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Magic mushrooms

Animal welfare

Substantial equivalence

Apple orchard assassin

Mushrooms and cancer therapy

The relationship between mushrooms and man can be traced far back into antiquity. More recently, certain mushrooms (medicinal mushrooms) have been shown to be a valuable source of bioactive compounds with potent and unique medicinal properties. Mushroom-derived polysaccharides can modulate animal and human immune responses and inhibit certain tumour growths. Several of these compounds are now used extensively and successfully in Asia as complimentary and mainstream therapies to treat various cancers in combination with chemo and radiotherapy.

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Title image: *Trametes versicolor*. Laurie Campbell/NHPA

Many mushroom fungi have long been valued as tasty, nutritious foods by different societies worldwide (Stamets, 2000). To the ancient Romans they were 'the foods of the Gods' resulting from bolts of lightning thrown to the earth by Jupiter during thunder storms; the Egyptians considered them as 'a gift from the God Osiris', while the Chinese viewed them as 'the elixir of life'. An extensive literature also implicates certain psycho-active, hallucinogenic mushrooms in ancient religious beliefs and practices involving, in particular, the use of *Psilocybe* and *Panaeolus* spp. in Meso America and *Amanita muscaria* in Northern Europe/Siberia, and also in the Sahara region dating back to at least Paleolithic times (Lhote, 1987; Arora, 1986; Samorini, 2001) (Fig. 1).

Intriguingly many cultures, but especially those in the Orient, identified long ago that certain mushroom species (later to become known as medicinal mushrooms) could display profound health-promoting benefits. The practice of using

fungi, especially mushrooms, in Chinese Traditional Medicine (TCM) has been recorded in early records of the *Materia Medica*. The earliest book on medicinal materials in China, the *Shen Noug's Herbal* (Shen Noug Pen Ts'ao Jing) (200-300 AD), recorded the medical effects of several mushrooms including *Ganoderma lucidum, Poria cocos, Tremella fuciformis* and many others. The most outstanding work on TCM *Pen Ts'ao Kang Mu* (Compendium of Materia Medica), compiled by Li Shi-Zhen of the Ming Dynasty and published in 1575, documented more than 20 mushroom species, together with a non-mushroom insect-infesting fungus, *Cordyceps senensis* which continues to be a major Chinese medicinal fungus (Bensky and Gamble, 1993). At the present time there are at least 270 species of mushroom that are known to possess distinct therapeutic properties (Ying *et al.*, 1987).

Especially in the Far East medicinal mushrooms have long been used as traditional medicinal ingredients, either alone or with other herbal components, for the treatment of various diseases and related health problems. Historically, in the Far East, the main medicinal mushrooms were gathered in the wild growing on dead or living trees. Now, however, almost all of the important species have been cultivated artificially by solid substrate fermentation, mainly on wood derivates, and have the potential to be produced in large pure quantities worldwide. Many of the edible species are also important items in Oriental cuisine because of their excellent nutritional and organoleptic qualities.

In the last 50 years mushroom producing technologies have advanced enormously and in 2002 the value of world mushroom production was over 20 billion US dollars, equivalent in value to the world coffee industry. While the predominantly Western white button mushroom *Agaricus bisporus* still represents a major proportion of this, its contribution is now being surpassed by medicinally valuable species, such as *Lentinula edodes* (Shiitake), *Grifola frondosa* (Maitaki), *Flammulina velutipes* (Enoki) and *Pleurotus* spp (Oyster). Other species of medicinal mushrooms such as *Ganoderma lucidum* (Reishi) and *Trametes versicolor*, while distinctly non-edible because of their bitter taste and coarse texture, have a long history of medicinal usage as hot water extracts dating back, for Reishi, at least several millennia. Current worldwide sales of extracts of Reishi as a tonic or nutriceutical are estimated at $1.5 billion annually.

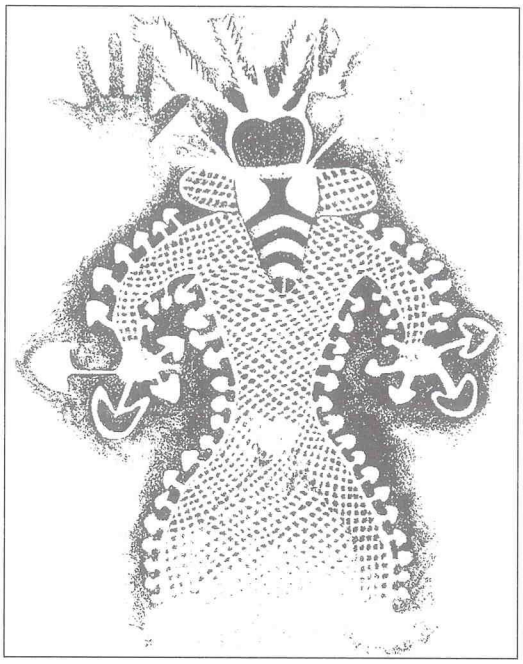

Figure 1. Tasseli cave art from Northern Algeria, circa 5000 years BC. The dancer is about 80 cm in height with the mask and stance typical of the historical period of rock paintings. The dancer is probably a Shaman and the repetitive mushroom symbols hallucinogenic mushrooms, probably *Amanita muscaria* (Lhote, 1987).

The unique shape of the Reishi mushroom has been encapsulated in much ancient Chinese artwork associated with Taoism and is symbolic of longevity (Willard, 1990) (Fig. 2). Interestingly, *Trametes* has been adopted by a florist association in Europe as a top fungal example for commercial advertising purposes (Fig. 3).

The extracts, preparations or partially purified substances derived from medicinal mushrooms find use in the Far East not as designated pharmaceuticals or medicines but as a novel class of products, namely dietary supplements (DSs) or

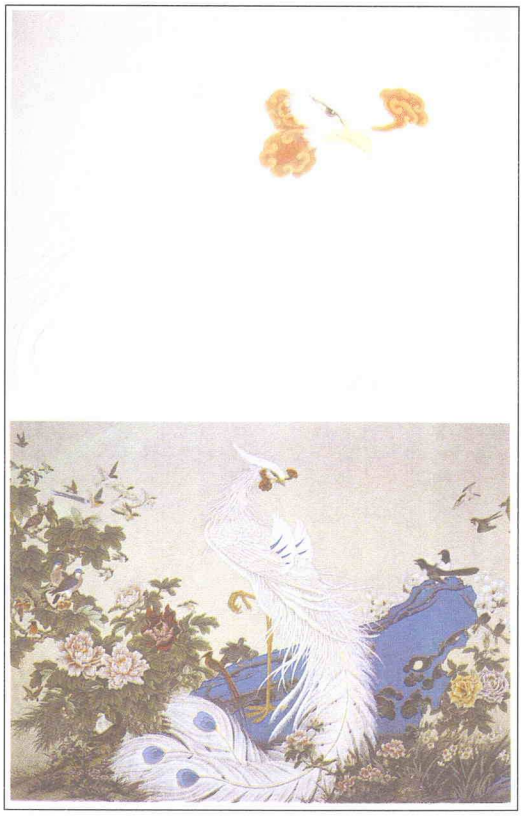

Figure 2. Contemporary Chinese painting depicting the Phoenix bird holding a Reishi mushroom both ancient Chinese symbols of longevity (Photo: Chilton Willard, 1990).

Figure 3. Trametes versicolor growing naturally on fallen timber (reproduced with permission from ISBN4-635-090 20, published by Yama-Kei Publishers Co. Ltd., Tokyo).

mushroom nutriceuticals. A mushroom nutriceutical is a refined or partially refined extract or dried biomass from either the fruitbody or the mycelium of a mushroom. It is used in the form of tablets, capsules or liquid extracts as a DS and has potential therapeutic applications (Wasser *et al.*, 2004).

As a result of large numbers of peer-assessed scientific and medical studies utilizing medicinal mushroom extracts and purified compounds in Japan, China and Korea over the past three decades many of the traditional uses have been confirmed and new applications developed (Wasser and Weis, 1999). Cancer therapy programmes in these Asian countries make considerable use of these mushroom-derived preparations in purified form as adjuvant drugs when administered in combination with chemotherapy and/or radiotherapy (Sugiyama *et al.*, 2002). Many pharmaceutical companies in the Far East are, furthermore, viewing medicinal mushrooms as a rich source of innovative biomedically useful molecules.

Regrettably, there is, as yet, scant awareness of the therapeutic value of these compounds in Western medical practice.

In 2000, the Cancer Research Campaign (now Cancer Research UK) commissioned a Report, (recently published) to collate and examine the current scientific and medical literature pertaining to the efficacy and safety of certain mushroom compounds with special emphasis on cancer treatment. This Report aimed to present a holistic coverage of an immensely complex scientific and medical area covering historical evolution, methods of large-scale production, chemical analysis of the medicinal compounds, interaction with animal and human immune systems, current status in cancer research and clinical practice and, above all, a full examination of the safety data. The aim of this Report was to assess the predominantly Oriental cancer therapy in light of Western medical practice in terms of the available evidence for safety, tolerability and efficacy in a range of site-specific cancers.[1]

The Key Medicinal Compounds

Recent advances in analytical chemical technology have resulted in the isolation and purification of some of the relevant medicinal compounds, especially polysaccharides such as ß-D-glucans, which can induce immunomodulatory and therapeutic effects in animals and humans (Wasser and Weis, 1999; Wasser, 2002; Zaidman *et al.*, 2005). The basic ß-D-glucan is a repeating structure with the D-glucose units joined together in linear chains by beta bonds. Mostly there is a main chain which is either ß 1-3, ß 1-4 or mixed ß 1-3, ß 1-4 with ß 1-6 side-chains of varying sizes occurring at different intervals (Bohm and DeMillar, 1995). Levels of medicinal activity have been related to their molecular weight, degree of branching and solubility in water. While water-soluble ß-D-glucans are widely distributed in many mushroom species, many species also contain ß-D-glucans with heterosaccharide chains of xylose, mannose, galactose etc. and yet other species can contain polysaccharide-peptides (variously called in the literature glycoproteins, proteoglycans or polysaccharopeptides) which are polypeptide chains or small proteins to which ß-D-glucans are stably attached (Borchers *et al.*, 1999; Mizuno, 1999). While ß-glucans are widely distributed in yeasts, filamentous fungi and seaweeds, the greatest range of ß-glucans have been isolated from the Basidiomycete mushrooms (Ohno, 2005). Mushroom glycoproteins have not yet been fully characterized but could be related to integrins and other signalling molecules found in plants and animals.

Several of these polysaccharide-related compounds are now produced commercially in the Far East for therapeutic applications, e.g. Lentinan from *Lentinula edodes*, Schizophyllan from *Schizophyllum commune*, Grifolan from *Grifola frondosa* and PSK and PSP (polysaccharide-peptides)-derived from different strains of *Trametes*

[1] A CD-ROM of the Report is available free from Cancer Research UK, or can be downloaded from at: http://sci.cancerresearchuk.org/labs/abs/med-mush/med-mush.html.

versicolor. A major application of these compounds has been their use in conjunction with chemotherapy and radiotherapy in cancer therapy. Lentinan, Schizophyllan and PSK in Japan and PSP in China have been approved in their respective countries as prescription drugs for cancer treatment (Mizuno, 1999).

A wide range of Basidiomycete mushrooms have now been shown to contain biologically-active antitumour and immunostimulating polysaccharides that can be derived from mushroom fruit-bodies, fermenter cultured mycelium or fermenter culture broths (Reshetnikov *et al.*, 2001). In general, there is a higher level and number of different polysaccharides extracted from fruit-bodies than from the other cultural sources and different strains of one Basidiomycete species can produce polysaccharides-type molecules with different properties (Wasser, 2002).

The role of the immune system in cancer therapy

It is now well recognized that the immune system plays an important role in the body's defense against infections and tumour formation. Defense against viral attack, and against spontaneously arising malignant tumour cells, most probably involves an orchestrated interplay of innate and acquired immune responses. Innate immunity (with macrophages, neutrophils and natural killer (NK) and dendritic cells) is regulated by chemical messengers or cytokines and by activation of inflammatory and acute phase responses. Stimulated macrophages and NK cells can create cytokines such as interferons, interleukins etc., which can destroy cancer cells. This is considered as the first line in the host defense system and could successfully eliminate infected or transformed cells prior to the formation of fully generated humoral and cell-mediated immunity (CMI) responses (Borchers *et al.*, 1999). Clearly, a functional immune response is critical to the recognition and elimination of tumour cells and the identification of mushroom-derived compounds that are capable of stimulating components of innate or acquired immunities could be of potential value in cancer therapy.

In the treatment of cancer it is now accepted that both radiotherapy and chemotherapy will also damage or weaken the patient's immunological defenses which could already have been damaged by the cancer itself. A novel approach in cancer therapy has been to modify the host biological response to the malignant invasion. Such compounds are termed Biological Response Modifiers (BRMs) and have evolved as a fourth method of cancer treatment in addition to surgery, radiotherapy and chemotherapy. Mushroom polysaccharides are now mainly considered to function locally as BRMs where they influence the immune system (Rowan *et al.*, 2003).

More recently, medical mushroom polysaccharide research has been focused on identifying the compounds that can modulate, positively or negatively, the biological responses of immune cells. Compounds that stimulate the human immune response are being appraised, not only for the treatment of cancer, but also for immune deficiency diseases; for generalised drug-induced immunosuppression following drug treatment; for combinatory therapy with antibiotics and as adjuncts

Edible Winter fungus, *Flammulina velutipes*. Photo: Laurie Campbell/NHPA.

for vaccines (Rowan *et al.*, 2003). Compounds that are capable of interacting with the immune system to upregulate or downregulate specific aspects of the host response can be classified as immunomodulators. Whether mushroom polysaccharide immunomodulators enhance or suppress immune responses can depend on a number of factors such as dosage, timing of application, route and frequency of administration (Tsianabos, 2000). Mushroom polysaccharides appear to immunostimulate without triggering autoimmune conditions.

Extensive studies in both animal and human systems have shown that certain mushroom polysaccharides can prevent oncogenesis, demonstrate direct antitumour activity against various allogeneic and syngeneic tumours and can also in many cases prevent tumour metastasis, i.e. not as cyto-static agents (Fisher and Yang, 2002; Smith *et al.*, 2003). Such polysaccharides do not appear to directly attack cancer cells but produce their antitumour effects by activating different immune responses in the host system. The antitumour activity of the polysaccharides needs an intact T-cell component in the host immune system and the activity is mediated through a thymus-dependent immune mechanism. Mushroom polysaccharides have been shown to stimulate NK cells, ß-cells and macrophage-dependent immune system responses (Wasser, 2002; Rowan *et al.*, 2003).

High molecular weight mushroom ß-glucans appear to be more biologically effective than those of low molecular weight (Wasser, 2002). It is now believed that the ß-D-glucans induce biological response through binding to membrane complement receptor type-2 (CR3; CD116/CD18) on immune effector cells, while dectin-1 could also be a new receptor (Adachi *et al.*, 2004; Ohno, 2005). The ligand-receptor complexes are then internalized. The intercellular signalling events that occur after ß-D-glucan receptor binding are now being deduced and it has recently been demonstrated that the mechanism for glucan-mediated killing of tumour targets is by interaction of anti-tumour antibodies with glucan-activated cells (Hong *et al.*, 2004). While previously ß-glucans were considered largely as non-specific immunostimulators they can now be identified as natural agents specifically affecting immune reactions. Mushroom cell wall components such as PSK are considered to interact with Langerhan cells and to have complex interactions with dendritic cells in the Peyer's patches in the small intestine (Tomochika *et al.*, 1989).

Mushroom polysaccharides and cancer therapy

There is an immense body of literature related to the anticancer effects of many mushroom polysaccharides on animals and humans. While many are now in clinical practice in the Far East, only three will be examined in more detail here, viz. Lentinan, a pure polysaccharide and PSK and PSP, polysaccharide peptides. In each case the respective polysaccharide/polysaccharide peptide when used in clinical practice, is of high pharmaceutical purity (Smith *et al.*, 2003).

Lentinan

Lentinan is a cell wall constituent extracted from fruit-bodies or fermenter-produced mycelium of *Lentinula edodes* (Xiang gu in China and Shiitake in Japan), and is a pure polysaccharide composed only of carbon, hydrogen and oxygen atoms. It is water soluble, heat and acid stable, and alkali labile. The molecular weight is approximately 500 k Da and since its bioavailability is uncertain, clinical application has normally, but not always, been by intravenous injection. The ß-glucan structure of Lentinan is comprised of a ß-(1-3)-D-glucopyranosyl backbone with ß-(1-6)-glucopyranosyl side chains.

Lentinan does not attack cancer cells directly but produces its antitumour effect by activating different immune responses in the host. Lentinan appears to act as a host defense potentiator restoring or augmenting the responsiveness of host cells to lymphocytokines, hormones and other biologically active substances (Chihara, 1992; Wasser, 2005). The immune-potentiation occurs by stimulating the maturation, differentiation or proliferation of cells involved in host defense mechanisms. Lentinan has displayed a variety of immune activities in both animals and humans (Wasser and Weiss, 1999). Lentinan has been shown to stimulate various kinds of immune cells including macrophages, NK cells and lymphocytes (T- and ß-cells) (Rowan *et al.*, 2003).

Preclinical studies on animal models with Lentinan have produced considerable information on antitumour activity, prevention of metastasis and prevention of chemical and viral-induced oncogenesis (Wasser and Weiss, 1999; Smith *et al.*, 2003).

While many anticancer clinical trials using Lentinan and other mushroom polysaccharides in conjunction with

radiotherapy or chemotherapy have been performed successfully in the Far East, they nearly all have flaws, such as inadequate methodologies for immunodynamic endpoints, and other inadequacies when contrasted with Western standards. Furthermore, the practice of involving placebos in Western clinical trials has, until recently, been an anathema to Asian thinking. Lentinan would appear to prolong overall survival in advanced gastric and colorectal carcinomas and in a number of trials on patients with inoperable or recurrent gastric carcinomas there have been good response rates with strongly implied increased median survival. There have been many enhanced response rates when Lentinan was included in a variety of conventional chemotherapy regimes in a number of site-specific cancers (Smith *et al.*, 2003).

Lentinan is well tolerated by patients with very few adverse reactions. A fascinating aspect of Lentinan use in cancer chemotherapy is its ability to ameliorate many of the associated debilitating side-effects, e.g. nausea, pain, hair loss and depressed immune function. Similar effects have also been observed with the clinical adjuvant use of several mushroom polysaccharides (Smith *et al.*, 2003).

PSK and PSP

PSK (Krestin) developed in Japan and PSP developed in China are derived by deep layer liquid cultivation of mycelium from different strains of *Trametes versicolor* (Yun Zhi). They are chemically very similar and have similar physiological activity profiles. PSK and PSP are glycoproteins comprising a mixture of polysaccharides covalently linked to a number of proteins or peptides at an approximate 60:40 ratio. The saccharide composition of PSK consists of glucose, mannose, galactose, xylose and fucose while PSP does not have fucose but does have arabinose and rhamnose. The glucan part of PSK and PSP consists of ß-(1-4) main chain and ß-(1-3) side-chains with ß-(1-6) side-chains that bond to the polypeptide component through O- or N-glycosidic bonds; the molecular weights of PSK and PSP range from 94-100k Da. PSK has been a major component in cancer therapy in Japan for over 20 years while PSP is now extensively used in China. By 1987 PSK accounted for more than 25% of the total national expenditure for anti-cancer agents in Japan. Clinical application has always been in tablet form and consumed orally.

PSK and PSP have been shown to be potent immunostimulators with specific activity for T-cells and for antigen-presenting cells such as monocytes and macrophages. Both compounds have been shown to have no substantial effect on immune responses of the host under normal conditions but can restore the immune potential to the normal level after the host has been depressed by tumour burden or anticancer chemotherapeutic agents (Rowan *et al.*, 2003; Hobbs, 2004). Both polysaccharide preparations have extensive documented anticancer activity *in vitro*, on human cancer cell lines and in human clinical trials (Fisher and Yang, 2002; Hobbs, 2004) (Table 1).

There have been several decades of successful clinical trials (predominantly in Japan) using PSK in conjunction with chemotherapy to treat head and neck, upper gastric intestine, colorectal and lung cancers with some reported successes also with treating breast cancer (Kidd, 2000). Success in most cases has been reflected in increased life expectancy and improvements in quality of life (Hobbs, 2004).

While PSK has been mainly produced and cultivated in Japan, PSP is a product of China and has been assessed for efficacy and safety by their medical scientists and oncologists. Following success with Phase I and II studies, there have been a number of Phase III trials, which showed that PSP improved disease-free survival of gastric, oesophageal, and non-small-cell lung cancers, while also substantially reducing the normal unpleasant side-effects of conventional treatments. In this way PSP can be considered as a clinical biological response modifier. Furthermore, a common adverse reaction of radiotherapy and chemotherapy is haematopoietic toxicity. Several studies have shown a strong amelioration of this toxicity by PSP (Sun *et al.*, 1999).

Table 1. Antitumour and anticancer effects of extracts of *Trametes versicolor* (adapted from Hobbs 2004)

- Inhibition of DNA of tumour cells
- Enhancement of cytokine production
- Antitumour activity in wide range of animal systems
- Tumour cell killing effect
- Inhibition of carcinogen-induced cancers in rats
- Antioxidant effects in tumour-bearing rats
- Induction of apoptosis
- Antiproliferative effect on many cancer cell lines
- Anti-invasion effects
- Angiogenesis effects
- Tumouricidal and cytotxicity effects
- Antimetastic activity
- Immunoprotective effects during radiation and chemotherapy

In view of the extensive documented physiological benefits of PSK and PSP extensive research is underway in Asiatic countries on the structure, composition and improved production methods for these therapeutic biopolymers.

Preclinical safety studies for the major medicinal mushroom polysaccharides have been extensive and supportive in their use in clinical trials and in long term treatment of cancer patients (Smith *et al.*, 2003). Furthermore, in large-scale clinical trials there have been no reports of any serious adverse reactions or evidence of drug-drug interaction. When compared to conventional chemotherapy, the mushroom polysaccharides are remarkably benign, have very low levels of toxicity and few or no side effects.

All of the current major clinical cancer trials utilising mushroom polysaccharides have used only individual types. This is to be expected since the purified compounds such as Lentinan, PSK and PSP are produced by individual pharmaceutical companies who, in turn, may fund the clinical trials. It might be anticipated that by utilising mixtures of these proven compounds the immune system could receive multiple stimuli possibly leading to stronger anticancer effects.

A novel approach to the treatment of human cancer has been by activation of the cell death programme (apoptosis). However, several cell cycle-specific agents successful in killing cancer cells are also toxic to normal cells. PSP enhanced the apoptic cell death activity of doxorubicin and etoposide and has been suggested as a possible adjuvant for leukaemia treatment (Hui *et al.*, 2005). Also the polysaccharide D-fraction from *Grifola frondosa* has been shown to decrease the effective dosage of the chemotherapeutic agent, mitomycin-C, used to control carcinoma in mice (Kodama *et al.*, 2005).

It should be noted that while the role of medicinal mushrooms in immunomodulation and anticancer activities have been to date their major therapeutic application (Smith *et al.*, 2003), many medicinal mushroom extracts have been considered for other medicinal properties including the treatment of hypercholestoremia, high blood pressure, diabetes, types I and II, as well as antimicrobials and antioxidant/free radical scavengers (Wasser and Weis, 1999). However, in the field of cancer, research to Western acceptable standards of evidence is only now being produced in these areas.

Potential regulatory issues

In current Western medical tradition drugs used to prevent or treat disease are subject to substantial regulatory control and are invariably pharmaceutical grade medicinal products. The single bioactive nature of most medicinal products coupled to, in most cases, a reasonable understanding of their mode of action, are further defining features. Mushroom polysaccharides on the other hand confound this classical regulatory taxonomy since they are multiple and heterogeneous compounds derived from a substantial range of fungal species. At the present time approximately 80% of mushroom nutriceuticals are obtained from fruit-bodies grown commercially or collected in the wild, resulting in the key medicinal products being unpredictable in concentration. The contents of mushroom fruit-bodies will reflect substrate composition which will normally be far from constant and repeatable. Increasingly, medicinal mushroom products are being derived from pure culture mycelium grown in submerged liquid culture. By optimising the composition of culture media and physiological parameters of growth the fungal metabolism can be regulated to achieve high yields of biomass with large levels of specific compounds in constant repeatable concentrations (Ciu and Chisti, 2003).

In Western medicine the use of mushroom polysaccharides will be governed by three broad regulatory categories:

1. Those dealing with fresh mushrooms or crude extracts (functional foods/dietary supplements (Katan and De Roos, 2003; Wasser *et al.* 2004);
2. Regulation of herbal medicines – in future all herbal medicinal products will be subject to regulations arising from a European Directive which will permit EU Member States to set up national regulatory schemes for traditional medicines within certain parameters, in particular, covering safety, quality and information to the consumer;[2]
3. The regulation of medicinal polysaccharides through the corpus of pharmaceutical quality, e.g. purity, stability etc.

Mushroom polysaccharides have a pivotal role in Traditional Chinese Medicine. Where traditional applications use them mostly as dietary supplements or tonics for health benefits (Wasser *et al.*, 2004) this

[2]http://www.mca.gov.uk/ourwork/licensingmeds/herbalmeds/herbalmed.htm

has also led on, in some instances, to the pharmaceuticalisation of certain polysaccharides such as discussed in this text for cancer therapy, e.g. Lentinan, PSK and PSP. Thus, they occupy an unusual regulatory position depending on the degree to which the polysaccharide has been purified and the therapeutic claims being made.

Once a mushroom polysaccharide has been purified to the point of a single bioactive species (i.e. PSP), in conjunction with a claim of efficacy towards its application, its manufacture is regulated by the most rigorous system defined by Good Manufacturing Process (particularly in the EU by Annex 13 of the GMP Directive). Despite advances in the GMP afforded by liquid fermentation technologies it remains a truism that the complex nature of the glycol chemistry involved in the production of mushroom polysaccharides means that no synthetic pathways exist for their manufacture (Bertozzi and Kiessling, 2001). Thus, despite substantial improvements in our understanding of the production of synthetic oligosaccharides and glycoconjugation, lead compounds for therapeutic intent derived from mushrooms are synthesized by the parent organism with all the inherent issues of batch-to-batch variability that this entails. However, it is also highly likely that it is this inherent structure-function complexity of mushroom polysaccharides that could provide the basis for the anti-cancer activities either through immunomodulation or direct activity (Sullivan *et al.*, 2006). Furthermore, the obsession with deriving a single pharmaceutical medicinal product, preferably by a controllable synthetic chemical route from the heterogeneity of relatively purified mushroom polysaccharides may be misplaced. Many of the associated compounds (often labelled as unknown HPLC peaks and, therefore, 'contaminants') may, in fact, be essential cofactors for mushroom polysaccharide structure function.

Conclusions

In the Far East the edible medicinal mushrooms have been part of the regular dietary intake of the populations for many generations. They mostly have excellent nutritional value coupled to good organoleptic qualities when either eaten alone or incorporated in various menus. People also believe that eating them regularly incorporates curative properties into their daily diet just as Westerners now believe in the health value of regular consumption of fruit and vegetables, i.e. as functional foods or dietary supplements. The availability of fresh, high quality medicinal mushrooms such as Shiitake, Maitaki and Enoki, together with information on their potential health value, in supermarkets would encourage their acceptance in the Western diet (Stamets, 2000).

From a medical viewpoint, it will be imperative to establish clinical trials that are randomized, double-blind, multi-centred and placebo-controlled using medicinal mushroom products that satisfy Western regulatory standards of manufacture. Such a programme is now under consideration by Cancer Research UK.

However, there is much to be applauded in the proposal of Kidd (2000) that 'glucan and proteoglycan mushroom immunoceuticals offer hope for cancer patients. These substances are prohomeostatic, uniquely effective immune boosters, which pose no threat of autoimmune backlash. As dietary supplements, they are safe and exhibit near perfect benefit-risk profiles. Mushroom immunoceuticals are a potential boon to individuals afflicted with cancer living with impaired immunity or merely descending into ill-health with the passing of time'.

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