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**Medicinal Mushrooms:
Their therapeutic properties and current
medical usage with special emphasis on cancer
treatments**

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Smith, Rowan and Sullivan

Index

	Page
Bibliographies	
Acknowledgements	
<i>Preamble</i>	(i)-(iv)
<i>Executive Summary</i>	A-I
Chapter 1: Introduction	1
Chapter 2: The nature of fungi with special emphasis on mushrooms	11
Chapter 3: Medicinally important mushrooms	24
Chapter 4: Technology of mushroom cultivation	64
Chapter 5: Extraction, development and chemistry of anti-cancer compounds from medicinal mushrooms	80
Chapter 6: Immunomodulatory activities of mushroom glucans and polysaccharide-protein complexes in animals and humans	106
Chapter 7: The role of polysaccharides derived from medicinal mushrooms in cancer	142
Chapter 8: Additional medicinal properties	180
Chapter 9: Regulatory and safety criteria for functional foods and dietary supplements and pharmaceutical medicines: the role for medicinal mushrooms	201
Chapter 10: Conclusions	220
<i>Appendix 1: Overview of the human immune system</i>	235
<i>Appendix 2: Standard antitumour activity test in Sarcoma 180/mice</i>	251
<i>Appendix 3: Medicinal mushrooms and cancer chemoprevention</i>	253

Biography

NEIL J ROWAN BSc MSc PhD MIBiol MIFST

Lecturer
Department of Bioscience
University of Strathclyde
Glasgow G1 1XW

Neil Rowan received the BSc degree and Higher Diploma in Applied Microbiology from the National University of Ireland, Galway, and the MSc and PhD degrees in Biomedical Microbiology from the University of Strathclyde, Glasgow, UK.

He is currently a lecturer in the Department of Bioscience (graded 5 in the recent National Research exercise) at the University of Strathclyde. He has authored or co-authored 25 research papers that have appeared in internationally-assessed Journals. His current research interests encompass the fields of Biomedical and Food Microbiology, including studies on the detection of microbial pathogens in foods for susceptible groups, the virulence properties of food-borne pathogens, and on resources that can be used to control the occurrence and transmission of food-borne pathogens. He has carried out considerable research in the area of Food Mycology, particularly studies on the axenic culture and growth of exotic mushrooms.

He is married to Michelle and has a daughter and a son.

Biography

JOHN E SMITH BSc MSc PhD DSc FIBiol FRSE

Emeritus Professor of Applied Microbiology
University of Strathclyde
204 George Street
Glasgow G1 1XW

Professor Smith has published over 250 peer-reviewed papers and authored/edited 20 books in Bioscience and Biotechnology with special emphasis on fungal technology, food biotechnology and mycotoxicology. He has served on a wide range of National and International Committees of Microbiology, Food Science and Biotechnology, and is currently Chief Scientific Adviser to MycoBiotech Ltd., an international company based in Singapore. In 1997 Professor Smith was elected to a Fellowship of the International Academy of Food Science and Technology. He is married to Evelyn and has two daughters and a son, and nine grandchildren.

Biography

RICHARD SULLIVAN BSc MD PhD

Head of Clinical Programmes
Cancer Research UK
PO Box 123
Lincoln's Inn Field,
London

Richard Sullivan qualified in medicine from St.Marys Hospital Medical School in Paddington and embarked on surgical training before taking a PhD at University College London in cell signalling.

After working in the pharmaceutical industry he became Head of Clinical Programmes at the Cancer Research Campaign, now Cancer Research UK.

Richard is married to Sam and they have one daughter, Alice. In his spare time he pursues an interest in paleopathology and the study of medical systems of ancient Egypt.

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PREAMBLE

Many clinically important drugs, such as aspirin, digitoxin, progesterone, cortison and morphine, have been derived directly or indirectly from higher plants. Less well-recognised but of great clinical importance are the widely used drugs from fungi such as the antibiotics, penicillin and griseofulvin, the ergot alkaloids and cyclosporin.

During the last two decades there has been an increasing recognition of the role of the human immune system for maintaining good health. Diseases now associated with immune dysfunction such as cancer, chronic fatigue syndrome, AIDS/HIV, hepatitis and autoimmune conditions are increasingly coming to the forefront and being given special attention from medical researchers and clinicians alike. Historically, the larger fungi, the mushrooms, have had a long and successful medicinal use especially in traditional Chinese clinical medicine for many forms of immune disorders. Chinese Pharmacopeias document the use of well over 100 species of mushroom by practitioners of traditional Chinese medicine, for a wide range of ailments. Many of these mushroom-derived medicinal products are now produced by major Japanese, Korean and Chinese pharmaceutical companies. Many of these products are being used worldwide by holistically oriented physicians, chiropractors, herbalists and naturopathic physicians in a clinical environment. To date, Western, medicine has made little use of these products in part due to their complex structure and lack of acceptable pharmaceutical purity.

Mushrooms are not a taxonomic group but do include well over 12,000 species which have macroscopic fruit-bodies, the mushrooms, which are large enough to be seen by the naked eye. Mushrooms are increasingly being evaluated in the West for their nutritional value and acceptability as well as their

pharmacological properties. Increasingly, many are being viewed nutritionally as functional foods as well as a source of physiologically beneficial and non-invasive medicines, while others are distinctly non-edible but considered purely as a source of medicinally beneficial compounds. Some of the most recently isolated and identified compounds originating from the medicinal mushrooms have shown promising immunomodulatory, antitumour, cardiovascular, antiviral, antibacterial, antiparasitic, hepatoprotective and antidiabetic properties. Modern scientific studies of the medicinal mushrooms have expanded exponentially during the last two decades primarily in Japan, Korea and China but also in the USA and scientific explanations of how these compounds function in the animal and human systems are increasingly appearing in peer-reviewed scientific and medical journals.

Mushroom-derived polysaccharides are now considered as compounds which are able to modulate animal and human immune responses and to inhibit certain tumour growths. While mushroom glucans are mostly non-cytotoxic, the same is not true of glucan-protein complexes. All of these compounds, however, have been shown to potentiate the host's innate (non-specific) and acquired (specific) immune responses and activate many kinds of immune cells that are important for the maintenance of homeostasis, *e.g.* host cells (such as cytotoxic macrophages, monocytes, neutrophils, natural killer cells, dendritic cells) and chemical messengers (cytokines such as interleukins, interferons, colony stimulating factors) that trigger complement and acute phase responses. Also, they can be considered as multi-cytokine inducers able to induce gene expression of various immunomodulatory cytokines and cytokine receptors. Lymphocytes governing antibody production (β -cells) and cell-mediated cytotoxicity (T-cells) are also

stimulated. However, for most of the mushroom-derived anti-cancer compounds, a detailed understanding of their exact mode of action has not yet been elucidated.

While many mushroom-polysaccharides have been shown to have considerable antitumour activity in several xenographs only a limited number have undergone clinical trials. At present the main products submitted for clinical testing include Lentinan from *Lentinus edodes* fruit-bodies, Schizophyllan from *Schizophyllum commune* mycelial broth, PSK and PSP, from mycelial cultures of *Trametes versicolor* and Grifon-D from fruit-bodies of *Grifola frondosa*. All have been through Phase I, II and III clinical trials mainly in Japan and China but now in US. However, in many cases the standards of these trials may not meet current Western regulatory requirements. In many cases there have been significant improvements in quality of life and survival. Increasingly, several of these compounds are now used extensively in Japan, Korea and China, as adjuncts to standard radio- and chemotherapy. While most of these clinical studies have used extracts from individual medicinal mushrooms, some recent studies from Japan have shown that mixtures of extracts from several known medicinal mushrooms, when taken as a supplement, have shown beneficial effects on the quality of life for some advanced cancer patients.

Perhaps the most encouraging observations from most of these studies is the ability of the mushroom-derived polysaccharides when taken prior to and during radiotherapy and/or chemotherapy to significantly reduce the side-effects of these treatments.

The safety criteria for the mushroom polysaccharides have been exhaustively studied with little evidence of any toxicity. In Phase I clinical trials, these compounds demonstrate remarkably few adverse reactions. Several purified mushroom

polysaccharides have been in clinical use in Japan, Korea, China and more recently in the USA for several years with no reports of any short-term or long-term toxicity.

Clinical efficacy of the mushroom polysaccharides will depend on understanding their precise scope of activity verifiable through *in vitro* and *in vivo* animal and tissue culture tests and human clinical trials, dose range, extraction methods, source and purity of the raw fungal material, duration and frequency of administration, and accuracy in matching the extracts to each particular patient based on traditional and modern diagnostic methods.

This Report, originally commissioned by the Cancer Research Campaign, aims to give a detailed and comprehensive appreciation of this complex area, derived from Oriental and Western literature together with the practical experience of the authors. It is to be hoped that Western oncologists will now have the opportunity to assess this area of cancer treatment and to judge whether it will have a realistic role in Western cancer research programmes.

Finally, from a holistic consideration, the consumption of whole edible medicinal mushrooms or extracts or concentrates (dietary supplements) may well offer novel, highly palatable, nutritious and health benefiting ingredients to the Western diet as functional foods.

EXECUTIVE SUMMARY

1. This literature study commissioned by the Cancer Research Campaign in November 2000, entailed searching computerized databases of published literature (e.g. Medline, BIDS/WOS, Embase, Science Citation Index, British Library Net) and searching of relevant specialised journals (as outlined in the proposal), many of which are not included in the computerized databases. Many original and peer-reviewed papers were obtained from the Document Supply Centre of British Library Net and scanning reference lists of appropriate review articles, books and other relevant publications (including symposia and conference proceedings). Consultations were achieved with key informants in the field, nationally and internationally. In addition to writing to many internationally-leading scientists in this field, Prof Smith spoke to a number of these scientists at an international conference held recently in Kiev where he presented an invited paper on this particular topic. However, while most of the aforementioned strategies proved successful, we were disappointed at the lack of response from some key scientific and medical centres in China and Japan who have specialised knowledge in this particular field.

We believe that this seminal literature study does contain the best up to date information on the therapeutic properties and current medical usage of medicinal mushrooms with special emphasis given on cancer treatment. It is proposed that the critical information in this report will be used to write reviews for appropriate journals. As a closing qualifying remark, while every effort was made to ensure that the best-published-data was gathered on the aforementioned, it must be appreciated that this particular field is enormous and a limited number of interesting papers may have been missed.

2. Scientific evidence supports the view that diet controls and modulates many functions of the human body and, accordingly, participates in the maintenance of the state of good health or homeostasis.
3. Arising from this awareness of the relationship between diet and disease has evolved the concept of functional foods and the development of functional food science. Foods as medicine underpins the paradigm of functional foods. The primary objectives of functional food science are to maintain good health, improve homeostasis and to create the conditions for disease reduction. It is seen to be quite distinct from the medical and pharmaceutical sciences where the objectives are mainly to cure or control diseases.
4. Mushrooms have long been valued as highly flavoursome and nutritional foods by many societies. In the Orient, there has long been the recognition that certain edible and non-edible mushrooms can have profound health benefits. When used as tonics the medicinal mushrooms are consumed whole or preferably as concentrated extracts and act as dietary supplements. A limited number of highly purified compounds derived from certain medicinal mushrooms are now being used in the Orient and the US as pharmaceutical-grade products in medicine – especially, but not exclusively, for cancer treatment.
5. Mycology is concerned with the study of the fungi, the term being derived from the Greek word *mykes*. They are heterotrophic, requiring organic carbon compounds of varying degrees of complexity for growth and reproduction. Most fungi exist as microscopic filaments or *hyphae* which form a complex *mycelium* or network. In some cases the mycelia form large complicated structures as exemplified in the mushrooms. This report deals

exclusively with large fleshy mushrooms, especially the medicinal mushrooms.

6. The use of psychotropic mushrooms by man dates far back into antiquity with the earliest records dating back to Palaeolithic times. There is an extensive literature implicating certain mushrooms in ancient religious beliefs and practices.
7. Consistent production of successful mushroom crops is built upon scientific knowledge and practical experience. To date about 35 mushroom species have been cultivated commercially with about 20 cultivated on an industrial scale. Most of these species are both edible and possess medicinal properties.
8. Mushroom cultivation involves several different operations each of which must be performed accurately if the enterprise is to be successful, *viz.* strain selection and maintenance, spawn production, mushroom production (log culture and enriched sawdust culture), and crop management for production. Mycelium production by liquid tank fermentation is now increasingly being used for the production of more uniform medicinal products. The ability to use pure substrates and controlled growth environments will aid in the final purity of the products.
9. The practice of using fungi, especially mushrooms, in Chinese Traditional Medicine (TCM), dates back into antiquity and has been recorded in ancient Chinese manuscripts. Increased scientific and medical research in recent decades, especially in Japan, Korea and China and more recently US, is confirming efficacy and identifying the bioactive molecules.
10. The main medicinal mushrooms both edible and non-edible are briefly depicted to identify their historical usage and their current commercial and

medical acceptance, viz. *Ganoderma lucidum* (Reishi or Ling Zhi), *Lentinus* (*Lentinula*) *edodes* (Shiitake), *Phellinus linteus*, *Porio cocos*, *Auricularia auricula*, *Hericium erinaceus*, *Grifola frondosa* (Maitake), *Flammulina velutipes*, *Pleurotus ostreatus* (Oyster mushroom), *Trametes* (*Coriolus*) *versicolor*, *Tremella fuciformis*, *Schizophyllum commune* and the non-mushroom *Cordyceps sinensis* (the caterpillar fungus).

11. Recent improvements in chemical technology have allowed the isolation and purification of the relevant compounds (especially the polysaccharides) which contain demonstrable anti-cancer activities. Most appear to act as immune system enhancers though some can have direct cytotoxic effects on cancer cells. Only a small number have progressed successfully to objective clinical assessment in trials.
12. The anti-tumour polysaccharides isolated from mushrooms (fruit-body, submerged, cultured mycelial biomass or liquid culture broth) are either water-soluble β -D-glucans, β -D-glucans with heterosaccharide chains of xylose, mannose, galactose or uronic acid or β -D-glucan-protein complexes - proteoglycans. Some are orally bioavailable.
13. Methods of extraction and purification of the various polysaccharides are now well worked out. The main medically important polysaccharide compounds that have undergone clinical trials include Lentinan (*Lentinus edodes*), Schizophyllan (*Schizophyllum commune*), PSK and PSP (*Trametes versicolor*) and Grifron-D (*Grifola frondosa*). Compounds from other medicinal mushrooms with proven anti-cancer properties have been studied in pre-clinical models and will increasingly be submitted for clinical trials.
14. Mushroom-derived glucan and polysaccharo-peptides can act as immunomodulators. The ability of these compounds to enhance or suppress

immune responses can depend on a number of factors including dosage, route of administration, timing and frequency of administration, mechanism of action or the site of activity. Several mushroom compounds have been shown to potentiate the host's innate (non-specific) and acquired (specific) immune responses and activate many kinds of immune cells that are important for the maintenance of homeostasis, e.g. host cells (such as cytotoxic macrophages, monocytes, neutrophils, natural killer cells, dendritic cells) and chemical messengers (cytokines such as interleukins, interferon, colony stimulating factors) that trigger complement and acute phase responses. They can also be considered as multi-cytokine inducers able to induce gene expression of various immunomodulatory cytokines and cytokine receptors. Lymphocytes governing antibody production (β -cells) and cell-mediated cytotoxicity (T-cells) are also stimulated.

15. Lentinan and Schizophyllan are T-cell oriented immunopotentiators and require a functional T-cell component for biological activity by way of increasing helper T-cell production, increased macrophage production leading to a stimulation of acute phase proteins and colony stimulating factors which in turn affect proliferation of macrophages, neutrophils and lymphocytes, and activation of the complement system.
16. PSK and PSP are potent immunostimulators with specific activity for T-cells and for antigen-presenting cells such as monocytes and macrophages. Their biological activity is characterised by their ability to increase white blood cell counts, interferon- γ and interleukin-2 production and delayed type hypersensitivity reactions.
17. There have been extensive *in vivo* studies demonstrating the anti-cancer activity of the glucan polysaccharides and polysaccharide-peptides in animal

models. These studies strongly suggest an immunomodulating mode of action. However, in *in vitro* studies on various cancer cell lines, there is strong evidence for direct cytotoxic effects on the cancer cells for some, but not all, of the polysaccharides.

18. While all of the proprietary mushroom polysaccharides successfully used in animal and human cancer treatments are effective by i.v.route, several can also be effective orally.
19. Many of the mushroom polysaccharides have proceeded through Phase I, II and III clinical trials mainly in Japan and China but now in US. Lentinan (*L. edodes*) has demonstrated strong anti-tumour activity in a wide range of xenography and with human clinical trials where it has proved successful in prolonging the survival especially those patients with gastric and colorectal cancer. Lentinan has been approved as a drug in Japan and is considered an important adjuvant treatment for several cancers. Schizophyllan (*S. commune*) has proved useful for recurrent and inoperable gastric cancer, as well as increasing survival times of patients with head and neck cancers. Neither of these compounds show any significant side-effects.
20. There are several on-going clinical trials with Grifon-D, GD (*G. frondosa*) on breast, prostate, lung, liver and gastric cancers underway in Japan and US. Results to date are promising. In *in vitro* studies GD appears to inactivate glyoxalase I, an enzyme believed to metabolise chemotherapeutic compounds used against cancer cells thus potentially enhancing their bioavailability.
21. Two compounds, PSK and PSP (derived from mycelial cultures of *T. versicolor*) have shown worthwhile anti-cancer properties when given with traditional chemotherapeutic agents with no increases in side-effects. PSK

has successfully been used in Phase I, II and III clinical trials with cancers of the stomach, oesophagus, nasopharynx, colon, rectum and lung, and with subsets of breast cancer. PSK gave protection against the immunosuppression that normally is associated with surgery and long-term chemotherapy. PSK continues to be used extensively in Japan as an adjunct to standard radio- and chemotherapy. PSP has been extensively studied by Chinese scientists and oncologists, with little evidence of side-effects. Clinical trials have shown efficacy in gastric, oesophageal and non-small cell (NSCLC) lung cancers, and PSP has been recognised as a drug by the Chinese Ministry of Public Health.

22. A significant observation from these studies is the apparent ability of all of the above mushroom-derived polysaccharides when administered with radiotherapy and/or chemotherapy to significantly reduce the side-effects so often encountered by patients.
23. While the role of medicinal mushrooms in immunomodulation and anti-cancer activities represents the central theme of this Report it is pertinent to observe that many of the medicinal mushrooms have been highly valued for other medicinal properties including hypercholesterolemia, high blood pressure, diabetes, anti-viral, anti-bacteria, and antioxidant and free radical scavenging; each of these features is briefly discussed.
24. The safety criteria for mushroom-derived β -glucans have been exhaustively carried out in pre-clinical experiments. Acute, subacute and chronic toxicity tests have been carried out together with administration during pregnancy and lactation with no adverse effects. There were no anaphylactic reactions and no effects in mutagenicity and haemolysis tests, blood coagulation and a wide range of other regulatory tests. There was no evidence of genotoxicity.

Similar results have been obtained with other β -glucans. When applied to humans in Phase 1 clinical tests, the β -glucans demonstrate remarkably few adverse clinical reactions.

25. Current laws on dietary supplements in Europe, Japan and US are discussed with reference to herbal and mushroom products.
26. The safety of all medicinal mushrooms or their extracts cannot be guaranteed simply because they have been used for many centuries with apparent safety. Recent proposals have carefully examined historical usage and have set out reasons for adopting a more cautionary approach but at the same time indicating the way forward to ensure adequate safety and efficacy for an expanding use of mushroom dietary supplements and pharmaceutical products.
27. The main advantage of using mushroom products with respect to safety (when compared to herbal preparations) are:
 - The overwhelming majority of medicinal mushrooms are cultivated commercially (not gathered from the wild). This guarantees proper identification and relatively pure, unadulterated products.
 - Mushrooms are easily propagated vegetatively and, thus, kept to one clone. The mycelium can be stored for a long time and the genetic and biochemical consistency may be checked over time.
 - The ability to grow most medicinal mushrooms as mycelium in fermenters under controlled conditions with consequent improved product purity. This may well be an important future trend in medicinal mushroom product formation.

28. Several purified mushroom polysaccharides have been in clinical use in Japan, China and the US for several years with no reports of any significant short-term or long-term adverse effects.
29. In view of the great interest in medicinal mushrooms and the absence of a specialised journal in this field, a special journal dedicated to medicinal mushrooms – “The International Journal of Medicinal Mushrooms (IJMM)” was established in 1999 by Begell House (USA) (www.begellhouse.com). The IJMM highlights new perspectives in the field of mycology and medicine. JES is a Senior Editor. In September 12-14, 2001, an International Conference “Perspectives of Medicinal Mushrooms in Health Care and Nutrition in the 21st Century” was held in Kiev, Ukraine. Three hundred and forty eight scientists from 38 countries presented their results of this fascinating and growing science.

CHAPTER 1 INTRODUCTION

Synopsis

This chapter briefly examines the relationship of diet to health and defines the concept of functional foods. A dietary supplement is considered as an addition to the diet to enhance health. Foods as medicine underpins the paradigm of functional foods. The recognition of medicinal mushrooms as functional foods or as dietary supplements is fully discussed especially in the concept of Chinese holistic medicine and modern immunology.

In the developed nations of this world many causes of death or disability such as coronary heart disease, strokes, diabetes, atherosclerosis, obesity and certain forms of cancer can, in considerable part, be attributed to diet (Barasi, 1997). Poor food selection and restricted dietary intake can affect the nutritional status of an individual at any stage of life and can lead to impairment of long term health. Increasingly, scientific evidence is supporting the view that diet controls and modulates many functions of the human body and accordingly participates in the maintenance of the state of good health or homeostasis necessary to reduce the risk of many chronic diseases (Carter, 1993). Over the last few decades the science of nutrition has progressed from being largely epidemiologically based to the greater understanding of the physiological and genetic mechanisms by which diet and individual food components influence health and disease. It is indeed a paradox that nutrition is essential to support life but can also be considered as a causation of many chronic diseases.

Arising from the awareness of the relationship between diet and disease, has evolved the concept of “functional foods” and the development of a new scientific discipline “functional food science” (Sadler and Saltmarsh, 1998). A food may be considered to be functional if it contains a food component (whether a nutrient or not)