

THE WESTERN APPROACH TO MEDICINAL MUSHROOMS

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ABSTRACT

Extracts of medicinal mushrooms have long been an important part of Traditional Chinese Medicine. Several purified compounds from medicinal mushrooms are used extensively in the Far East as adjuncts to cancer therapy. The Western regulatory issues with respect to medicinal mushrooms are examined and safety and quality control aspects set out.

1. INTRODUCTION

It is now increasingly recognised that correct diet controls and modulates many functions of the human body and, consequently, participates in the maintenance of the state of good health, or homeostasis, necessary to reduce the risk of many diseases. In recent times the science of nutrition has progressed from being largely epidemiologically-based on 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 [1]. A food may be considered to be functional if it contains a food component (whether a nutrient or not) which affects one or more identified functions in the body in a positive manner. The US Academy of Science has defined functional foods as those

that "encompass potentially healthful products" including "any modified or food ingredient that may provide a health benefit beyond the traditional nutrients it contains" [2].

Functional foods come in a plethora of name forms, e.g. dietary supplements, nutra- and nutri-ceuticals, medical foods, vita foods, pharma foods, phytochemicals, mycochemicals, biochemopreventatives, designer foods and foods for specific health uses [3]. However, the term dietary supplement (DS) is now being more widely accepted and recognised. The term DS was formally defined by the US administration in 1994 as "a product intended to supplement the diet to enhance health".

Foods as medicine underpins the paradigm of functional foods. Fermented foods cannot claim to cure diseases but, increasingly, evidence is being produced that supports the role of some functional foods in disease prevention [4]. The concept of foods as medicine does not fit easily within the current expertise of either pharmaceutical or food companies and the full creative development of functional foods may require new alliances between these companies with respect to regulatory issues. Functional foods are set to play an increasingly important role in national efforts in Western nations to curtail medical expenditure and also to improve dietary habits of their populace. Consumers in the West are becoming increasingly more health-conscious and discerning in the types of foodstuffs that are purchased. Many types of cancer can now be linked to inappropriate diets. In contrast, regular consumption of fruits and vegetables (now viewed as classical examples of functional foods) are now considered as essential ingredients in cancer prevention programmes [4].

2. MUSHROOMS AS FUNCTIONAL FOODS

Nutritional values

Mushrooms have long been valued as tasty, nutritional foods, by different societies worldwide. The relationship between mushrooms and man can be traced far back into antiquity. Early civilisations, by trial and error, built up a practical knowledge of those suitable to eat and those that were poisonous and to be avoided. Running parallel to this -

more specifically but not exclusively, in the Orient – was the identification that certain mushrooms could have profound health benefits.

However, fear of mushroom poisoning pervades many cultures and can, in places, achieve phobic extremes. Profound mycophobic reactions can be seen in UK, Ireland and much of North America. In contrast, mycophobic or fungus-loving societies are to be found throughout Asia and in many parts of Europe, notably Russia, Poland, Italy, France and Germany, where wild, edible mushrooms are regularly collected and used as a main source of food or added to soups, stews and teas. In these countries food markets regularly display a wide range of edible wild mushrooms, e.g. the truffle, Chanterelles and *Boletus* at prices well above the cultivated mushroom *Agaricus bisporus*.

Mushrooms are considered a good source of digestible proteins with protein content above most vegetables and somewhere less than milk and meats. Protein content can vary from 10-40% on a dry weight basis. They contain all the essential amino acids but can be limiting in sulphur-containing amino acids, cystine and methionine [5]. Fresh mushrooms contain 3-21% carbohydrates and 3-35% fibre on dry weight basis. Thus a considerable proportion of the carbohydrates of mushrooms consist of dietary fibre which cannot easily be digested by humans and which function essentially as dietary fibre; in this way the calorific value of most mushrooms is low. Mushrooms are an excellent source of minerals and vitamins. The main classes of lipid compounds including free fatty acids levels are generally low, around 2-8% of dry weight.

Without doubt, edible mushrooms in fresh, cooked or processed forms are a nutritionally sound, tasteful food source for most people and can be a significant dietary component for vegetarians; but, can they be considered as a functional food? [5]

Medicinal merits

It has long been recognised, especially but not exclusively, in the Far East that many edible and non-edible types of mushrooms can have profound medicinal values and are routinely

incorporated into health tonics, teas, soups and herbal formulas. Furthermore, a limited number of highly purified compounds derived from such medicinal mushrooms are now being used, particularly in Japan, China and Korea, as pharmaceutical products in medicine.

The edible mushrooms which demonstrate medicinal or functional properties include species of *Lentinula*, *Auricularia*, *Hericium*, *Grifola*, *Flammulina*, *Pleurotus* and *Tremella* while others known only for their medicinal properties, e.g. *Ganoderma* and *Trametes* (*Coriolus*) are definitely non-edible due to their coarse and hard texture or bitter taste. The historical evolution of usage of these essentially scarce, forest-derived mushrooms would most certainly not have been as fresh, whole mushrooms, but as hot water extracts, concentrates, liquors or powders and used in health tonics, in many forms. Thus, their originally human use was medicinal rather than nutritional.

Nowadays, almost all of the important medicinal mushrooms have been subjected to large-scale artificial cultivation thus removing the historical scarcity factor. [6] This also ensures accuracy of identification and increased reliability and consistency of derived extracts. As a result of their increased availability many of the edible species of medicinal mushrooms are gaining worldwide popularity because of their unique flavours, texture and amenability to culinary inclusion. While they have long been used in Oriental cuisine, some are now entering Western cuisine subject to availability [7]. Regular consumption of whole medicinal, edible mushrooms could introduce a functional or medicinal contribution within the individual's diet. The extent of the health beneficial effects will be dependent on the level and regularity of consumption of whole fresh mushrooms and concentrates.

When used for a therapeutic intention the medicinal mushrooms are normally consumed as powdered concentrates or extracts in hot water, and the extract concentrated and used as a drink or freeze-dried or spray-dried to form granular powders which allow easier handling, transportation and consumption [8]. As such, these liquid concentrates or dried powdered mushrooms contained in capsules can be considered as *dietary supplements* (DS) with potential health benefits [9]. Such DS are usually crude mixtures and should not be

confused with pharmaceuticals which are almost invariably a defined chemical preparation, the specifications for which are listed in pharmacopoeia. Regular intake of these concentrates is believed to enhance the immune responses of the human body, thereby increasing resistance to disease and, in some cases, causing regression of the disease state [10, 11].

These mushroom dietary supplements are used extensively in traditional Chinese Medicine (TCM) in various combinations, often with other herbal products, to treat many medical conditions. Immune system modulation has long been a feature of Chinese holistic medicine and is referred to as Fu Zheng therapy, which can be considered as the Oriental equivalent of Western immunotherapy. Compounds derived from certain medicinal mushrooms are used extensively in the Orient to increase disease resistance and to normalise body functions. Such extracts are used to treat deficient principles of *qi* or *chi*, the 'vital' of life energy, blood and *yin* (fluid) and *yang* functionality (especially the kidney).

Such relatively crude dietary supplements have an immense market in the Orient and increasingly worldwide, but mostly to consumers of Asian background. Sales to Western consumers are still relatively small, but increasing. Also such crude mixtures may well soon be subjected to critical regulatory considerations being drafted by the European Parliament.

Purified compounds from medicinal mushrooms

A limited number of relatively or highly purified compounds derived from certain medicinal mushrooms are now being used in the Orient as pharmaceutical products in medicine. Such compounds have been extracted from the mushroom fruitbody, from fermenter cultured mycelial biomass or the liquid culture broth of such fermentations [11]. Of significant relevance and importance is the ability of certain extracts or compounds to modulate the human immune system, to lower blood pressure and blood lipid concentrations, to inhibit certain tumour growths and control microbial infections and to reduce inflammation. All of these areas are of immense concern in modern medicine worldwide and there is extensive ongoing research for new and appropriate therapeutic solutions. It is appropriate to note that

these mushroom compounds show little or no adverse side-effects to humans unlike many highly purified and widely used modern pharmaceuticals [11].

The most significant factors of many mushroom compounds are their roles as biological response modifiers. These purified compounds have been shown to modify the host's biological response by stimulating the immune system and causing various therapeutic effects. Modern biological science is unravelling the immensely complicated human immune system. The immune system of an organism plays an important role in the defence against infections and tumour formation. Several purified mushroom compounds, e.g. Lentinan, PSK, PSP, Grifolan D, etc., have been shown to enhance or potentiate host resistance in the treatment of various cancers, immuno-deficiency diseases or immune suppression after drug treatments as adjuvants for vaccines and for combination therapy with antibodies.

The most important aim in cancer therapy is to prevent recurrence after surgery. Several of the above-mentioned medicinal mushroom compounds have been highly effective in clinical use against post-operative recurrence and metastasis. Increased survival rates have been recorded with several human cancers and any side-effects have been transitional and not serious.

Currently, there are several such purified products from medicinal mushrooms now being used in the Far East for post-operative cancer therapy. Such compounds are produced by internationally-recognised pharmaceutical companies. The most common components of these therapies are polysaccharides or polysaccharide-protein complexes. These bioactive biopolymers are mostly in the form of glucans with different types of glucosidic linkages, such as (1-3),(1-6)- β glucans and (1-3)- α glucans while some occur bound to protein residues as polysaccharide-protein complexes. Such purified 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, and can also be considered as multi-cytokine inducers able to induce gene expression of various immunomodulatory cytokines and cytokine receptors [11].

Many of these mushroom polysaccharides have proceeded through Phases I, II and III clinical trials mainly in Japan, China and Korea. A further significant observation is the apparent ability of all of the mushroom polysaccharides when administered with radiotherapy and/or chemotherapy to significantly reduce the side-effects so often encountered by patients [10, 11].

The medicinal mushrooms are destined to have worldwide use as functional foods and also to produce an increasing range of purified biochemicals for direct use in human health and disease management. Why then is there such scant recognition of their value in Western medicine?

3. REGULATORY CONSIDERATIONS FOR HERBAL (FUNGAL) PREPARATIONS

The regulatory and safety aspects of dietary supplements including fungal products with reference to European and US laws have recently been reviewed [11, 12]. The Working Party of the Pharmaceutical Committee of the European Commission has proposed a draft Directive on the regulation of herbal "medicines". These proposals would permit herbal/fungal medicines to be granted a license if the product, or a product with the same ingredients, dosage and oral route of administration, has been in "traditional use" over a period of 30 years for a particular indication. Manufacturers would also be required to provide a bibliographic review of safety data and an expert report on those data. A significant aspect of this document would be to improve the current inadequate quality control in most herbal products. At present, herbal type products are immensely variable in composition and the user has no reliable means of knowing exactly what they are consuming. Such products could well be contaminated with other organics (possibly toxic) as well as microbial presence and toxic metals [13]. Dosages are also problematic within identical remedies and may actually contain very different amounts of active ingredients. Furthermore, most often the amount of the active ingredient(s) is not shown on the label. Indeed, it is often the case that the pharmacological

active substance(s) has not been properly identified. Invariably, the benefit from the herbal product may well rely on synergism between several ingredients.

As a consequence of the current lack of regulatory requirements, reliable safety and efficacy data on herbal-type medicines is not easily available. Attempts at clinical trials for several plant-derived products have mostly been badly designed or the results poorly interpreted. Products were mainly not standardised, with different methods of preparation and administration which could lead to variation in the amounts of active principles reaching the patient [13]. Series of *randomised controlled trials* (RCTs) are now being operated where the herbal product is compared either with a placebo *or* an alternative drug on patients who do not know what treatment they are receiving. From such studies three questions will be answered:

1. Does the treatment offer therapeutic benefits over placebos?
2. Is it safe?
3. How does it compare in terms of medical outcome and cost-effective with other treatments?

Germany is by far the leading country in Europe for the consumption of herbal products. The German Commission E is an independent division of the German Federal Health Agency (Bundesgesund Leitsamt) which collects information on herbal medicines and evaluates them in relation to safety and efficacy [11, 12]. In China also there is growing concern over the quality, safety and reproducibility of herbal products [14].

In the US the National Centre for Complementary and Alternative Medicine (NCCAM) is now conducting rigorous research on CAM practices to evaluate the benefits and risks of CAM agents so as to optimise their effects on human diseases or conditions. The US Food and Drug Administration (FDA) characterises botanicals and other dietary supplements according to their use, not according to their composition. When the intended use is to "promote" health, the agent is viewed as a dietary supplement; when the intended use is to treat or prevent a disease, the agent is considered to be a drug.

Many synthetic or semi-synthetic drugs are produced from botanicals and strict methods of production have been standardised. However, unlike synthetic drugs, botanical drugs and dietary supplements are mixtures of uncharacterised constituents and it is accepted in most cases that the mixture provides the therapeutic effect. Thus, the active chemical compounds could comprise flavonoids, alkaloids, polysaccharides, sterols, triterpenes, saponins, lignans etc. Consequently, their pharmacological actions are not due to a single compound or even a group of compounds but rather to a synergistic effect of all the compounds present [15].

NCCAM have set out clearly defined protocols of plant description and sources and how the plant product(s) should be analysed, to ensure a level of quality control and reproducibility for clinical trials. With plants the major sources of variability of product(s) will be conditions of growth which will be severely influenced by soil types and the vagaries of weather – all of which can cause major fluctuations in the level of biochemical compounds [14].

For mushroom dietary supplements the NCCAM proposals for botanicals can be paraphrased as follows:

1. Fungal description – pure cultures.
2. Growth conditions – solid substrate or liquid fermentation. Good Manufacturing Procedure must prevail throughout.
3. Extraction procedures.
4. Analysis of commonly accepted or supposed active independent(s) via chemical or biological parameters. Analysis of a sizeable chemical constituent (analytical marker compounds, i.e. polysaccharides). Analysis via chemical fingerprint (analytical markers).
5. Analysis for lack of contamination by pesticides, heavy metals etc.
6. Storage conditions and stability.

It is hoped that these proposals will result in the production of high quality medical mushrooms and their extracts suitable for Western pharmaceutical and dietary supplement use at consistently high levels of bioactive ingredients.

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