

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.