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Review Article

Therapeutic potential of medicinal mushrooms - A review of bioactive compounds and clinical application

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Abstract

All through human history, mushrooms have been valued as nutritional foods. They have been extensively used as nutraceuticals and as a source for the generation of pharmaceutical-grade medicines to treat a wide variety of diseases, including cancer. During the past more than 3 decades, numerous scientific studies on medicinal mushrooms have been conducted in Japan, China, Korea, the USA, Russia, the UK, Pakistan, Turkiye, as well as other countries. A limited number of highly purified compounds derived from some of these mushrooms are now used as pharmaceutical-grade products in medicine-especially for cancer treatment. The most well-known medicinal mushrooms worldwide, both edible and inedible, include *Ganoderma lucidum, Lentinus edodes, Phellinus linteus, Porio cocos, Auricularia auricula, Hericium erinaceus, Grifola frondosa, Flammulina velutipes, Pleurotus ostreatus, Trametes versicolor, Tremella fuciformis*, and *Schizophyllum ensemble*. The regular consumption of edible mushrooms is said to offer significant health benefits. Some compounds recently isolated from these mushrooms have been found to exhibit potent immunomodulatory, antitumor, cardiovascular, antiviral, antibacterial, antiparasitic, hepatoprotective, and antidiabetic characteristics. This study provides an overview of mushrooms with medicinal potential and explores the unique health-promoting properties of some bioactive compounds derived from them.

Keywords: Medicinal Mushrooms, Functional Food, Cancer.

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Introduction

The saying "Let food be your medicine and medicine be your food" from Hippocrates, c 400 B.C., as well as the old Chinese proverb stating, "medicine and food have a common origin". These sayings have become a truism for majority of us [1 - 9]. A food can be regarded as functional when it contains a component that affects some functions in the body positively. Functional food science is thus one of the fast-

developing branches that has evolved from the awareness of interrelationships between diet and disease [10]. It is quite distinct from the medical and pharmaceutical sciences. It is also defined as a food that encompasses potentially healthful products, including any modified food or food ingredient providing a health benefit beyond the traditional nutrients it contains [11]. Several names are used for functional foods: dietary supplements, Nutra-or nutraceuticals, medical foods, vita foods, pharma foods, phytochemicals, mycochemicals, biochemopreventatives, designer foods, and foods for specific health uses [12 - 15]. A lot of confusion is observed over these names on a commercial scale. However, the term dietary supplement (DS) is now being more widely accepted and recognized, which means a product intended to supplement enhance health [2]. Today diet is accepted as a factor closely associated with human health, controlling and regulating many functions in our body necessary to reduce the risk of many chronic diseases together with participation in the maintenance of homeostasis. It is indeed a paradox that nutrition is essential to support life but can also be considered as a causation of many chronic diseases. Many causes of death or disability such as coronary heart disease, strokes, diabetes, atherosclerosis, obesity and certain forms of cancer are now attributed to diet [16 - 27]. On the other hand, regular consumption of classical functional foods like fruits and vegetables are now considered as essential ingredients in cancer prevention programmes [28 - 33]. Nutrition science has lately developed into a field mainly dealing with greater understanding of the physiological and genetic mechanisms by which diet and individual food components influence.

Functional foods cannot claim to cure diseases but, their increasing role in the prevention is clear [28, 34]. The main aim of the functional food science is to identify beneficial interactions between the presence or absence of a food component and a specific function in the body, and to understand their mechanisms. Today many types of cancer are linked to inappropriate diets. This presentation will discuss mainly large fleshy mushrooms which play a role in the prevention and cure of cancer. Many reports enlighten the fact that some mushrooms could have profound health-promoting benefits [35 - 39]. Presently many wild forms are regularly collected and used directly as a source of food in several countries. However, the fear of mushroom poisoning does exist [40 - 44].

Historical background of mushrooms

The mushrooms have been used by humans in antiquity with the earliest records dating back to Palaeolithic times. In fact, early civilizations developed a practical knowledge of edible and poisonous or psychotropic forms by trial and error. Many papers published up till now clearly depict their ancient usage related to the psycho-active, hallucinogenic properties of some like species of *Psilocybe* and *Panaeolus,* and *Amanita muscaria.* These mushrooms have been used in ancient religious beliefs and practices, and several mushroom stones dating back to 3000 BC have been found at Mayan excavation sites in Guatemala [2]. Ancient Romans regarded them as “the foods of the Gods” resulting from bolts of lightning thrown to the earth by Jupiter during thunderstorms, Egyptians considered them as “a gift from the God Osiris” Chinese accepted them as “the elixir.

There are many stories related to the deadly poisonous mushrooms like *Amanita phalloides*. Claudius II and Pope Clement VII are strongly believed to have died by mushroom poisoning. Some legends even suggest that the Buddha died in this way. Several thousand years ago Orient people knew that several edible and non- edible mushrooms were beneficial for health [35, 45].The outstanding work on traditional

Chinese medicines published in 1575 documents some 20 mushroom species, but presently at least 270 species are known to have various therapeutic properties and more than 100 species are used by traditional practitioners for a wide range of ailments like hypercholesterolemia, high blood pressure, diabetes, anti-viral, anti-bacteria, and antioxidant and free radical scavenging, in addition to their nutritional value [5, 6. 45 - 52]. Many of these mushroom-derived medicinal products are now produced by major Japanese, Korean and Chinese pharmaceutical companies and are used worldwide by holistically oriented physicians, chiropractors, herbalists and naturopathic.

Characteristics of mushrooms

Mushrooms are a large and heterogeneous group including more than 12,000 species, all having macroscopic fruit-bodies, and are large enough to be seen by the naked eye [53]. They are non-photosynthetic organisms with different growth behavior, occupying a special place in Eumycota, and are divided into Ascomycetes (Morchella, truffles) and Basidiomycetes (most species). The mushrooms in general have a wide range of shapes (umbrella, kidney, flower, stalk etc.), sizes (1-20 cm or more), cap diameter, weighing from few to several hundred grams, and a great color diversity. Most species are saprophytic flourishing in nature on fallen leaves droppings, and stumps of dead wood [40].

The mushrooms multiply by producing millions of spores, which germinate and branch to form a mycelium in a suitable environment. Later colonizes the substrate and uses the available nutrients but change into a productive sexual stage if nutrients run out or weather changes. In the cultivation process the spores are not used due to their small size as well as the genetic characteristics which are a little different from their parent. Some mycelia are pre-grown under sterile conditions, and this is called spawn. It has ability to colonize the growing substrate. Consistent production of successful mushroom crops greatly depends upon the practical experience [54]. Up till now 35 species of mushrooms have been cultivated commercially with about 20 cultivated on scale.

Nutritional value of mushrooms

Mushrooms have long been valued as nutritional foods [55]. Fresh mushrooms have a high moisture content reaching 90 percent, so the shelf life is short. They are a good source of digestible proteins, values being above most vegetables but less than most meats and milk, varying between 10-40 percent on dry weight basis. They contain all essential amino acids, but amount varies according to the species, growth medium, growth conditions and stage of maturation at the time of picking. The Sulphur containing amino acids, methionine and cystine are limited [54, 56], whereas lysine is dominant amino acid in almost all mushrooms. Most mushrooms are relatively poor in crude fat (2-8 percent on dry bases), but less than 1% on fresh weight basis. Most of their fatty acids are unsaturated but include all the main classes of lipid compounds including free fatty acids, mono-, di- and triglycerides, sterol esters and ds [56].

They are regarded as low calorific foods. Total carbohydrates generally represent more than 50 percent of dry matter; pentoses, hexoses and their derivatives; disaccharides being the main component of carbohydrates. The fresh mushrooms contain 3-21% carbohydrates. They are rich in crude fiber which cannot be digested easily by humans and varies between 3-35 percent on dry weight basis, in this way the calorific value of most mushrooms is low. They are a good source for several vitamins such as thiamine (B1), riboflavin (B2), niacin, biotin and ascorbic acid (Vit C). B1, B2, niacin as well as ergo sterol, provitamin D2 which can be converted to vitamin D,

but are poor in vitamin C. Vitamins A and D are relatively uncommon although several species contain detectable amounts of β-carotene and ergosterol which change into active vitamin D under light. Mushrooms are considered as a good source of minerals including substantial quantities of phosphorous and potassium, lesser amounts of calcium and trace elements.

Medicinal value of mushrooms

The best-known medicinal mushrooms on global scale both edible and non-edible are *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,* and *Schizophyllum commune*. Regular consumption of edible mushrooms is reported to introduce a functional or medicinal contribution in the diet of humans [57 - 5]. Some of the compounds recently isolated and identified from the medicinal mushrooms are reported to show very good immunomodulatory, antitumor, cardiovascular, antiviral, antibacterial, antiparasitic, hepatoprotective, and antidiabetic properties.

Therapeutically the medicinal mushrooms are normally consumed as powdered concentrates or extracts in hot water. The extract is also concentrated and used as a drink or freeze-dried or spray-dried to form granular powders permitting easier handling, transportation and consumption [59]. In capsular form these can be considered as dietary supplements or mushroom nutraceuticals [60]. Nutritional's are crude mixtures and differ from pharmaceuticals which are chemical preparation. Continuous use of these concentrates is said to increase the immune responses of body, thus resistance to disease and causing even regression of the disease state [35, 61 - 62].

During the last 30 years many scientific investigations have been undertaken on medicinal mushrooms in Japan, China, Korea and lately USA, Turkiye and Pakistan [63 - 69]. All these demonstrate that the compounds extracted from these mushrooms have unique health improving characteristics. The most important feature of these extracts is their ability to function as immunomodulators. Therefore, the physiological constitution of host defense mechanisms is improved by their intake which restores homeostasis. Cancer immunology has become a rapidly growing field in basic cancer research. The anti-tumor polysaccharides isolated from mushrooms 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.

Among the main medically important polysaccharide compounds that have undergone clinical trials, Lentinan (*Lentinus edodes*) has demonstrated strong anti-tumor activity in human clinical trials by prolonging the survival of patients with gastric and colorectal cancer with no side effects. It has been approved as a drug in Japan and is considered an important adjuvant treatment for several cancers. *Schizophyllum* (*Schizophyllum commune*) has proved useful in gastric cancers and has also increased the survival time of patients with head and neck cancers without any side effects. Similarly, very promising results have been obtained from Grifron-D (*Grifola frondosa*) on breast, prostate, lung, liver, and gastric cancers in Japan and US. Two compounds, PSK and PSP, derived from mycelial cultures of *Trametes versicolor* have shown good anti-cancer properties: cancers of the stomach, esophagus, nasopharynx, colon, rectum and lung, and subsets of breast cancer, when given with traditional chemotherapeutic

agents with no side-effects. The ability of these compounds to enhance or suppress immune responses depends on several factors such as dosage, administrative route and frequency, timing and mechanism of activity.

The mushroom polysaccharides used in cancer treatments are generally effective by the intravenous route, but some are effective orally. In Japan, Korea, and China these compounds are also used now on a large scale singly or in mixtures as adjuncts to standard radio- and chemotherapy, and when taken as a supplement, they show beneficial effects on the quality of life for some advanced cancer patients. Perhaps the most encouraging observations from most of these studies are the ability of the mushroom-derived polysaccharides when taken before and during radiotherapy and/or chemotherapy to significantly reduce the side-effects of these treatments.

Conclusions

All through human history, mushrooms have been valued as nutritional foods but act as dietary supplements when used as tonics. They have been extensively used as nutraceuticals and as a source for the generation of pharmaceutical-grade medicines to treat a wide variety of diseases, including cancer. A limited number of highly purified compounds derived from some of these mushrooms are now used as pharmaceutical-grade products in medicine-especially for cancer treatment. No significant short or long-term adverse effects have been reported in connection with the use of the purified mushroom polysaccharides derived from *Ganoderma spp., Lentinus edodes, Schizophyllum commune*, *Tremella fusiformis, Trametes versicolor*, *Grifola frondosa* and more recently *Phellinus* and *Hericium erinaceus*. Many of the traditional uses have been confirmed and new applications developed [70 -77]. The safety criteria for mushroom- derived β-glucans have been studied at length in pre-clinical trials. Acute, subacute and chronic toxicity tests have been carried out together with administration during pregnancy and lactation without any adverse effects, as well as no Similar results have been obtained from the safety point of view advantages in using mushroom products are: Most medicinal mushrooms are commercially cultivated (no wild collection), which guarantees identification and relatively pure, unadulterated products; Easy vegetative propagation kept to one clone; The mycelium can be stored for a long time; Genetic and biochemical consistency can be checked at any time; The ability to grow most medicinal mushrooms as mycelium in fermenters under co conditions ensures reliability.

Several pharmaceutical companies accept medicinal mushrooms as a rich source of biomedical molecules. Many polysaccharide-bound proteins produced by Basidiomycete fungi have been classified as anti-tumor chemicals by the US National Cancer Institute [61].

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 as functional foods [78].

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