanced candidacidal activity characterized by higher levels of H2O2 and increased mannose receptor expression by peritoneal macrophages (involved in the attachment and phagocytosis of non-opsonized microorganisms)[40].

It has also been suggested that chitin present in mushroom cell walls may help prevent colonisation of the intestinal mucosa by candida species[41].

Trametes versicolor has traditionally been used in Mexico to treat thrush and clinically is seen to reduce *Candida* overgrowth. PSK has also been shown to have a pronounced protective effect against lethal infection with *C. albicans* in mice. An injection of 250mg/kg 24 hours before inoculation of $1x10^6$ *C. albicans* increased the 30 day survival rate by 60% and mean survival time by 209%[42]. Oral PSK supplementation of tumour-bearing mice challenged with *C. albicans* also resulted in a prolongation of the mean survival period together

with a reduction in fungal counts[43].

CLINICAL NOTE

While polysaccharides are responsible for potentiating the immune response, many anti-fungal compounds produced by mushrooms are excreted into the substrate and captured by mycelial biomass products.

T. versicolor and L. edodes mycelia biomass products show good anti-candida activity (2-3g/day).

Cardiovascular Health

Ganoderma lucidum, Tremella fuciformis and *Auricularia auricula* show particular promise for supporting cardiovascular health, with actions including:

- Antioxidant
- Anti-inflammatory
- Cholesterol-lowering
- Anti-thrombotic

One clinical study reported a polysaccharide extract of *G. lucidum* to reduce chest pain, palpitations and shortness of breath in patients with coronary heart disease (5.4g/day) while triterpenoid ganoderic acids from *Ganoderma tsugae* have demonstrated cardioprotective properties through reduction in oxidative stress and *T. fuciformis* polysaccharides have been shown to help protect the cells lining the blood vessels, damage to which is an important contributory factor in the development of cardiovascular disease[44-48].

Cordyceps species also show significant cardioprotective properties and are approved in China for the treatment of arrythmia, at least partially due to their adenosine content. In addition, cordycepin has

been shown to prevent ischaemia and reperfusion injury in animal models[49-51].

CLINICAL NOTE

Polysaccharide extracts of G. lucidum, T. fuciformis and A. auricula/A. polytricha (1-3g/day) can provide useful cardiovascular support and be used at higher levels or in combination with G. lucidum ethanolic extract or cordycepin-rich cordyceps in more severe cases.

Chronic Fatigue Syndrome (CFS - ME)

CFS patients show immune dysfunction, including low NK cell activity, and the condition has been linked to high viral counts, especially Epstein-barr virus (EBV). Recent research confirms the elevated levels of Th2 cytokines in patients with CFS and prevailing Th2 inflammatory milieu, together with highly attenuated Th1 immune response[52-54].

The proven ability of mushroom nutrition to promote a shift away from a Th2 dominant immune response and increase anti-viral activity makes it a natural source of support for CFS patients with good clinical results, including increased NK cell activity and improved lifestyle scores. *Trametes versicolor* mycelial biomass produced a 35% increase in NK cell activity in patients with mild CFS at a dose of 1.5-3g/day (more severe cases are reported to respond to higher dosages)[55].

CLINICAL NOTE

CFS is a condition that responds well to a range of medicinal mushrooms with polysaccharide extracts giving particularly good results (1-3g/day).

Dementia

Compounds in *Hericium erinaceus* are able to stimulate the production of nerve growth factor (NGF), which promotes repair and regeneration of neurons, and there is growing clinical evidence showing benefit for *H. erinaceus* in cases of mild dementia.

In a double-blind placebo controlled trial, 50-80-year old Japanese men and women with mild cognitive impairment given 3g/day *H. erinaceus* as tablets showed significant increases on a cognitive function scale compared with a placebo group over a 16 week period[56].

In another study 7 patients with different types of dementia were given 5g a day of *H. erinaceus* in soup. After six months all seven demonstrated improvement in their Functional Independence Measure score (eating, dressing, walking, etc.), while six out of seven demonstrated improvements in their perceptual capacities (understanding, communication, memory, etc.)[57].

CLINICAL NOTE

The above clinical trials both used H. erinaceus fruiting body (3-5g/day).

Depression

Many patients taking *Hericium erinaceus* report increased feelings of well-being and reduction in depression was reported in a clinical trial with 30 women given 2g/day[58].

Ganoderma lucidum has traditionally been been considered to have beneficial effects on mental status and anti-depressive effects were noted in a clinical trial of 48 breast cancer patients given 3g/day *G. lucidum* spore powder[59,60].

The ability of mushroom polysaccharides to help rebalance the immune system away from a Th2 dominant immune state suggests that they may also have a role to play in the treatment of depression, where elevations in pro-inflammatory cytokines have been shown to be involved in the development of depression-like behaviour in pre-clinical and clinical populations[61-64].

CLINICAL NOTE

H. erinaceus fruiting body (3-5g/day) or mycelial biomass (2-3g/day). Patients taking G. lucidum spore and spore oil products often also report improvement in mental outlook. 2-5g broken spore powder or 500-1,000mg spore oil.

Diabetes

Fungal beta-glucans, along with beta-glucans from oats and barley, have been shown to help control blood glucose levels and it has been suggested that a possible mechanism is activation of P13K/Akt through binding to receptors including Dectin 1 and Scavenger[65]. However, daily supplementation of a normal diet with 3.5g/day beta-glucan in type II diabetics over 8 weeks failed to produce any change in fasting glucose levels[66].

All the main medicinal mushrooms have been investigated for potential benefits in cases of diabetes with several modes of action proposed[67].

Agaricus subrufescens - Consumption of 1.5g of polysaccharide extract in combination with metformin and gliclazide for 12 weeks reduced insulin resistance in patients with type II diabetes[68].

Auricularia auricula - A water-soluble polysaccharide from *A. auricularia* at 3% of feed reduced fasting glucose levels and improved

glucose tolerance in mice[69].

Ophiocordyceps sinensis - Animal studies at a dose of 250mg/kg showed improved insulin sensitivity and reduced fasting blood glucose. In one clinical trial 3g/day of a proprietary *O. sinensis* preparation improved blood sugar control in 95% of patients compared to 54% of a control group treated by other methods[70-72].

Ganoderma lucidum - Consumption of 5.4g of polysaccharide extract for 8 weeks produced a 13% reduction in blood sugar levels in patients with type II diabetes mellitus who were not taking insulin and also led to significant improvement in peripheral neuropathy in diabetic patients[73,74].

Grifola frondosa - Improved glucose tolerance in diabetic rats at 20% of feed and in a separate experiment at 1g/day. A water soluble extract, X-fraction also increased insulin sensitivity[75-77].

Hericium erinaceus - Blood sugar levels decreased by 19-26% in rats fed *H. erinaceus* extract at 100mg/kg[78].

Pleurotus ostreatus - Reduced plasma glucose levels at 4% of feed and was reported to reduce blood glucose in diabetic patients at an unspecified dosage[79,80].

Tremella fuciformis - 200mg/kg of a polysaccharide extract produced a 52% reduction in plasma glucose levels[81].

Some practitioners report good results with *Coprinus comatus* but published research either relates to vanadium-enriched *C. comatus* or to high supplementation levels[82-87].

CLINICAL NOTE

O. sinensis biomass at a dose of 3-5g/day can be helpful for stabilising blood sugar levels in both insulin dependent and non-insulin dependent diabetes and in reducing diabetes-related depression.

Epilepsy

Armillaria mellea exhibits anti-convulsant activity and it, as well as *Gastrodia elata*, a herb with which it grows symbiotically, has traditionally been used in cases of epilepsy[88,89].

In-vivo and *in vitro* studies also indicate possible benefit of *Ganoderma lucidum* with polysaccharides showing anti-convulsant activity in rats and the spores showing inhibition of epileptiform discharge in hippocampal neurons[90-92].

CLINICAL NOTE

Armillaria mellea tablets used clinically in China (3-5g/day) combine mycelium with culture medium extract and can be combined with G. lucidum shell-broken spore powder (3-5g/day).

Erectile Dysfunction

Ophiocordyceps sinensis has traditionally been used to treat male sexual dysfunction and *in vitro* and *in vivo* studies have shown it to increase the level of male sex hormones[93-95].

Clinical experience with *O. sinensis* mycelial biomass confirms its benefits in this area when taken over an extended period.

CLINICAL NOTE

O. cordyceps mycelial biomass (3g/day).

Exercise-induced Immune Suppression

Mushroom polysaccharide extracts show promise for helping counter

the depression in immune function that accompanies strenuous prolonged exertion and heavy training[96].

Polysaccharides from *Ganoderma lucidum* prevented exercised-induced suppression of haematopoetic parameters in mice and 100mg/day of a purified beta-glucan preparation from *Pleurotus ostreatus* maintained natural killer cell activity and reduced the frequency of upper respiratory tract infections (URTI) in elite athletes[97-99].

CLINICAL NOTE

The ability of mushrooms to help prevent URTI is due to their common immune-modulating action and is not specific to any one species (1-3g/day).

Fluid Retention

Polyporus umbellatus and *Poria cocos* are traditionally used in the treatment of fluid retention with *P. umbellatus* considered stronger. Multiple diuretic components have been isolated from *P. umbellatus* [100,101].

CLINICAL NOTE

Traditional dose of P. umbellatus is 6-15g/day dried herb.

Gastric Ulcers

Hericium erinaceus has traditionally been used in the treatment of gastric ulcers and gastritis and extracts have been shown to be effective clinically and in animal models with reported inhibition rates

of 70-90%[102-106].

CLINICAL NOTE

Animal experiments showed maximum efficacy at a dose of 500mg/kg and the Chinese Pharmacopoeia gives a daily dose of 25-50g for the raw mushroom.

Hepatitis

Several polysaccharide extracts have shown benefit in treatment of hepatitis B virus (HBV). Concentrated polysaccharide extracts from *Polyporus umbellatus* (92% polysaccharide) are used in China to treat patients with chronic HBV (40mg/day) with significant effect on clearing serum hepatitis B surface antigen (HBsAg) and HBV DNA[107,108], while a small study with *Agaricus subrufescens* polysaccharide extract (1500mg/day) in patients with HBV reported reductions in AST from 246 to 61.3 and ALT from 151 to 46.1 over 12 months[109].

A study of a *Ganoderma lucidum* polysaccharide extract (5.4g/day) showed a 41% reduction in AST values in HBV patients with AST values <100 and a 65% reduction in patients with AST values >100[110]. By the end of 6 months 33% of patients had normal AST readings and 13% had cleared hepatitis B surface antigen (HBsAg) from serum whereas none of the controls had normal ALT values or had lost HBsAg. Inhibition of HBV replication as well as hepatoprotective properties have also been demonstrated for ganoderic acid[111].

A number of small Chinese clinical studies report beneficial effects from supplementation with *Ophiocordyceps sinensis* in patients with HBV at a dose of 24 capsules a day[112-115].

CLINICAL NOTE

Beneficial results are also reported for O. sinensis mycelial biomass in cases of hepatitis C (2-3g/day).

Herpes

In patients with recurrent genital herpes supplementation with 3-5g/day PSK resulted in increased immunity and fewer sick days[116]. *In vitro* research showed PSK to inactivate a laboratory-cultured strain of herpes simplex virus (HSV) type 1 (HSV-1-GC+), together with clinically isolated strains of HSV-2, but found clinically isolated strains of HSV-1 to be resistant[117].

An HSV-1 inhibitory protein has also been reported from *Grifola frondosa*[118].

CLINICAL NOTE

T. versicolor, or combinations of mushroom polysaccharide extracts help prevent recurrence of HSV outbreaks by maintaining immune competence.

HIV

The nucleoside derivatives found in *Cordyceps* species, including cordycepin (3'-deoxyadenosine), are reverse transcriptase inhibitors of the type now being used to treat HIV and *in vitro* studies confirm their efficacy in inhibiting HIV replication[119-121]. PSK and PSP from *Trametes versicolor* have also been shown to inhibit both HIV-1 reverse transcriptase and protease, two key enzymes in the life cycle of HIV[122-124], as have triterpenes from *Ganoderma lucidum*, which also

inhibit NF-kappaB expression and viral binding[125,126].

There is *in vitro* evidence that betulinic acid analogues (present in *Inonotus obliquus*) disrupt HIV fusion to the cell membrane in a post-binding step through interaction with the viral glycoprotein gp41 as well as disrupting assembly and budding of the HIV-1 virus[127,128], while proteins from *Flammulina velutipes* have been shown to inhibit HIV-1 reverse transcriptase, beta-glucosidase and beta-glucuronidase.

T. versicolor mycelial biomass supplementation (3g/day) given as part of traditional Chinese medicine treatment for patients with HIV produced improvements in CD4 count and reductions in viral load as well as fading of Kaposi's sarcoma (caused by human herpes virus 8) in AIDS patients[129,130].

CLINICAL NOTE

C. militaris shows particular promise in the treatment of HIV and other viral conditions, especially in combination with mushroom polysaccharide extracts.

HPV

In a trial using *Trametes versicolor* mycelial biomass (3g/day) 9 of 10 women with high risk strains of HPV had cleared them after 1 year, while only 1 of 12 women in a control group had. Also 13 of 18 patients showed normal cervical cytology after 1 year compared to 10 of 21 in the control group[131].

Supplementation with FVe, a protein from *Flammulina velutipes*, significantly enhanced the anti-tumour protection given by vaccination against HPV-16 with the percentage of vaccinated mice remaining tumour free 167 days after challenge with tumour cells increasing from 20% to 60%[132].

CLINICAL NOTE

The immune supporting action of mushroom polysaccharides make them important supplements for assisting recovery from viral infections such as HPV.

Hypercholesterolaemia

Because of their high fibre content, sterol content and low calorific value, mushrooms are an ideal food for diets designed to prevent cardiovascular disease and have been extensively investigated for their potential therapeutic application in this regard.

In animal models a range of mushrooms, including *Agaricus bisporus* (common button mushroom), *Grifola frondosa*, *Lentinula edodes*, *Ganoderma lucidum* and *Flammulina velutipes*, all show increased excretion of cholesterol, decreases in LDL and triglycerides and increase in HDL when included in the diet at 5% of feed[133-137].

Similar effects are seen from dietary inclusion of other beta-glucan sources such as oats and barley and it is considered that the action of beta-glucans on cholesterol levels is mediated by their binding affinity for bile acids, leading to activation of cholesterol 7α-hydroxylase and upregulation of low-density lipoprotein receptor and thus increased transportation of LDL into hepatocytes and conversion of cholesterol into bile acids[138].

In addition, several medicinal mushrooms are natural sources of lovastatin (also called monakolin K or mevinolin) with high levels in a number of *Pleurotus* species as well as *Ganoderma lucidum* and higher levels in the mycelium than the fruiting bodies[139-141]. Levels of Lovastatin show significant variation from one strain to another however, making standardised protocols difficult, and better results

are achieved clinically with another lovastatin-producing fungus, *Monascus purpureus* (*Hong Qu Mi* - Red Yeast Rice), for which standardised strains are available and for which a much greater impact on cholesterol levels has been demonstrated than achieved by the equivalent dosage of pure lovastatin, implying synergistic action between it and other compounds found in *M. purpureus*.

Eritadenine, a compound isolated from *L. edodes* has demonstrated strong cholesterol lowering properties and it has been suggested that it acts through alteration of hepatic phospholipid metabolism by inhibition of S-adenosylhomocy steine hydrolase, increased excretion and decomposition of ingested cholesterol, and reduced secretion of VLDL by the liver[142]. *L. edodes* fed at 10-50g/kg of diet led to significant decreases in both plasma cholesterol concentration and PC:PE ratio of liver microsomes in rats and eritadenine included at 50mg/kg diet had a similar effect[143].

In clinical trials dried *L. edodes* (9g/day) decreased serum cholesterol 7-10% in patients suffering from hypercholesterolemia and 90g/day fresh *L. edodes* (equivalent to 9g/day dried mushroom) led to a decrease in total cholesterol of 9-12% and triglycerides of 6-7%[144].

Saito *et al* reported levels of eritadenine of 400-700mg/kg, although Enman *et al* suggest that the true level may be 10 times greater[145,146]. However, without standardised strains, levels of eritadenine in *L. edodes* are hard to quantify. It has also been shown that stirring rather than shaking during mycelial fermentation can produce a five-fold increase in production of eritadenine, implying significant potential variability in response to cultivation parameters[147].

CLINICAL NOTE

Two strains of M. purpureus are commercially available, one containing

0.4% lovastatin and the other 0.8%, with clinical trials showing 1200mg/day of the the 0.4% strain to be effective at lowering cholesterol in patients not on prescription statins and 1200mg/day of the 0.8% strain (or 2400mg/day of the 0.4% strain) to be an effective substitute for lovastatin at 10mg/day.

Because the eritadenine present in L. edodes works via a different enzymatic pathway from prescription statins or statin-containing fungi, it can usefully be combined with them to enhance their impact on cholesterol control.

Hypertension

Ganoderma lucidum has traditionally been used in the treatment of hypertension[148] and ACE inhibitory activity has been demonstrated for the triterpene Ganoderic acid K[149]. It has also been suggested that the CNS inhibiting action of triterpenes from *G. lucidum* may play a part in its anti-hyertensive action[150].

In the light of recent data, which suggests that subsets of T lymphocytes play critical roles in the development of angiotensin II, deoxycorticosterone salt-sensitive and Dahl salt-sensitive hypertension, and in the progression of vascular remodeling, it is possible that mushrooms may have a beneficial effect on blood pressure by virtue of their immune regulating properties[151]. However, beneficial effects for other mushrooms have only been demonstrated at unrealistic dietary levels of between 5-20%[152-154] or, in the case of *Agaricus subrufescens*, with a GABA-enriched extract[155].

CLINICAL NOTE

Triterpene-rich G. lucidum extracts (1-3g/day).

Infertility

Ophiocordyceps sinensis has a traditional history of use in the treatment of both male and female infertility and *in vitro* studies have shown it to stimulate production of sex hormones through activation of both the protein kinase A and protein kinase C signal transduction pathways[156]. As these pathways are activated by cAMP it is probable that the active component of *O. sinensis* in this regard is one or more of the nucleoside derivatives that it contains. As well as enhancing levels of 17β-estradiol (oestrogen) and thus the quality of maturing oocytes in women, animal studies have shown *O. sinensis* to increase sperm quantity and quality in mouse models and *Cordyceps militaris* to do so in subfertile boars[157-159].

In cases where infertility is associated with elevated cytokine and NK cell levels *Phellinus linteus* mycelial biomass has been shown to be effective in restoring immune balance at a dose of 3g/day[160].

Where infertility is associated with Polycystic Ovary Syndrome (PCOS) resoration of ovulation was seen in 20 of 26 women given *Grifola frondosa* polysaccharide extract, with all 3 women who wanted to become pregnant able to do so[161].

CLINICAL NOTE

Cordyceps mycelial biomass or, in immune-related cases, P. linteus mycelial biomass or, for PCOS-related cases, G. frondosa polysaccharide extract (all 3g/day).

Inflammatory Bowel Disease (IBD)

As sources of soluble and insoluble fibre mushrooms and mushroom polysaccharides have been investigated for their potential in the treatment of inflammatory bowel disease. In one *in vivo* study whole

white button mushroom exhibited a protective effect at 2% of feed while in another beta-glucan from *Pleurotus ostreatus* given at 10% of feed was effective in reducing mucosal damage and myeloperoxidase activity in healthy sections[162,163].

Polysaccharide extracts from other mushrooms, including *Ganoderma lucidum*, *Lentinula edodes* and *Grifola frondosa* also show protective action in animal models of IBD and an *Agaricus subrufescens* based extract has been reported to produce positive changes in cytokine profiles in patients with ulcerative colitis and Crohn's disease at 60ml/day[164-167]. A triterpene extract from *G. lucidum* has also been shown to prevent colitis-associated carcinogenesis in mice[168].

Inonotus obliquus has traditionally been used to treat bowel disorders and an aqueous extract alleviated inflammation in a murine colitis model while an ethanolic extract reduced DNA damage in lymphocytes from patients with IBD[169,170].

CLINICAL NOTE

Many of the conditions such as Crohn's Disease and Ulcerative Colitis that fall within the umbrella of IBD are autoimmune in character and hence offer promising targets for the immune modulating action of mushroom polysaccharides (1-3g/day).

Influenza

Extracts and polysaccharides from different mushrooms, including *Ophiocordyceps sinensis*, *Trametes versicolor*, *Lentinula edodes* and *Grifola frondosa* have been shown to exert an inhibitory effect on influenza virus *in vitro* and *in vivo* through their modulation of immune response[171-174]. Mycelial extracts of edible mushrooms have also been shown to be effective as adjuvants for intranasal influenza

vaccine producing a high influenza virus specific IgA and IgG response in nasal washings and serum respectively[175].

CLINICAL NOTE

Medicinal mushrooms can be used prophylacticlly at the start of the 'flu season' to maintain immune competency, or taken at the onset of symptoms to lessen the duration and severity of colds.

Insomnia/Anxiety

Ganoderma lucidum has traditionally been indicated for the treatment of insomnia[176-178] and aqueous extract from *G. lucidum* fruiting body decreased sleep latency, increased sleeping time, non-REM sleep time and light sleep time in pentobarbital-treated rats in a benzodiazepine-like manner[179].

Clinically *Hericium erinaceus* (3-5g/day) produces consistent improvements in anxiety and insomnia, especially in menopausal and peri-menopausal women and one study reports reduction in anxiety from 2g/day[58].

CLINICAL NOTE

Both G. lucidum and H. erinaceus are helpful in the treatment of anxiety and insomnia and Christopher Hobbs reports preferring G. lucidum to valerian for deficiency type insomnia[180].

Liver Damage

In a study on 14 patients with alcohol-induced liver steatosis, supplementation with *Ophiocordyceps sinensis* mycelial biomass at

3g/day resulted in a 70% reduction in AST, a 63% reduction in ALT and a 64% reduction in GGT over a 90 day period[181]. Animal studies also show that *O. sinensis* can inhibit alcohol-induced hepatic fibrogenesis, retard the development of cirrhosis and improve liver function[182].

Antrodia camphorata has traditionally been used for the side effects from excess alcohol consumption (including hangovers) and animal studies confirm its ability to protect the liver against chronic alcohol consumption in rats at a dose of 0.1mg/kg[183].

Aqueous extracts of both *Lentinula edodes* and *Grifola frondosa* showed significant protection from paracetamol-induced liver damage, as did *Coprinus comatus* polysaccharide extract from the effects of alcohol[184,185].

Ganoderma lucidum extracts also demonstrate significant protective action against a range of hepatotoxins, including CCl4, thioacetamide and BCG[186-191].

CLINICAL NOTE

A. camphorata and G. lucidum are similar in effect and are especially useful where there is active inflammation. Either can also be combined with O. sinensis in more chronic situations.

Meniere's Syndrome

In China *Armillaria mellea* tablets are prescribed for a range of neurological disorders, including Meniere's Syndrome[192-195].

CLINICAL NOTE

A. mellea (3-5g/day).

Multiple Sclerosis (MS)

Together with its ability to promote neuronal repair and regeneration, *in vitro* studies have shown *Hericium erinaceus* to promote nerve myelination, with the process of myelination beginning earlier and proceeding at a higher rate in the presence of *H. erinaceus* extract[196].

CLINICAL NOTE

H. erinaceus has obvious potential for MS. To date no clinical studies have been reported but 5-10g/day of H. erinaceus fruiting body has produced positive results in the author's experience, with noted reductions in MS-associated neuropathic pain.

Nerve Damage

Daily administration of aqueous extract of *Hericium erinaceus* fresh fruiting bodies showed a beneficial effect on the recovery of injured rat peroneal nerve in the early stages of regeneration with faster recovery in the treated group than the untreated group[197].

G. lucidum spores have also shown beneficial activity in a mouse nerve damage model while *Tremella fuciformis* and *Grifola frondosa* polysaccharides and *Cordyceps militaris* ethanolic extract increased neurite outgrowth in PC12 and N2a cells indicating potential to promote nerve repair[198-201].

CLINICAL NOTE

H. erinaceus 3-5g/day dried fruit body can be combined with T. fuciformis or G. frondosa polysaccharides or G. lucidum sporoderm-broken spores.

Parasitic Infection

As well as in bacterial, fungal and viral infections the ability of mushroom polysaccharides to help promote an effective immune response has implications for parasitic infections with Lentinan from *Lentinula edodes* and aqueous and ethanolic extracts from *Ganoderma lucidum* showing protection against malarial infection in murine models[202-204].

In addition aqueous extracts of *Agaricus subrufescens* showed *in vitro* activity against different species of *Leishmania* while a number of compounds produced by *Cordyceps* species showed anti-parasitic activity including cordycepin from *Cordyceps militaris* and pyridones from *Cordyceps nipponica*[205-209].

CLINICAL NOTE

The main role of medicinal mushrooms in parasitic infections is in supporting the immune system and other herbs have stronger direct anti-parasitic activity.

Parkinson's Disease (PD)

Several papers report increased levels of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-alpha, IL-1beta and IL-6, and decreased levels of neurotrophins such as brain-derived neurotrophic factor (BDNF) in patients with sporadic PD, with the possibility that the ability of mushroom polysaccharides to promote a shift in immune response away from a pro-inflammatory Th2 cytokine profile to a Th1 dominant state may be of benefit to patients with early stage PD[210].

The tyrosinase inhibiting activity of mushrooms like *Ganoderma lucidum* and *Flammulina velutipes* may also play a role in controlling the development of PD. Tyrosinase catalyses the oxidation of tyrosine

and dopamine, producing dopaquinone, which besides being the common precursor of the different forms of melanin, is a dopaminergic neuron-specific cytotoxic molecule[211,212]. Dopaquinone can also covalently modify and inactivate tyrosine hydroxylase, the rate limiting enzyme in catecholamine biosynthesis, leading to further reductions in levels of dopamine[213].

In addition tyrosinase contributes to the formation of neuromelanin, which identifies neurons susceptible to Parkinson's disease in cell culture systems and has been implicated in the development of the disease[214].

CLINICAL NOTE

Culinary mushrooms such as F. velutipes are often preferred for long term supplementation in chronic conditions like PD.

Polycystic Ovary Syndrome (PCOS)

As well as helping the insulin resistance often associated with PCOS, *Grifola frondosa* polysaccharide extracts show benefit in the management of PCOS itself, with one study reporting ovulation in 20 of 26 women given a *G. frondosa* polysaccharide extract, including 6 of 8 women who failed to ovulate after other treatments, and positive results in cases of PCOS-related infertility[215].

CLINICAL NOTE

It is possible that other mushrooms with benefits for insulin resistance such as Ganoderma lucidum and Cordyceps species may also be of benefit (3g/day).

Psoriasisya

As with other autoimmune conditions, medicinal mushrooms can be helpful in cases of psoriasis with one study using an extract of *Inonotus obliquus* extract reporting a 76% cure rate, with improvement in a further 16% of cases[216].

CLINICAL NOTE

Extracted products delivering high levels of both polysaccharides and triterpenes are preferred. Clinically extracts of Ganoderma lucidum, another mushroom containing high levels of polysaccharides and triterpenes, also show benefit (2-3g/day).

Renal Health

Cordyceps has traditionally been used to strengthen the kidneys. In one study of 51 patients with chronic renal failure, 3-5g/day *O. sinensis* significantly improved kidney function and in another 4.5g/day speeded recovery from gentamycin-induced kidney damage with 89% of those taking *O. sinensis* having recovered normal kidney function after 6 days compared to 45% of a control group[11].

Antroquinonol, a ubiquinone derivative from the mycelium of *A. camphorata* has been shown to reduce protein and blood in the urine, renal dysfunction and changes in the kidney glomerular basement membrane (a histological hallmark of SLE) at a dose of 400mg/kg in a mouse model of SLE, suggesting ability to protect the kidney from autoimmune disease[217,218].

CLINICAL NOTE

O. sinensis mycelial biomass (2-3g/day).

Rheumatoid Arthritis (RA)

A polysaccharide extract from the fruiting body of *Phellinus linteus* reduced expression of pro-inflammatory cytokines and increased expression of anti-inflammtory cytokines, resulting in subsidence of the autoimmune response in the joints of mice[219]. Fungal polysaccharides have also been shown to reduce inflammation and have a positive modulating effect on plasma cytokine levels in experimentally induced arthritis in rats, while triterpenes from *Ganoderma lucidum* exhibit strong anti-inflammatory action[220-222].

CLINICAL NOTE

While mushroom polysaccharides, such as those from P. linteus, are excellent for promoting a shift away from the Th2 cytokine profile characteristic of RA, the stronger anti-inflammatory properties of triterpene-rich G. lucidum extracts are better during more active phases.

Skin Repair

In a controlled human study daily consumption of 320mg *S. crispa* fruiting body by healthy volunteers over a period of 28 days dramatically reduced transepidermal water loss in the treatment group with no change in the control group, indicating enhanced skin integrity, and *in vivo* studies show increased collagen production and enhanced wound healing from *S. crispa* supplementation[223-225].

CLINICAL NOTE

Although 320mg/day was shown to enhance skin integrity, higher doses may be necessary with in vivo studies showing enhanced collagen synthesis at 70mg/kg b.w.

Stroke

Sparassis crispa given to stroke-prone spontaneously hypertensive rats as 1.5% of their feed delayed incidence of stroke and death with significantly decreased blood pressure and amelioration of cerebrovascular endothelial dysfunction[226].

CLINICAL NOTE

S. crispa fruiting body (2-5g/day).

REFERENCES

1. Anti-allergic constituents in the culture medium of *Ganoderma lucidum*. (I). Inhibitory effect of oleic acid on histamine release. Tasaka K, Akagi M, Miyoshi K, Mio M, Makino T. Inflammation Research. 1988;23(3-4):153-6.
2. Anti-allergic constituents in the culture medium of *Ganoderma lucidum*. (II). The inhibitory effect of cyclooctasulfur on histamine release. Tasaka K, Mio M, Izushi K, Akagi M, Makino T. Inflammation Research. 1988;23(3-4):157-60.
3. Effectiveness of Dp2 nasal therapy for Dp2-induced airway inflammation in mice: using oral *Ganoderma lucidum* as an immunomodulator. Liu YH, Tsai CF, Kao MC, Lai YL, Tsai JJ. J Microbiol Immunol Infect. 2003;36(4):236-428.
4. The use of *Ganoderma lucidum* (Reishi) in the management of Histamine-mediated allergic responses. Powell M. Nutritional Practitioner Magazine. October 2004.
5. Effect of *Ganoderma lucidum* on pollen-induced biphasic nasal blockage in a guinea pig model of allergic rhinitis. Mizutani N, Nabe T, Shimazu M, Yoshino S, Kohno S. Phytother Res. 2012 Mar;26(3):325-32.
6. Suppression of Inflammatory and Allergic Responses by Pharmacologically Potent Fungus *Ganoderma lucidum*. Bhardwaj N, Batra P, Sharma AK. Recent Pat Inflamm Allergy Drug Discov. 2014 Jun 19.
7. Effects of *Hericium erinaceus* on amyloid β(25-35) peptide-induced learning and memory deficits in mice. Mori K, Obara Y, Moriya T, Inatomi S, Nakahata N. Biomed Res. 2011 Feb;32(1):67-72.
8. *Auricularia polytricha* in processed and unprocessed form exhibited inhibitory activity against APP-cleaving enzyme (BACE1), which is responsible for releasing toxic β-amyloid peptide in the brain. Bennett L, Sheean P, Zabaras D, Head R. Int J Med Mushrooms. 2013;15(3):233-49.
9. Heat-Stable Components of Wood Ear Mushroom, *Auricularia polytricha* (Higher Basidiomycetes), Inhibit *In Vitro* Activity of Beta Secretase (BACE1). Bennett L, Sheean P, Zabaras D, Head R. Int J Med Mushr.

2013;15(3):233-249.

10. Antagonizing beta-amyloid peptide neurotoxicity of the anti-aging fungus *Ganoderma lucidum*. Lai CS, Yu MS, Yuen WH, So KF, Zee SY, Chang RC. Brain Res. 2008;1190:215-24.
11. Medicinal value of the caterpillar fungi species of the genus Cordyceps. Holliday J, Cleaver M. Int J Med Mushr. 2008; 10(3):219-234.
12. Effect of dongchong xiacao capsule on airway inflammation of asthmatic patients. Wang NQ, Jiang LD, Zhang XM, Li ZX. Zhongguo Zhong Yao Za Zhi. 2007;32(15):1566-8.
13. Effects of fermented Cordyceps powder on pulmonary function in sensitized guinea pigs and airway inflammation in sensitized rats. Lin XX, Xie QM, Shen WH, Chen Y. Zhongguo Zhong Yao Za Zhi. 2001;26(9):622-5.
14. Effects of *Cordyceps sinensis*, *Cordyceps militaris* and their isolated compounds on ion transport in Calu-3 human airway epithelial cells. Yue GG, Lau CB, Fung K, Leung P, Ko W. Journal of Ethnopharmacology. 2008;117(1):92-1014.
15. Regulation of bronchoalveolar lavage fluids cell function by the immunomodulatory agents from *Cordyceps sinensis*. Kuo YC, Tsai WJ, Wang JY, Chang SC, Lin CY, Shiao MS. Life Sci. 2001;68(9):1067-82.
16. *Ganoderma tsugae* supplementation alleviates bronchoalveolar inflammation in an airway sensitization and challenge mouse model. Lin JY, Chen ML, Chiang BL, Lin BF. Int Immunopharmacol. 2006;6(2):241-51.
17. Effects of triterpenoid-rich extracts of *Ganoderma tsugae* on airway hyperreactivity and Th2 responses *in vivo*. Chen ML, Lin BF. Int Arch Allergy Immunol. 2007;143(1):21-30.
18. Amelioration of skewed Th1/Th2 balance in tumour-bearing and asthma-induced mice by oral administration of *Agaricusblazei* extracts. Takimoto H, Kato H, Kaneko M, Kumazawa Y. Immunopharmacol Immunotoxicol. 2008;30(4):747-60.
19. Potential of the beta-glucans to enhance innate resistance to biological agents. Thompson IJ, Oyston PC, Williamson DE. Expert Rev Anti Infect Ther. 2010;8(3):339-52.
20. An examination of antibacterial and antifungal properties of constituents of Shiitake (*Lentinula edodes*) and oyster *(Pleurotus ostreatus*) mushrooms.

Hearst R, Nelson D, McCollum G, Millar BC, Maeda Y, Goldsmith CE, Rooney PJ, Loughrey A, Rao JR, Moore JE. Complement Ther Clin Pract. 2009;15(1):5-7.

21. Screening of Basidiomycetes for antimicrobial activities. Suay I, Arenal F. Antonie van Leeuwenhoek 2000;78:129-139.
22. Anti-MRSA compounds of *Hericium erinaceus*. Kawagishi H *et al*. Int J Med Mushr. 2005;7(3):350
23. Two cyathane-type diterpenoids from the liquid culture of *Strobilurus tenacellus*. Shiono Y, Hiramatsu F, Murayama T, Koseki T, Funakoshi T. Chem Biodivers. 2008;5(9):1811-6.24.
24. Antibacterial activity of the bio-multidrug (*Ganodermalucidum*) on Multidrug resistant Staphylococcus aureus (MRSA). Y Prasad, WEG Wesely - Advanced Biotech, 2008.
25. Naturally Occurring Medicinal Mushroom-Derived Antimicrobials: A Case-Study Using Lingzhi or Reishi *Ganoderma lucidum* (W. Curt.:Fr.) P. Karst. (Higher Basidiomycetes). Alka S. Karwa, Mahendra K. Rai. Int J Med Mushr. 2012;14(5):481-490.
26. Anti-androgenic activities of *Ganoderma lucidum*. Fujita R, Liu J, Shimizu K, Konishi F, Noda K, Kumamoto S, Ueda C, Tajiri H, Kaneko S, Suimi Y, Kondo R. J Ethnopharmacol. 2005; 102(1):107-12.
27. The anti-androgen effect of ganoderol B isolated from the fruiting body of *Ganoderma lucidum*. Liu J, Shimizu K, Konishi F, Kumamoto S, Kondo R. Bioorg Med Chem. 2007; 15(14):4966-72.
29. 5alpha-reductase inhibitory effect of triterpenoids isolated from *Ganoderma lucidum*. Liu J, Kurashiki K, Shimizu K, Kondo R. Biol Pharm Bull. 2006;29(2):392-5.
30. *Ganoderma lucidum* is an inhibitor of testosterone-induced prostatic hyperplasia in rats. Nahata A, Dixit VK. Andrologia. 2012 May;44 Suppl 1:160-74.
31. Effect of an extract of *Ganoderma lucidum* in men with lower urinary tract symptoms: a double-blind, placebo-controlled randomized and dose-ranging study. Noguchi M *et al*. Asian J Androl. 2008 Jul;10(4):651-8. Epub 2007 Dec 20.
32. Randomized clinical trial of an ethanol extract of *Ganoderma lucidum* in

men with lower urinary tractsymptoms. Noguchi M *et al*. Asian J Androl. 2008 Sep;10(5):777-85.

33. Effect of *Phellius linteus* water extract on benign prostatic hyperplasia. Kim YN, Kim MS, Chun SS, Choi JH. Nutr Res Pract. 2013 Jun;7(3):172-7.
34. Antifungal secondary metabolites from fungal fruiting bodies. Dunek C, Volk TJ. Int J Med Mushr. 2007;9(3):227-228.
35. An examination of antibacterial and antifungal properties of constituents of Shiitake (*Lentinula edodes*) and oyster *(Pleurotus ostreatus*) mushrooms. Hearst R, Nelson D, McCollum G, Millar BC, Maeda Y, Goldsmith CE, Rooney PJ, Loughrey A, Rao JR, Moore JE. Complement Ther Clin Pract. 2009;15(1):5-7.
36. Antimicrobial properties of shiitake mushrooms (*Lentinulaedodes*). Rao JR, Smyth TJ, Millar BC, Moore JE. Int J Antimicrob Agents. 2009;33(6):591-2.
37. Antagonistic effect of edible mushroom extract on *Candiaalbicans* growth. Paccola E, Maki CS, Nobrega GMA, Paccola-Meirelles L.D. Braz J Microbiol. 2001;32:3.
38. Antimicrobial and antineoplasic activity of *Pleurotus ostreatus*. Wolff ER, Wisbeck E, Silveira ML, Gern RM, Pinho MS, Furlan SA. Appl Biochem Biotechnol. 2008;151(2-3):402-12.
39. Antimicrobial action of *Lentinus edodes* juice on human microflora. Kuznetsov OI, Mil'kova EV, Sosnina AE, Sotnikova NI. Zh Mikrobiol Epidemiol Immunobiol. 2005; 1:80-2.
40. Polysaccharide-rich fraction of *Agaricus brasiliensis* enhances the candidacidal activity of murine macrophages. Martins P.R, Gameiro M.C, Castoldi L, Romagnoli GG, Lopes FC, Pinto AV, Loyola W, Kaneno R. Mem Inst Oswaldo Cruz. 2008;103(3):244-50.
41. Fungal Chitin in medicine: prospects for its application. Ludmila IB, Leontij FG. Int J Med Mushr. 2001;3(2-3)126-127.
42. Protective effects of a protein-bound polysaccharide, PSK, on Candida albicans infection in mice via tumour necrosis factor-alpha induction. Ohmura Y, Matsunaga K, Motokawa I, Sakurai K, Ando T. Int Immunopharmacol. 2001;1:1797-1811.
43. Protective effects of a protein-bound polysaccharide, PSK, against *Candida albicans* infection in syngeneic tumour-bearing mice via Th1 cell functions.

Ohmura Y, Matsunaga K, Motokawa I, Sakurai K, Ando T. Cancer Biother Radiopharm. 2003;18(5):769-80.

44. A phase I/II study of ling zhi mushroom *Ganoderma lucidum*(W.Curt.:Fr.) Lloyd (Aphyllophoromycetideae) extract in patients with coronary heart disease. Gao Y, Chen G, Dai X, Ye J, Zhou S. Int J Med Mushrooms 2004;6(4):30.
45. Research advances in primary biological effects of Tremella polysaccharides. Chen FF, Cai DL. Zhong Xi Yi Jie He Xue Bao. 2008;6(8):862-6.
46. Chemical characterization of *Auricularia auricula* polysaccharides and its pharmacological effect on heart antioxidant enzyme activities and left ventricular function in aged mice. Wu Q *et al*. Int J Biol Macromol. 2010 Apr 1;46(3):284-8.
47. *Auricularia auricular* polysaccharide protects myocardium against ischemia/reperfusion injury. Ye TM, Qian LB, Cui J, Wang HP, Ye ZG, Xia Q. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2010 May;26(2):154-8.
48. The triterpenoids of *Ganoderma tsugae* prevent stress-induced myocardial injury in mice. Kuok QY, Yeh CY, Su BC, Hsu PL, Ni H, Liu MY, Mo FE. Mol Nutr Food Res. 2013 Oct;57(10): 1892-6.
49. Medicinal value of the caterpillar fungi species of the genus Cordyceps. Holliday J, Cleaver M. Int J Med Mushr. 2008; 10(3):219-234.
50. Cardiovascular protection and antioxidant activity of the extracts from the mycelia of *Cordyceps sinensis* act partially via adenosine receptors. Yan XF *et al*. Phytother Res. 2013 Nov;27(11):1597-604.
51. Cordycepin, 3'-deoxyadenosine, prevents rat hearts from ischemia/reperfusion injury via activation of Akt/GSK-3β/p70S6K signaling pathway and HO-1 expression. Park ES *et al*. Cardiovasc Toxicol. 2014 Mar;14(1):1-9.
52. A formal analysis of cytokine networks in Chronic Fatigue Syndrome. Broderick G, Fuite J, Kreitz A, Vernon SD, Klimas N, Fletcher MA. Brain Behav Immun. 2010;24(7):1209-17.
53. Plasma cytokines in women with chronic fatigue syndrome. Fletcher MA, Zeng XR, Barnes Z, Levis S, Klimas NG. J Transl Med. 2009;7:96.
54. High levels of type 2 cytokine-producing cells in chronic fatigue syndrome.

Skowera A, Cleare A, Blair D, Bevis L, Wessely SC, Peakman M. Clin Exp Immunol. 2004;135(2): 294-302.

55. Pioneering work at Breakspear Hospital on Coriolus Supplementation for CFIDS/ME patients. Mycology News. 2000;1(4):4.
56. Improving effects of the mushroom Yamabushitake (Hericium erinaceus) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. Mori K, Inatomi S, Ouchi K, Azumi Y, Tuchida T. Phytother Res. 2009;23(3):367-72.
57. The anti-Dementia effect of Lion's mane mushroom and its clinical application. Kawagishi H, Zhuang C, Shnidman E. Townsend Letter for Doctors and Patients. April, 2004.
58. Reduction of depression and anxiety by 4 weeks *Hericiumerinaceus* intake. Nagano M, Shimizu K, Kondo R, Hayashi C, Sato D, Kitagawa K, Ohnuki K. Biomed Res. 2010 Aug; 31(4): 231-7.
59. Antidepressant-like effects of a water-soluble extract from the culture medium of *Ganoderma lucidum* mycelia in rats. Matsuzaki H *et al*. BMC Complement Altern Med. 2013 Dec 26;13:370.
60. Spore Powder of *Ganoderma lucidum* Improves Cancer-Related Fatigue in Breast Cancer Patients Undergoing Endocrine Therapy: A Pilot Clinical Trial. Zhao H, Zhang Q, Zhao L, Huang X, Wang J, Kang X. Evid Based Complement Alternat Med. Epub 2011 Dec 10.
61. From inflammation to sickness and depression: when the immune system subjugates the brain. Dantzer R., O'Connor J. C., Freund G. G., Johnson R. W., Kelley K. W. Nat. Rev. Neurosci. 2008;9:46–56.
62. Evidence for a cytokine model of cognitive function. McAfoose J., Baune B. T. Neurosci. Biobehav. Rev. 2009;33:355–366.
63. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Miller A. H., Maletic V., Raison C. L. Biol. Psychiatry, 2009;65:732–741.
64. Neuroplastic changes in depression: a role for the immune system. Eyre H, Baune BT. Psychoneuroendocrinology. 2012 Sep;37(9):1397-416.
65. Beta-glucans in the treatment of diabetes and associated cardiovascular risks. Chen J, Raymond K. Vasc Health Risk Manag. 2008;4(6):1265-72.
66. A controlled study of consumption of beta-glucan-enriched soups for 2

months by type 2 diabetic free-living subjects. Cugnet-Anceau C, Nazare J.A, Biorklund M, Le Coquil E, Sassolas A, Sothier M, Holm J, Landin-Olsson M, Onning G, Laville M, Moulin P. Br J Nutr. 2010;103(3):422-8.

67. Medicinal Mushrooms for Glycemic Control in Diabetes Mellitus: History, Current Status, Future Perspectives, and Unsolved Problems (Review). Lo HC, Wasser SP. Int J Med Mushr. 2011;13(5):401-426.
68. The mushroom *Agaricus Blazei* Murill in combination with metformin and gliclazide improves insulin resistance in type 2 diabetes: a randomized, double-blinded, and placebo-controlled clinical trial. Hsu CH, Liao YL, Lin SC, Hwang KC, Chou P. J Altern Complement Med. 2007;13(1):97-102.
69. Hypoglycemic effect of water-soluble polysaccharide from *Auricularia auricula*-judae Quel. on genetically diabetic KK-Ay mice. Yuan Z, He P, Cui J, Takeuchi H. Biosci Biotechnol Biochem. 1998;62(10):1898-903.
70. Clinical observations of adjunctive treatment of 20 diabetic patients with JinShuiBao capsule. Guo QC, Zhang C, Lo HC, Tu ST, Lin KC, Lin SC. J Admin Trad Chin Med. 1995; 5:223.
71. The anti-hyperglycemic activity of the fruiting body of Cordyceps in diabetic rats induced by nicotinamide and streptozotocin. Lo HC, Tu ST, Lin KC, Lin SC. Life Sci. 2004;74(23):2897-908.
72. CordyMax Cs-4 improves glucose metabolism and increases insulin sensitivity in normal rats. Zhao CS, Yin WT, Wang JY, Zhang Y, Yu H, Cooper R, Smidt C, Zhu JS. J Altern Complement Med. 2002;8(3):309-14.
73. A phase I/II study of Ling Zhi mushroom *Ganoderma lucidum* (W.Curt.:Fr.) Lloyd (Aphyllophoromycetideae) extract in patients with type II Diabetes mellitus. Gao Y, Lan J, Dai X, Ye J, Zhou S. Int J Med Mushr. 2004;6(1).
74. A randomized, double-blind and placebo-controlled study of a *Ganoderma lucidum* polysaccharide extract in neurasthenia. Tang W, Gao Y, Chen G, Gao H, Dai X, Ye J, Chan E, Huang M, Zhou S. J Med Food. 2005;8(1):53-8.
75. Anti-diabetic activity present in the fruit body of *Grifola frondosa* (Maitake). Kubo K, Aoki H, Nanba H. I. Biol Pharm Bull. 1994;17(8):1106-10.
76. Maitake (*Grifola frondosa*) improve glucose tolerance of experimental diabetic rats. Horio H, Ohtsuru M. J Nutr Sci Vitaminol (Tokyo). 2001;47(1):57-63.

77. Antihypertensive and metabolic effects of whole Maitake mushroom powder and its fractions in two rat strains. Talpur NA, Echard BW, Fan AY, Jaffari O, Bagchi D, Preuss HG. Mol Cell Biochem. 2002;237(1-2):129-36.

78. Hypoglycemic effect of extract of *Hericium erinaceus*. Wang JC, Hu SH, Wang JT, Chen KS, Chia YC. Journal of the Science of Food and Agriculture. 2005;85(4):641-646.

79. Effect of the oyster fungus on glycaemia and cholesterolaemia in rats with insulin-dependent diabetes. Chorváthová V, Bobek P, Ginter E, Klvanová J. Physiol Res. 1993;42(3):175-9.

80. Oyster mushroom reduced blood glucose and cholesterol in diabetic subjects. Khatun K, Mahtab H, Khanam PA, Sayeed MA, Khan KA. Mymensingh Med J. 2007;16(1):94-9.

81. Hypoglycemic effects of exopolysaccharides produced by mycelial cultures of two different mushrooms *Tremella fuciformis* and *Phellinus baumii* in ob/ob mice. Cho EJ, Hwang HJ, Kim SW, Oh JY, Baek YM, Choi JW, Bae SH, Yun JW. Appl Microbiol Biotechnol. 2007;75(6):1257-65.

82. Effect of *Coprinus comatus* on plasma Glucose concentrations in mice. Bailey CJ, Turner SL, Jakeman KJ, Hayes WA. Planta Med. 1984;50(6):525-526.

83. Vanadium uptake by biomass of *Coprinus comatus* and their effect on hyperglycemic mice. Han C, Cui B, Wang Y. Biol Trace Elem Res. 2008;124(1):35-9.

84. Comparison of vanadium-rich activity of three species fungi of basidiomycetes. Han C, Cui B, Qu J. Biol Trace Elem Res. 2009;127(3):278-83.

85. Comparison of hypoglycemic activity of trace elements absorbed in fermented mushroom of *Coprinus comatus*. Lv Y, Han L, Yuan C, Guo J. Biol Trace Elem Res. 2009;131(2):177-85.

86. Hypoglycemic activity of fermented mushroom of *Coprinus comatus* rich in vanadium. Han C, Yuan J, Wang Y, Li L. J Trace Elem Med Biol. 2006;20(3):191-6.

87. Determination of trace elements in three mushroom samples of Basidiomycetes from Shandong, China. Wang C, Hou Y. Biol Trace Elem Res. 2010 Jul 28.

88. Tian ma, an ancient Chinese herb, offers new options for the treatment of epilepsy and other conditions. Ojemann L.M, Nelson W.L, Shin D.S, Rowe A.O, Buchanan R.A. Epilepsy & Behavior. 2006;8(2):376-383.

89. The cultivation, bioactive components and pharmacological effects of *Armillaria mellea*. Gao L.W, Li W.Y, Zhao Y.L and Wang J.W. Afr J Biotech. 2009;8(25):7383-7390.

90. Intervention effects of *Ganoderma lucidum* spores on epileptiform discharge hippocampal neurons and expression of neurotrophin-4 and N-cadherin. Wang SQ *et al*. PLoS One. epub 2013 Apr 24;8(4):e61687.

91. Anticonvulsant and neuroprotective effects of oligosaccharides from Lingzhi or Reishi medicinal mushroom, *Ganoderma lucidum* (Higher Basidiomycetes). Tello I *et al*. Int J Med Mushrooms. 2013;15(6):555-68.

92. Anti-Epileptic Effect of *Ganoderma Lucidum* Polysaccharides by Inhibition of Intracellular Calcium Accumulation and Stimulation of Expression of CaMKII α in Epileptic Hippocampal Neurons. Wang SQ *et al* . PLoS One. 2014 Jul 10;9(7):e102161.

93. Regulatory mechanism of *Cordyceps sinensis* mycellium on mouse Leydig cell steroidogenesis. Hsu CC, Tsai SJ, Huang YL, Huang BM. FEBS Lett. 2003;543(1-3):140-3.

94. The *in vivo* effect of *Cordyceps sinensis* mycelium on plasma corticosterone level in male mouse. Leu SF, Chien CH, Tseng CY, Kuo YM, Huang B.M. Biol Pharm Bull. 2005;28(9):1722-5.

95. Regulation of steroidogenesis by *Cordyceps sinensis* mycelium extracted fractions with (hCG) treatment in mouse Leydig cells. Wong KL, So EC, Chen CC, Wu RS, Huang BM. Arch Androl. 2007;53(2):75-7.

96. Exercise and the immune response. Keast D, Cameron K, Morton AR. Sports Med. 1988 Apr;5(4):248-67.

97. Immunomodulatory effect of *Ganoderma lucidum* polysaccharides (GLP) on long-term heavy-load exercising mice. Shi Y, Cai D, Wang X, Liu X. Int J Vitam Nutr Res. 2012 Dec;82(6):383-90.

98. Effect of Pleuran (β-glucan from *Pleurotus ostreatus*) supplementation on cellular immune response after intensive exercise in elite athletes. Bobovĉák M, Kuniaková R, Gabriž J, Majtán J. Appl Physiol Nutr Metab. 2010 Dec;35(6):755-62.

99. Pleuran (β-glucan from *Pleurotus ostreatus*) supplementation, cellular immune response and respiratory tract infections in athletes. Bergendiova K, Tibenska E, Majtan J. Eur J Appl Physiol. 2011 Sep;111(9):2033-40.

00. An anti-aldosteronic diuretic component (drain dampness) in *Polyporus sclerotium*. Yuan D, *et al*. Biol Pharm Bull. 2004; 27(6):867-70.

01. Bioactivity-directed isolation, identification of diuretic compounds from *Polyporus umbellatus*. Zhao YY, Xie RM, Chao X, Zhang Y, Lin RC, Sun WJ. J Ethnopharmacol. 2009;126(1):184-7.

02. Gastroprotective effects of Lion's Mane mushroom *Hericium erinaceus* (Bull.:Fr.) Pers. (Aphyllophoromycetideae) extract against ethanol-induced ulcer in rats. JY Wong *et al*. Evid Based Complement Alternat Med. Epub 2013 Nov 5.

03. *In Vitro* Anti-Helicobacter pylori Effects of Medicinal Mushroom Extracts, with Special Emphasis on the Lion's Mane Mushroom, *Hericium erinaceus* (Higher Basidiomycetes). Shang X, Tan Q, Liu R, Yu K, Li P, Zhao GP. Int J Med Mushr. 2013;15(2):165-174.

04. A double-blind study of effectiveness of *Hericium erinaceus* pers therapy on chronic atrophic gastritis. A preliminary report. Xu CP, Liu WW, Liu FX, Chen SS, Liao FQ, Xu Z, Jiang LG, Wang CA, Lu XH. Chin Med J (Engl). 1985;98(6):455-6.

05. Cytoprotective effects of *Hericium erinaceus* on gastric mucosa in rats. Yu CG, Xu ZM, Zhu QK *et al*. Chinese J Gastrent. 1999-02.

06. Effect of culinary-medicinal Lion's Mane mushroom, *Hericiumerinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae), on Ethanol-induced gastric ulcers in rats. Abdulla MA, Noor S, Sabaratnam V, Abdullah N, Wong KH, Ali HM. Int J Med Mush. 2008;10(4):325-330.

07. Clinical and experimental research on *Polyporus umbellatus* polysaccharide in the treatment of chronic viral hepatitis. Yan SC, Zhong Xi Yi Jie He Za Zhi. 1988;8(3):141-3

08. Chinese medicinal herbs for chronic hepatitis B: a systematic review. Liver. Liu J, McIntosh H, Lin H. 2001;21(4):280-6.

09. The mushroom *Agaricus blazei* Murill extract normalizes liver function in patients with chronic hepatitis B. Hsu CH, Hwang KC, Chiang YH, Chou P. J Altern Complement Med. 2008; 14(3):299-301.

10. A phase I/II study of a *Ganoderma lucidum* (Curt.: Fr.) P. Karst. (Ling Zhi, Reishi Mushroom) extract in patients with chronic Hepatitis B. Gao Y, Zhou S, Chen G, Dai X, Ye J, Gao H. Int J Med Mush. 2002.
11. Anti-hepatitis B activities of ganoderic acid from *Ganodermalucidum*. Li YQ, Wang SF. Biotechnol Lett. 2006;28(11): 837-41.
12. Short-term curative effect of cultured *Cordyceps sinensis* (Berk.) Sacc. Mycelia in chronic hepatitis B. Zhou L, Yang W, Xu Y, Zhu Q, Ma Z, Zhu T, Ge X, Gao J. Zhongguo Zhong Yao Za Zhi. 1990;15(1):53-5.
13. Effects of Cordyceps polysaccharides in patients with chronic hepatitis C. Ma X, Qiu DK, J Xu, Zeng MD. Huaren Xiaohua Zazhi 1998;6:582-584 6.
14. Effects of *Cordyceps sinensis* on T lymphocyte subsets and hepato-fibrosis in patients with chronic hepatitis B. Gong HY, Wang KQ, Tang SG. Hunan Yi Ke Da Xue Xue Bao. 2000;25(3):248-50.
15. Clinical research of xinganbao capsule on the treatment of chronic hepatitis B liver fibrosis. Wang XB, Jiang YY, Zhao CY. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2012Mar;32(3):325-8.
16. Treatment of recurrent genital herpes with PSK. Kawana T. Proceedings of the International Symposium on Pharmacological and Clinical Approaches to Herpes Viruses and Virus Chemo-therapy. Oiso, Japan, Sept. 10-13, 1984.
17. *In vitro* inactivation of herpes simplex virus by a biological response modifier, PSK. Monma Y, Kawana T, Shimizu F. Antiviral Res. 1997;35(3):131-8.
18. Isolation, identification and function of a novel anti-HSV-1 protein from *Grifola frondosa*. Gu CQ, Li JW, Chao F, Jin M, Wang XW, Shen ZQ. Antiviral Res. 2007;75(3):250-7.
19. Emerging antiviral drugs from medicinal mushrooms. Pirano FF. Int J Med Mushr. 2006;8(2):20.
20. Phosphorothioate and cordycepin analogues of 2', 5'-oligoadenylate: Inhibition of human immunodeficiency virus type 1 reverse transcriptase and infection *in vitro*. Robinson W *et al*. Proc Natl Acad Sci USA. 1989;86:7191-7194.
21. Synthesis, characterization, and biological activity of monomeric and trimeric cordycepin-cholesterol conjugates and inhibition of HIV-1 replication. Wasner M, Henderson EE, Suhadolnik RJ, Pfleiderer W.

Helvetica Chimica Acta. 1994;77:1757-1761.

22. Polysaccharopeptide from the Turkey tail fungus *Trametes versicolor* (L.:Fr.) Pilát inhibits human immunodeficiency virus type 1 reverse Transciptase and Protease. Ng TB, Wang HX, Wan DCC. Int J Med Mushr. 2006;8(1):40.
23. Polysaccharopeptide from *Coriolus versicolor* has potential for use against human immunodeficiency virus type 1 infection. Collins RA, Ng TB. Life Sci. 1997;60(25):383-7.
24. A biological response modifier, PSK, inhibits reverse transcriptase *in vitro*. Hirose K, Hakozaki M, Kakuchi J, Matsunaga K, Yoshikumi C, Takahashi M, Tochikura TS, Yamamoto N. Biochem Biophys Res Commun. 1987;149(2): 562-7.
25. Anti-HIV-1 and anti-HIV-1-protease substances from *Ganoderma lucidum*. el-Mekkawy S, Meselhy MR, Nakamura N, Tezuka Y, Hattori M, Kakiuchi N, Shimotohno K, Kawahata T, Otake T. Phytochemistry. 1998;49(6):1651-7.
26. Triterpenes from the spores of *Ganoderma lucidum* and their inhibitory activity against HIV-1 protease. Min BS, Nakamura N, Miyashiro H, Bae KW, Hattori M. Chem Pharm Bull (Tokyo). 1998;46(10):1607-12.
27. Chemistry, biological activity, and chemotherapeutic potential of betulinic acid for the prevention and treatment of cancer and HIV infection. Cichewicz RH, Kouzi SA. Med Res Rev. 2004;24(1):90-114.
28. Betulinic acid derivatives as human immunodeficiency virus type 2 (HIV-2) inhibitors. Dang Z, Lai W, Qian K, Ho P, Lee KH, Chen CH, Huang L. J Med Chem. 2009; 52(23):7887-91.
29. The effectiveness of *Coriolus versicolor* supplementation in the treatment of Kaposi sarcoma in HIV+Patients. Tindall J, Clegg E. Presented at the 10th International Congress of Mucosal Immunology in Amsterdam, June 28th - July 1st, 1999.
30. The clinical use of *Coriolus versicolor* supplementation in HIV+ patients and the impact on CD4 count and viral load. Pfeiffer M. Presented at the III International Symposium on Mushroom Nutrition in Milan on Saturday, March 10th, 2001.
31. *Coriolus versicolor* supplementation in HPV patients. Silva-Couto J, Pereira da Silva D. 20th European Congress of Obstetrics and Gynaecology. March

7th, 2008.

32. Coadministration of the fungal immunomodulatory protein FIP-Fve and a tumour-associated antigen enhanced antitumour immunity. Ding Y, Seow SV, Huang CH, Liew LM, Lim YC, Kuo IC, Chua KY. Immunology. 2009;128(1Suppl):e881-94.
33. White button mushroom (*Agaricus bisporus*) lowers blood glucose and cholesterol levels in diabetic and hypercholesterolemic rats. Jeong SC, Jeong YT, Yang BK, Islam R, Koyyalamudi SR, Pang G, Cho KY, Song CH. Nutr Res. 2010;30(1):49-56.
34. Cholesterol-lowering effects of maitake (*Grifola frondosa*) fiber, shiitake (*Lentinus edodes*) fiber, and enokitake (*Flammulinavelutipes*) fiber in rats. Fukushima M, Ohashi T, Fujiwara Y, Sonoyama K, Nakano M. Exp Biol Med (Maywood). 2001; 226(8):758-65.
35. Maitake extracts and their therapeutic potential - A Review. Mayell M. Alt Med Rev, 2001;6:1.
36. Cholesterol-lowering properties of *Ganoderma lucidum invitro, ex-vivo*, and in hamsters and minipigs. Berger A, Rein D, Kratky E, Monnard I, Piguet-Welsch C, Hauser J, Mace K, Niederberger P. Lipids in Health and Disease 2004;3:2.
37. Dose and time dependent hypercholesterolemic effect of oyster mushroom (*Pleurotus ostreatus*) in rats. Nutrition. 1998;14: 282-286.
38. Effect of high beta-glucan barley on serum cholesterol concentrations and visceral fat area in Japanese men - A randomised, double-blinded, placebo controlled trial. Shimizu C, Kihara M, Aoe S *et al*. Plant Foods Hum Nutr. 2008;63:21-5.
39. Pleurotus fruiting bodies contain the inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase - lovastatin. Gunde-Cimerman N, Cimerman A. Exp Mycol. 1995;19(1):1-6.
40. Comparative study of contents of several bioactive components in fruiting bodies and mycelia of culinary-medicinal mushrooms. Lo YC, Lin SY, Ulziijargal E, Chen SY, Chien RC, Tzou YJ, Mau JL. Int J Med Mushrooms. 2012;14(4):357-63.
41. Comparative study of contents of several bioactive components in fruiting bodies and mycelia of culinary-medicinal mushrooms. Lin SY, Chen YK, Yu HT, Barseghyan GS, Asatiani MD, Wasser SP, Mau JL. Int J Med

Mushrooms. 2013;15(3):315-23.

42. Hypocholesterolemic action of eritadenine is mediated by a modification of hepatic phospholipid metabolism in rats. Sugiyama K, Akachi T, Yamakawa A. J Nutr. 1995;125(8):2134-44.
43. Eritadenine-induced alterations of plasma lipoprotein lipid concentrations and phosphatidylcholine molecular species profile in rats fed cholesterol-free and cholesterol-enriched diets. Shimada Y, Morita T, Sugiyama K. Biosci Biotechnol Biochem. 2003 May;67(5):996-1006.
44. Shiitake (*Lentinus edodes*) Wasser SP. Encyclopedia of Dietary Supplements. 2005.
45. Quantitative analysis of eritadenine in 'Shiitake' mushroom and other edible fungi. Saito M, Yamashita T, Kaneda T. Eiyo to Shokuryo. Pub Informa Healthcare. 1975;28:503-505.
46. Quantification of the bioactive compound eritadenine in selected strains of shiitake mushroom (*Lentinus edodes*). Enman J, Rova U, Berglund KA. J Agric Food Chem. 2007; 55(4):1177-80.
47. Production of the bioactive compound eritadenine by submerged cultivation of shiitake (*Lentinus edodes*) mycelia. Enman J, Hodge D, Berglund K.A, Rova U.J. Agric Food Chem. 2008;56(8):2609-12.
48. Dietary effect of *Ganoderma lucidum* mushroom on blood pressure and lipid levels in spontaneously hypertensive rats (SHR). Kabir Y, Kimura S, Tamura T. J Nutr Sci Vitaminol (Tokyo). 1988;34(4):433-8.
49. Effect of *Ganoderma lucidum* on the quality and functionality of Korean traditional rice wine, yakju. Kim JH, Lee DH, Lee SH, Choi SY, Lee JS. J Biosci Bioeng. 2004;97(1):24-8.
50. Cardiovascular effects of mycelium extract of *Ganodermalucidum*: inhibition of sympathetic outflow as a mechanism of its hypotensive action. Lee SY, Rhee HM. Chem Pharm Bull (Tokyo). 1990;38(5):1359-64.
51. T lymphocytes: a role in hypertension? Schiffrin EL. Curr Opin Nephrol Hypertens. 2010;19(2):181-6.
52. Effect of shiitake (*Lentinus edodes*) and maitake (*Grifolafrondosa*) mushrooms on blood pressure and plasma lipids of spontaneously hypertensive rats. Kabir Y, Yamaguchi M, Kimura S. J Nutr Sci Vitaminol (Tokyo). 1987;33(5):341-6.

53. Antihypertensive and metabolic effects of whole Maitake mushroom powder and its fractions in two rat strains. Talpur NA, Echard BW, Fan AY, Jaffari O, Bagchi D, Preuss HG. Mol Cell Biochem. 2002;237(1-2):129-36.

54. Dietary mushrooms reduce blood pressure in spontaneously hypertensive rats (SHR). Kabir Y, Kimura S. J Nutr Sci Vitaminol (Tokyo). 1989;35(1):91-4.

55. Antihypertensive effect of γ-aminobutyric acid-enriched *Agaricus blazei* on mild hypertensive human subjects. Watanabe T, Kawashita A, Ishi S, Mazumder TK, Nagai S, Tsuji K, Dan T. Nippon Shokuhin Kagaku Kogaku Kaishi. 2003;50(4):167-173.

56. *Cordyceps sinensis* mycelium activates PKA and PKC signal pathways to stimulate steroidogenesis in MA-10 mouse Leydig tumour cells. Chen YC, Huang YL, Huang BM. Int J Biochem Cell Biol. 2005;37(1):214-23.

57. Upregulation of steroidogenic enzymes and ovarian 17beta-estradiol in human granulosa-lutein cells by *Cordyceps sinensis* mycelium. Huang BM, Hsiao KY, Chuang PC, Wu MH, Pan HA, Tsai SJ. Biol Reprod. 2004;70(5):1358-64.

58. *In vivo* stimulatory effect of Cordyceps sinensis mycelium and its fractions on reproductive functions in male mouse. Huang YL, Leu SF, Liu BC, Sheu CC, Huang BM. Life Sci. 2004;75(9):1051.

59. Improvement of sperm production in subfertile boars by *Cordyceps militaris* supplement. Lin WH, Tsai MT, Chen YS, Hou RC, Hung HF, Li CH, Wang HK, Lai MN, Jeng KC. Am J Chin Med. 2007;35(4):631-41

60. Immune Related Infertility. Wing T. TCM Kongress Rothenburg, 2012.

61. Maitake mushroom (*Grifola frondosa*) extract induces ovulation in patients with polycystic ovary syndrome: a possible monotherapy and a combination therapy after failure with first-line clomiphene citrate. Chen JT, Tominaga K, Sato Y, Anzai H, Matsuoka R. J Altern Complement Med. 2010 Dec;16(12): 1295-9.

62. The effects of whole mushrooms during inflammation. Yu S, Weaver V, Martin K, Cantorna MT. BMC Immunol. 2009;10:12.

63. Effects of pleuran (beta-glucan isolated from *Pleurotus ostreatus*) on experimental colitis in rats. Nosál'ová V, Bobek P, Cerná S, Galbavý S, Stvrtina S. Physiol Res. 2001;50(6):575-81.

64. *Grifola frondosa* water extract alleviates intestinal inflammation by suppressing TNF-alpha production and its signaling. Lee JS *et al*. Exp Mol Med. 2010 Feb 28;42(2):143-54.

65. The water-soluble extract from cultured medium of *Ganoderma lucidum* (Reishi) mycelia (Designated as MAK) ameliorates murine colitis induced by trinitrobenzene sulphonic acid. Hanaoka R, Ueno Y, Tanaka S, Nagai K, Onitake T, Yoshioka K, Chayama K. Scand J Immunol. 2011 Nov;74(5):454-62.

66. Intestinal anti-inflammatory activity of lentinan: influence on IL-8 and TNFR1 expression in intestinal epithelial cells. Nishitani Y, Zhang L, Yoshida M, Azuma T, Kanazawa K, Hashimoto T, Mizuno M. PLoS One. 2013 Apr 22;8(4):e62441.

67. Effect of an extract based on the medicinal mushroom *Agaricusblazei* Murill on expression of cytokines and calprotectin in patients with ulcerative colitis and Crohn's disease. Førland DT, Johnson E, Saetre L, Lyberg T, Lygren I, Hetland G. Scand J Immunol. 2011 Jan;73(1):66-75.

68. Mushroom *Ganoderma lucidum* prevents colitis-associated carcinogenesis in mice. Sliva D *et al*. PLoS One. Epub 2012 Oct 30.

69. Orally administered aqueous extract of *Inonotus obliquus* ameliorates acute inflammation in dextran sulfate sodium (DSS)-induced colitis in mice. Mishra SK, Kang JH, Kim DK, Oh SH, Kim MK. J Ethnopharmacol. 2012 Sep 28;143(2):524-32.

70. Chaga mushroom extract inhibits oxidative DNA damage in lymphocytes of patients with inflammatory bowel disease. Najafzadeh M, Reynolds .D, Baumgartner A, Jerwood D, Anderson D. Biofactors. 2007;31(3-4):191-200.

71. *In vivo* anti-influenza virus activity of an immunomodulatory acidic polysaccharide isolated from *Cordyceps militaris* grown on germinated soybeans. Ohta Y, Lee JB, Hayashi K, Fujita A, Park DK, Hayashi T. J Agric Food Chem. 2007;55(25):10194-9.

72. Inhibitory effect of TNF-alpha produced by macrophages stimulated with *Grifola frondosa* extract (ME) on the growth of influenza A/Aichi/2/68 virus in MDCK cells. Obi N, Hayashi K, Miyahara T, Shimada Y, Terasawa K, Watanabe M, Takeyama M, Obi R, Ochiai H. Am J Chin Med. 2008;36(6): 1171-83.

73. Antiviral and interferon-inducing activities of a new peptidomannan, KS-2,

extracted from culture mycelia of *Lentinus edodes*. Suzuki F, Suzuki C, Shimomura E, Maeda H, Fujii T, Ishida N. J Antibiot (Tokyo). 1979;32(12):1336-45.

74. Depression of early protection against influenza virus infection by cyclophosphamide and its restoration by protein-bound polysaccharide. Kitasato TS. Arch Exp Med. 1992;65(2-3):97-110.
75. Induction of cross-protective immunity against influenza A virus H5N1 by an intranasal vaccine with extracts of mushroom mycelia. Ichinohe T *et al*. J Med Virol. 2010;82(1):128-37.
76. Sleep-promoting effects of Ganoderma extracts in rats: comparison between long-term and acute administrations. Honda K, Komoda Y, Inoué S. Tokyo Ika Shika Daigaku Iyo Kizai Kenkyusho Hokoku. 1988;22:77-82.
77. The hypnotic and sedative actions of the spores of *Ganodermalucidum* (Curt.: Fr.) P. Karst. (Aphyllophoromycetideae) in mice. Yu L, Wei H. Int J Med Mushr. 2000;2(4):323-328.
78. *Ganoderma lucidum* : a potent pharmacological macrofungus. Sanodiya BS, Thakur GS, Baghel RK, Prasad GB, Bisen *PS*. Curr Pharm Biotechnol. 2009;10(8):717-42.
79. Extract of *Ganoderma lucidum* potentiates pentobarbital-induced sleep via a GABAergic mechanis. Chu QP, Wang LE, Cui XY, Fu HZ, Lin ZB, Lin SQ, Zhang YH. Pharmacology Biochemistry and Behavior. 2007;86(4):693-698.
80. Hobbs C. Medicinal Mushrooms: An Exploration of Tradition, Healing and Culture. 1986 Botanica Press, Williams
81. Cordyceps sinensis supplementation in alcohol-induced liver steatosis. Santos C. Mycology News, 2004;1(9)
82. Inhibitive effect of *Cordyceps sinensis* on experimental hepatic fibrosis and its possible mechanism. Liu YK, Shen W. World J Gastroenterol. 2003;9(3):529-33.
83. Fruiting body of Niuchangchih (*Antrodia camphorata*) protects livers against chronic alcohol consumption damage. Huang CH, Chang YY, Liu CW, Kang WY, Lin YL, Chang HC, Chen YC. J Agric Food Chem. 2010;58(6):3859-66.
84. Hepatoprotective effects of mushrooms. Soares AA, de Sá-Nakanishi AB, Bracht A, da Costa SM, Koehnlein EA, de Souza CG, Peralta RM.

Molecules. 2013 Jul 1;18(7):7609-30.

85. Consumption of *Coprinus comatus* polysaccharide extract causes recovery of alcoholic liver damage in rats. Ozalp FO, Canbek M, Yamac M, Kanbak G, Van Griensven LJ, Uyanoglu M *et al*. Pharm Biol. 2014 Aug;52(8):994-1002.

86. Immunopharmacologic agents in the amelioration of hepatic injuries. Farghali H, Masek K. Int J Immunopharmacol. 1998;20(4-5):125-39.

87. Beta-glucuronidase-inhibitory activity and hepatoprotective effect of *Ganoderma lucidum*. Kim DH, Shim SB, Kim NJ, Jang IS. Biol Pharm Bull. 1999;22(2):162-4.

88. Evaluation of the hepatic and renal-protective effects of *Ganoderma lucidum* in mice. Shieh YH, Liu CF, Huang YK, Yang JY, Wu IL, Lin CH, Li SC. Am J Chin Med. 2001;29(3-4):501-7.

89. Hepatoprotective role of *Ganoderma lucidum* polysaccharide against BCG-induced immune liver injury in mice. Zhang GL, Wang YH, Ni W, Teng HL, Lin ZB. World J Gastroenterol. 2002;8(4):728-33.

90. Protection against D-galactosamine-induced acute liver injury by oral administration of extracts from *Lentinus edodes* mycelia. Biol Pharm Bull. 2006;29(8):1651-4.

91. Post-treatment of *Ganoderma lucidum* reduced liver fibrosis induced by thioacetamide in mice. Wu YW, Fang HL, Lin WC. Phytother Res. 2010;24(4):494-9.

92. Pharmacological actions of gastrodia watery preparation and fermentation liquid of *Armellaria mellea* on nervous system. Chinese Journal of Medicine. 1977;(8):470-472.

93. To use Armellaria fungus tablet to replace gastrodia tuber in treating 45 cases with syndrome of deficiency of yin and flourishing yang. Chinese Journal of Medicine. 1977;(8):473-474.

94. Observation on curative effects of *Armellaria mellea* fungus tablet in treating 100 cases of neurasthenia and hypertension, *etc.* Zhou LS. Journal of New Medicine. 1978;(10):13.

95. Jiangsu Provincial Cooperation Research Group on Gastrodia Tuber, Curative effects of gastrodia tuber Armellaria fungus tablet in treating some diseases of the nervous system, Jiangsu Journal of TCM. 1980;(1):35-37.

96. The influence of *Hericium erinaceus* extract on myelination process *in vitro*. Kolotushkina EV, Moldavan MG, Voronin KY, Skibo GG. Fiziol Zh. 2003;49(1):38-45.

97. Functional recovery enhancement following injury to rodent peroneal nerve by Lion's Mane mushroom, *Hericium erinaceus* (Bull.: Fr.) Pers. (Aphyllophoromycetideae). Wong KH, Naidu M, David RP, Abdulla MA, Abdullah N, Kuppusamy UR, Sabaratnam V. Int J Med Mushr. 2009;11(3):20.

98. Primary study on proteomics about *Ganoderma lucidium* spores promoting survival and axon regeneration of injured spinal motor neurons in rats. Zhang W, Zeng YS, Wang Y, Liu W, Cheng JJ, Chen SJ. Zhong Xi Yi Jie He Xue Bao. 2006;4(3):298-302.

99. Neuronal health - can culinary and medicinal mushrooms help? Sabaratnam V, Kah-Hui W, Naidu M, Rosie David P. J Tradit Complement Med. 2013 Jan;3(1):62-8.

100. Neurite outgrowth stimulatory effects of culinary-medicinal mushrooms and their toxicity assessment using differentiating Neuro-2a and embryonic fibroblast BALB/3T3. Phan CW, David P, Naidu M, Wong KH, Sabaratnam V. BMC Complement Altern Med. 2013 Oct 11;13:261.

101. Therapeutic potential of culinary-medicinal mushrooms for the management of neurodegenerative diseases: diversity, metabolite, and mechanism. Phan CW, David P, Naidu M, Wong KH, Sabaratnam V. Crit Rev Biotechnol. 2014 Mar 24

102. The shiitake mushroom-derived immuno-stimulant lentinan protects against murine malaria blood-stage infection by evoking adaptive immune-responses. Zhou LD, Zhang QH, Zhang Y, Liu J, Cao YM. Int Immunopharmacol. 2009 Apr;9(4):455-62.

103. Modulation of Lipoprotein Cholesterol Levels in Plasmodium berghei Malarial Infection by Crude Aqueous Extract of *Ganoderma lucidum*. Oluba OM, Olusola AO, Eidangbe GO, Babatola LJ, Onyeneke EC. Cholesterol. Epub 2012 Jul 25.

104. Antimalarial and hepatoprotective effects of crude ethanolic extract of Lingzhi or Reishi medicinal mushroom, *Ganoderma lucidum* (W.Curt.:Fr.)P.Karst. (higher Basidiomycetes), in Plasmodium berghei-infected mice. Oluba OM, Olusola AO, Fagbohunka BS, Onyeneke E. Int J

Med Mushrooms. 2012;14(5):459-66.

105. Leishmanicidal activity of the *Agaricus blazei* Murill in different Leishmania species. Valadares DG *et al*. Parasitol Int. 2011 Dec;60(4):357-63.

106. Prophylactic or therapeutic administration of *Agaricus blazei* Murill is effective in treatment of murine visceral leishmaniasis. Valadares DG *et al*. Exp Parasitol. 2012 Oct;132(2):228-36.

107. Therapeutic efficacy induced by the oral administration of *Agaricus blazei* Murill against Leishmania amazonensis. Valadares DG *et al*. Parasitol Res. 2012 Oct;111(4):1807-16.

108. The effects of cordycepin on malaria parasites. Trigg PI, Gutteridge WE, Williamson J. Trans R Soc Trop Med Hyg. 1971;65(4):514-20.

109. Structures of cordypyridones A-D, antimalarial N-hydroxy- and N-methoxy-2-pyridones from the insect pathogenic fungus *Cordyceps nipponica*. Isaka M, Tantichareon M, Thebtaranonth Y. J Org Chem 2001;66:4803–08.

110. Inflammatory process in Parkinson's disease: role for cytokines. Nagatsu T, Sawada M. Curr Pharm Des. 2005;11(8):999-1016.

111. Dopamine-or L-DOPA-induced neurotoxicity: the role of dopamine quinone formation and tyrosinase in a model of Parkinson's disease. Asanuma M, Miyazaki I, Ogawa N. Neurotox Res. 2003;5(3):165-76.

112. Parkin protects against tyrosinase-mediated dopamine neurotoxicity by suppressing stress-activated protein kinase pathways. Hasegawa T, Treis A, Patenge N, Fiesel FC, Springer W, Kahle PJ. J Neurochem. 2008;105(5):1700-15.

113. Dopamine, in the presence of tyrosinase, covalently modifies and inactivates tyrosine hydroxylase. Xu Y : Stokes A.H : Roskoski, R: Vrana, K.E. J-Neurosci-Res. 1998;54(5):691-7.

114. Tyrosinase exacerbates dopamine toxicity but is not genetically associated with Parkinson's disease. Greggio E *et al.* J Neurochem. 2005;93(1):246-56.

115. Maitake Mushroom (*Grifola frondosa*) Extract Induces Ovulation in Patients with Polycystic Ovary Syndrome: A Possible Monotherapy and a Combination Therapy After Failure with First-Line Clomiphene Citrate. Chen J *et al*. J Alt Comp Med, 2010;16(12):1295-1299.

116. Treatment of Psoriasis with Using Chaga Mushroom Preparations. Dosychev EA, Bystrova VN. 1973. Vestn Dermatol Venerol. May;47(5):79-83.

17. An extract of *Antrodia camphorata* mycelia attenuates the progression of nephritis in systemic lupus Erythematosus-Prone NZB/W F1 mice. Chang JM, Lee YR, Hung LM, Liu SY, Kuo MT, Wen WC, Chen P. Evid Based Complement Alternat Med. 2008 Sep.

18. Review of biological and pharmacological activities of the endemic Taiwanese bitter medicinal mushroom, *Antrodia camphorata* (M. Zang et C. H. Su) Sh. H. Wu *et al.* (higher Basidiomycetes). Yue PY, Wong YY, Chan TY, Law CK, Tsoi YK, Leung KS. Int J Med Mushr. 2012;14(3):241-56.

19. Oral administration of proteoglycan isolated from *Phellinuslinteus* in the prevention and treatment of collagen-induced arthritis in mice. Kim GY *et al*. Biol Pharm Bull. 2003;26(6):823-31.

20. Study of new ways of supplementary and combinatory therapy of rheumatoid arthritis with immunomodulators. Glucomannan and Imunoglukán in adjuvant arthritis. Bauerová K, Paulovicová E, Mihalová D, Svík K, Ponist S. Toxicol Ind Health. 2009;25(4-5):329-35.

21. Anti-inflammatory and antitumour-promoting effects of triterpene acids and sterols from the fungus *Ganodermalucidum*. Akihisa T, Nakamura Y, Tagata M, Tokuda H, Yasukawa K, Uchiyama E, Suzuki T, Kimura Y. Chem Biodivers. 2007;4(2):224-3.

22. Suppression of the inflammatory response by triterpenes isolated from the mushroom *Ganoderma lucidum*. Dudhgaonkar S, Thyagarajan A, Sliva D. Int Immunopharmacol. 2009;9(11):1272-80.

23. Effects of medicinal mushroom (*Sparassis crispa*) on wound healing in streptozotocin-induced diabetic rats. Kwon AH, Qiu Z, Hashimoto M, Yamamoto K, Kimura T. Am J Surg. 2009 Apr;197(4):503-9.

24. Orally and topically administered *Sparassis crispa* (Hanabiratake) improved healing of skin wounds in mice with streptozotocin-induced diabetes. Yamamoto K, Kimura T. Biosci Biotechnol Biochem. 2013;77(6):1303-5.

25. *Sparassis crispa* (Hanabiratake) ameliorates skin conditions in rats and humans. Kimura T, Hashimoto M, Yamada M, Nishikawa Y. Biosci Biotechnol Biochem. 2013;77(9):1961-3.

26. Beneficial effect of *Sparassis crispa* on stroke through activation of Akt/eNOS pathway in brain of SHRSP. Yoshitomi H, Iwaoka E, Kubo M, Shibata M, Gao M. J Nat Med. 2011 Jan;65(1):135-41.

Appendix:
Medicinal Mushrooms according to Traditional Chinese Medicine

Glossary

Index

Additional Resources

APPENDIX

Medicinal Mushrooms according to Traditional Chinese Medicine

An overview of medicinal mushroom's TCM energetics is presented here in order to facilitate their use by traditionally trained practitioners.

In compiling this list I have used several sources (see list at end). Wherever possible I have used multiple sources but for *Sang Huang* and *Hou Tou Gu* I have relied exclusively on the Chinese Pharmacopoeia, 2010.

Some mushrooms are included in the main body of the text but not listed here and for these I have been unable to find reliable energetic descriptions.

Bai Mu Er/Yin Er (*Tremella fuciformis*)

Taste - Sweet and bland

Energy - Neutral

Channels Entered - Lung, Stomach (and Kidney - Hsu) Actions - Nourishes Lung-and Stomach -Yin and treats cough due to Lung Deficiency

The actions listed above are according to contemporary materia medica. Ying et. al. add that it ‘Stimulates the Heart and Nourishes the Brain, Enriches the Kidneys and Strengthens Semen’, actions which find some resonance in modern research, especially its ability to benefit cardiovascular health and neurological function.

Dong Chong Xia Cao (*Ophiocordyceps sinensis*)

Taste - Sweet

Energy - Slightly Warm

Channels Entered - Lung and Kidney

Actions - Tonifies Kidney-Yang and Lung-Yin. Augments the Essence. Transforms Phlegm and Stops Cough

Fu Ling (*Poria cocos*)

Taste - Sweet and bland

Energy - Neutral

Channels Entered - Heart, Spleen, Kidney Actions - Promotes urination and drains Damp. Strengthens the Spleen. Calms the Shen

Fu Ling Pi, the outer skin of the sclerotium, is considered the most Damp draining and *Fu Shen*, the innermost portion, the most calming, while *Chi Fu Ling* (the reddish portion just inside the skin) is considered to clear Heat and drain Damp.

Hou Tou Gu (*Hericium erinaceus*)

Taste - Sweet and bland

Energy - Neutral

Channels Entered - Spleen, Stomach, Heart Actions - Strengthens the Stomach and Regulates Qi, tonifies the Spleen and promotes digestion, calms the Shen and strengthens the Brain

Ling Zhi (*Ganoderma lucidum*)

Taste - Sweet and slightly bitter

Energy - Neutral (slightly Warm - Yeung) Channels Entered - Heart, Liver, Lung

Actions - Tonifies Qi and Nourishes Blood. Calms the Shen. Transforms Phlegm and Stops Cough

Long considered analagous to the mythological herb *Chi* referred to in a number of Taoist works as a plant that brings happiness and immortality, *Ling Zhi* equates to the red variety (also called Dan 'cinnabar'), which according to Hobbs is classified in the *Shen Nong Ben Cao* as having a bitter taste and acting on the Heart. This is contrary to modern materia medica, which ascribe a sweet taste to *Ling Zhi* but I am inclined to side with the earlier description, a bitter taste being apparent in good quality *Ling Zhi*.

Mi Huan Jun (*Armillaria mellea*)

Taste - Sweet

Energy - Neutral

Channels Entered - Liver

Actions - Calms the liver to extinguish internal wind and restrain floating yang

Mu Er (*Auricularia auricula/Auricularia polytricha*)

Taste - Sweet

Energy - Neutral

Channels Entered - Spleen, Liver

Actions - Enriches energy and blood, invigorates blood circulation, nourishes lungs, stops haemorrhage, invigorates bowel movement

As with *Ling Zhi*, *Mu Er* was originally sub-divided according to colour with different properties ascribed to each colour. However, today it is the black colour that is the standard type and the qualities given above are accordingly those of *Hei Mu Er* (Black Wood Ear).

Sang Huang (*Phellinus linteus*)

Taste - Slightly bitter

Energy - Cold

Channels Entered - Liver, Stomach, Large Intestine
Actions - Clears Damp-Heat and Stomach Fire, resolves Phlegm, invigorates Blood, stops Bleeding and relieves Pain

Xiang Gu (*Lentinula edodes*)

Taste - Sweet

Energy - Neutral

Channels Entered - Stomach, Spleen, Lungs Actions - Tonifies Qi and Blood

Yun Zhi (*Trametes versicolor*)

Taste - Sweet and slightly bitter

Energy - Slightly warm

Channels Entered - Lung, Liver, Spleen

Actions - Dispels Damp, reduces Phlegm, nourishes the Mind

Zhu Ling (*Polyporus umbellatus*)

Taste - Slightly sweet

Energy - Slightly cool

Channels Entered - Spleen, Kidney, Bladder
Actions - Promotes urination and leaches out Damp

The description in *Li Shi Zhen* that it 'Disperses invading vicious factors and facilitates urination. Long term use makes one feel happy and vigorous and look younger' indicates that the modern usage of this mushroom is narrower than earlier.

REFERENCES

Chinese Herbal Materia Medica. Bensky D, Clavey S, Stoger E. 2004. Seattle:Eastland Press Chinese Medical Herbology and Pharmacology. Chen JK, Chen TT. 2004. City of Industry:Art of Medicine Press Chinese Pharmacopoeia, 2010. Beijing:Chinese Medicine Science and Technology Publishing House Compendium of Materia Medica (Ben Cao Gang Mu). Li Shi Zhen. Tran. Luo Xiwen. 2003. Beijing:Foreign Languages Press Handbook of Chinese Herbs. Yeung HC. 1996. Rosemead: Institute of Chinese Medicine Icones of Medicinal Fungi from China. Ying J *et al.* 1987. Beijing: Science Press Medicinal mushrooms - An Exploration of Tradition, Healing and Culture. Hobbs C. 1986. Williams:Botanica Press Medicinal Mushrooms in TCM. Maciocia G. Mycology News. 1999;1(2):1-2 Oriental Materia Medica - A Concise Guide. Hsu HY. 1986. New Canaan:Keats Publishing Inc.

Glossary

Activator protein-1	Protein involved in the control of a number of cellular processes, including differentiation, proliferation and apoptosis.
Adjuvant	Pharmacological or immunological agent that modifies the action of other drugs or vaccines.
Akt	Akt (also called Akt1) is a protein kinase involved in cellular survival pathways by inhibiting apoptotic processes.
ALP	Alkaline phospatase - raised levels of this enzyme may be indicative of liver damage.
ALT	Alanine transferase - raised levels of this enzyme may be indicative of liver damage.
Angiogenesis	Process of blood vessel formation important in growth and development, wound-healing and tumour spread.
AP-1	See Activator protein-1.
Apoptosis	Process of programmed cell death that plays an important role in controlling cancers and viral infections.
AST	Aspartate aminotransferase - raised levels of this enzyme may be indicative of liver damage.
B-cells	Type of white blood cell that plays a major role in humoral (antibody-mediated) immunity.
	Microbial enzyme involved in the breakdown of

Beta-glucosidase	Microbial enzyme involved in the breakdown of beta-linked polysaccharides.
Beta-glucuronidase	Enzyme involved in the breakdown of complex carbohydrates.
CCl4	Carbon tetrachloride.
Cell-signalling pathways	Chains of molecular interactions, initiated by activation of receptors on the cell surface and controlling cell processes such as gene regulation, cell proliferation and apoptosis.
Cheilitis	A medical condition involving inflammation of the lip.
Cholinergic	Related to the neutransmitter acetylcholine (the brainstem and parasympathetic nervous system are cholinergic, as are some parts of the sympathetic nervous system).
Colony-stimulating factor	Stimulates proliferation and differentiation of white blood cells.
Complement C3	Immune system protein that contributes to innate immunty.
Cytokine	Chemical messenger.
Dendritic cells	Immune cells whose main function is to process antigen material and present it to other immune cells.
DEVD	Amino acid sequence cleaved during cell death by apoptosis.
Eosinophil	Class of white blood cells involved in asthma and allergy control mechanisms.
GABA (γ-	Chief inhibitory neurotransmitter in the

Aminobutyric acid)	mammalian central nervous system.
Genoprotective	Helps protect DNA from damage.
Genotoxic	Capable of damaging DNA.
GGT	Gamma-glutamyltransferase - raised levels of this enzyme may be indicative of liver damage.
Glutathione peroxidase	The general name of an enzyme family whose main biological role is to protect the organism from oxidative damage.
GTP	Guanosine triphosphate - a nucleotide with an important role in signal transduction.
Gut dysbiosis	Microbial imbalance in the intestines.
HbeAg	Hepatitis B protein that is an indicator of active viral replication.
Hepatodynia	Pain in the liver.
IFN-γ	Interferon-gamma - Cytokine secreted by Th1 cells, NK cells and dendritic cells and critical for immunity against viral and bacterial infections and against cancer.
Immunomodulatory	Having an effect on the immune system.
Innate immune system	The part of the immune system that defends us against cancer and infection in a non-specific manner.
Kappa opiod receptor	Opiod receptor widely distributed in the brain, binding to which has dysphoric (mood lowering) and hallucinogenic effects.
Lectins	Sugar-binding proteins or glycoproteins with important physiological roles, including in the

	important physiological roles, including in the immune system.
Lentinan	Beta-glucan extracted from Lentinus edodes and licensed as an anti-cancer agent in Japan.
Leukopenia	Decreased number of white blood cells.
Lymphokine activated killer cell	White blood cell that has been stimulated to kill cancer cells.
Macrophages	White blood cells within tissues that phagocytose pathogens and stimulate other immune cells.
MAPK/ERK pathway	Chain of proteins that communicates a signal from a receptor on the cell surface to the DNA with effects including changes in cell division. In many cancers it is a defect in this pathway that leads to uncontrolled cell division.
Mitomycin C	Chemotherapeutic agent.
Monocyte	White blood cells that differentiate into either macrophages or dendritic cells.
Mycelium	Network of hyphae forming the vegetative part of the mushroom.
Natural killer cell	Type of white blood cells important in destroying cancer cells and virally infected cells.
Neutrophils	Phagocytic cells that are the most abundant type of white blood cell.
NF-kappaB	Protein complex that controls transcription of DNA.
NK cell	See Natural killer cell.
Nuclease	An enzyme able to cleave the bonds between nucleotides within DNA/RNA chains.

	nucleotide units in a DNA/RNA chain.
Nucleoside	Molecule which becomes a nucleotide on addition of a phosphate group
Nucleotide	Building block of nucleic acids (DNA/RNA).
Opsonin	A molecule that acts as a binding enhancer to facilitate phagocytosis.
P13K	Phosphatidylinositol 3-kinase - one of a family of enzymes involved in cellular functions such as growth, proliferation, differentiation, motility, survival and intracellular communication, which in turn are involved in cancer.
p53	Tumour suppressor protein important in preventing cancer.
PC12	Cell line derived from rat adrenal medulla that stops dividing and differentiates when treated with nerve growth factor.
Phagocytosis	The process by which cells engulf solid particles. Used to remove cell debris and pathogens.
Prostaglandins	Group of lipid compounds with diverse physiological actions, levels of which are elevated in inflammation.
Protein kinases	Enzymes which modify other proteins by the addition of phosphate groups and are known to regulate the majority of cellular pathways, especially those involved in signal transduction.
PSK (Polysaccharide K 'Krestin')	Japanese extract of protein-bound polysaccharides from Trametes versicolor.
PSP (Polysaccharide	Chinese extract of protein-bound polysaccharides from Trametes versicolor

Peptide)	from Trametes versicolor.
Reticuloendothelial system	Immune cells present in secondary immune organs, such as the lymph nodes and spleen, and which are involved in mobilising the immune system against foreign antigens.
Reverse transcriptase	Enzyme involved in DNA formation.
S-adenosylhomocysteine hydrolase	Enzyme which hydrolyses S-adenosylhomocysteine to adenosine and homocysteine, high levels of which have been linked to increases in cardiovascular disease and Alzheimers Disease.
Sarcoma 180	Transplantable, non-metastasizing, connective tissue tumour used extensively in evaluation of anti-cancer activity.
Sclerotium	Underground hyphal mass forming a hard tuber-like structure in certain mushrooms.
Scopolamine	Anti-cholinergic agent that impairs memory in humans and mimics Alzheimer's Disease.
Signal transduction pathways	See Cell-signalling pathways.
Specific immune system	Also called the Adaptive Immune System. Part of the immune system that learns from challenges in order to mount a stronger response when next exposed to the same pathogen.
Sporoderm	Hard outer coating of fungal spores.
T-cells	Group of white blood cells that play a major role in cell-mediated immunity.
Teratogenic	Causing abnormalities in physiological

	development, especially birth defects.
Thromboembolism	Blood vessel blockage due to blood clot formation.
Triterpenes	Terpenes are oily compounds that are the major components of resins and essential oils. Triterpenes are terpenes composed of 6 isoprene units with the molecular formula C30H48.
Tumour necrosis factor	Also called tumor necrosis factor alpha (TNFα). Cytokine able to induce apoptosis and inhibit tumour growth and viral replication.

Index

Additional Resources

Research Updates

Knowledge and understanding of medicinal mushrooms and their therapeutic potential is continually expanding and a book such as this can only be complete up to the point it is published.

Readers wishing to access regular research updates can do so at:
www.mycotherapyonline.com

Clinical Support

Questions or requests can be directed to the author at:
martin@mycotherapyonline.com

Selected Further Reading

Medicinal Mushrooms - An Exploration of Tradition, Healing and Culture.
Hobbs C. 1986. Botanica Press, Williams.

Mycelium Running: How Mushrooms Can Help Save the World.
Stamets PE. 2005. Ten Speed Press, Berkeley.

The Fungal Pharmacy - The Complete Guide to Medicinal Mushrooms & Lichens of North America.

2011. North Atlantic Books, Berkeley.

Medicinal mushrooms: their therapeutic properties and current medical usage with special emphasis on cancer treatments.
Smith J, Rowan N, Sullivan R. May 2002. Cancer Research UK.
www.academia.edu/305933

Additional Books by the Author

Medicinal Mushrooms - The Essential Guide.
Powell M. 2013. Mycology Press, Eastbourne.