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Medicinal Mushrooms, an Emerging Resource for Human Well-Being in Supplementation and Nutrition. A Special Focus on Ganoderma Lucidum and Agaricus Subrufescens

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ABSTRACT

Health professionals often know mushrooms mainly from their toxicological aspect. Throughout history, however, mushrooms have occupied an inseparable part of the diet in many countries and are considered a rich source of phytonutrients such as polysaccharides, dietary fiber and other micronutrients, as well as proteins of high biological value. In general, mushrooms offer a wide range of health benefits with a broad spectrum of pharmacological properties, including antitumoral, antidiabetic, antioxidant, antiviral, antibacterial, osteoprotective, nephroprotective, hepatoprotective, etc. In fact, mushrooms are used in the production of nutraceuticals and pharmaceuticals to act as key ingredient in the so-called mycotherapy. This review aims to provide a quick overview of the food and medicinal aspects of mushrooms with an in-depth look at the two most commonly used mushrooms, *Ganoderma lucidum* and *Agaricus subrufescens*.

Keywords: Mushroom; Active Compounds; Functional Foods; Ganoderma; Agaricus; Nutraceuticals; Pharmacological Properties; Mycotherapy

Introduction

This article aims to provide a glimpse of a vast and ever-expanding world such as that of mycotherapy. The use of macro mushrooms for curative purposes has a long tradition in Asian regions, while their use in western regions has only been growing in recent decades with a flourishing diffusion of commercial products. After a historical and botanical introduction, two of the most studies mushrooms will be reviewed. Knowledge of their chemical composition, nutritional value and health-promoting effects has expanded dynamically over the last few years, making mycotherapy a sector of sure interest for the near future.

Hints of Historical Use

The first most ancient ethnomycological testimony, so far identified, dates back to a period between 9,000 and 7,500 years ago, in a cave engraving in south-eastern Algeria, which reproduces (Figure 1) in movement, holding in their right hand a fungus [1]. The most significant artifacts that resemble mushrooms are certainly the "mushroom stones" found in the archaeological excavations of various sites in Guatemala and southern Mexico. Over two hundred objects classified as mushroom stones are known, originating from Central America, mostly from the Maya area and interpreted as intentional representations of hallucinogenic mushrooms [1,2]. In southern India, prehistoric megalithic, mushroom-shaped constructions are dat-

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ed back to the first millennium BC. In the Ötztal Alps "the mummy of Similaun", dated between 3300 and 3200 BC, was found in 1991 having with it both a specimen of "Piptoporus betulinus" (with antibiotic and vermifuge activities) and of "Fomes fomentarius". In Greek literature there are numerous references to edible and poisonous mushrooms, for which the Greeks elaborated an articulated terminology. Theophrastus, who lived between the 3rd and 2nd century BC, differentiates the hydnon, underground mushrooms, from the mykes, soil-dwelling mushrooms with a cap and stem, and the keraneon (keraunion), round in shape like the human head - perhaps bladders - and the pezes (pòxos), sessile and hollow-shaped mushrooms.

Figure 1.

The Latin Pliny the Elder, from the 1st century AD, reports the first reference in western literary documentation to Amanita muscaria. He also writes that some boletes "have white drops on the top, which come out of the casing". In the history of ethnomycology, there is also ample space for an inferior fungus, a parasite on the ears of numerous wild and cultivated grasses: ergot. The sclerotia of this mushroom are rich in indole alkaloids, from which Hofmann synthesized LSD in 1938. [1-3] Great evidence, however, on the therapeutic use of mushrooms comes from the East, from Traditional Chinese Medicine (TCM), of Taoist tradition, with a history of clinical practice of 4000 years. Mushrooms have been used in TCM for millennia, both as food and in therapy. The first news on the use of mushrooms in TCM dates back to the treatise Shen Nong Ben Cao Jing (Divine Farmer's Materia Medica) written in 250 BC. Natural remedies are divided into 3 classes, the most important of which consists of 120 substances, to be used "if one intends to make one's body light, increase qi, prevent aging, and prolong life". Various mushrooms belong to this "superior class", including: Ling Zhi (or Reishi or Ganoderma lucidum), Zhu Ling (or Chorei or Polyporus umbellatus), Fu Ling (or Bukuryo or Poria cocos), Dong Chong Xia Cao (or Tochukas or Cordyceps sinensis). [1,2] Many of the mushrooms used today are known by their corresponding Japanese names, in which the suffix "take" means precisely "mushroom".

Hints of Fungal Botany

Everyone knows that mushrooms constitute a separate kingdom in the taxonomic classification, but perhaps it is less known that this "definitive catalogue", compared to the vegetable kingdom, is rather recent. Linnaeus' classification united them with Thallophyte plants and only later were they included in the kingdom of Fungi or Mycota. However, the decisive cataloging criteria are only from 1968, which

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take into account the morphological characteristics, nutrition, cellular structure, energy reserve mechanisms and reproductive structures; characteristics that, from an evolutionary point of view, make mushrooms closer to animals than to plants. [1,4] There are about 1.5 million species, second only to insects in number and diversity, and it is estimated that only 5% of them are clearly identified. Mushrooms therefore outnumber plants by about 6 times and make up 25% of the Earth's biomass. Their dimensions vary from about 2 microns up to a kilometer and more. In fact, the largest living being in the world is a fungus identified in 1988 in the eastern part of the state of Oregon in the Malehur National Forest: it is a specimen of Armillaria solidipes which develops over an area of 161 km2, occupying 965 hectares with an estimated weight of about 6,286 tons and with an age between 8560 years in the oldest area and 1950 years in the "youngest" area [1]. Macroscopic mushrooms such as porcini, morels and button mushrooms, grown and available in grocery stores, represent only a small fraction of the diversity of the mushroom kingdom.

Molds, for example, are a large group of microscopic fungi that include many major plant pests, allergenic species, and opportunistic pathogens of humans and other animals [4]. Fungi are generally characterized by filamentous vegetative cells called hyphae. A mass of hyphae forms the thallus (vegetative body without specialized structures) of the fungus, called mycelium. The more phylogenetically primitive molds (e.g., water molds, bread molds, and other sporangial forms) produce coenocytic filaments (multinucleated cells without cross-walls), while the more advanced forms produce cross-walled hyphae (septa) which divide the filament into uninucleate and multinucleate compartments. The septum, however, still provides for cytoplasmic communication, including intercellular migration of nuclei. Many fungi do not appear as filiform hyphae, but as unicellular forms called yeasts with a more spherical shape, which reproduce by vegetative budding, with a diameter of a few microns. Some of the fungal pathogens have dual morphology such as Candida albicans whose ability to change from the normal yeast form to the filamentous form for invasion of host tissues is part of the success of its attack strategy. [4] The main difference with plants consists in the inability of fungi to perform chlorophyll photosynthesis: they are therefore unable to produce organic matter and must draw nourishment from other organic substrates of vegetable, animal, bacterial or fungal origin. They are in fact heterotrophic organisms [1,4].

Fungi can obtain the compounds necessary for their survival from non-living organic substrates (saprophytes), or living organic structures (parasites) by absorbing nutrients through their cell wall. Small molecules (for example, simple sugars and amino acids) accumulate in an aqueous film surrounding the hyphae or yeast and simply diffuse through the cell wall. Macromolecules and insoluble polymers (for example, proteins, glycogen, starch and cellulose), on the other hand, must undergo preliminary digestion before being absorbed by the fungal cell. This process involves the release of specific enzymes that cause extracellular digestion of the substrate, with subsequent diffusion of the digestion products through the fungal cell envelope. It is through the action of these digestive enzymes that fungal pathogens are able to penetrate through the natural barriers of the host. Individual fungi can communicate with each other by means of pheromones, chemical compounds that activate social relationships between different organisms. If they recognize an opponent, they can also inject toxins into the substrate to repel it or, in the presence of a competing fungus, absorb nutrients from its hyphae until it dies. [1,4].

The Cell Wall

Not all fungal species have cell walls, but, in those that do, cell wall synthesis is an important factor in determining the final morphology of fungal elements. The fungal wall also protects cells against mechanical damage and blocks the entry of toxic macromolecules. This filtering effect may be particularly important in the protection against fungal pathogenic compounds present in the surrounding environment or produced by the host. The fungal cell wall is also essential to prevent osmotic lysis. Even a small lesion in the cell wall can cause extrusion of cytoplasm as a result of the internal pressure (turgor) of the protoplast. The composition of fungal cell walls is relatively simple and does not include substances typically found in plant and animal cells. Mushrooms have cell walls mainly made up of chitin and not cellulose like plants. Chitin is much more resistant to microbial attack, drought and cold. It is a major component of the exoskeleton of insects and other arthropods [2]. In the wall, in addition to chitin, there is chitosan (deacylated with respect to chitin in position 2 on the amino group of N-acetylglucosamine) and other polysaccharides among which the most important are beta-glucans. The latter are the subject of many studies and are responsible for many therapeutic activities. Their importance is such as to merit specific study elsewhere [3].

Habitat Reproduction and Classification

Fungi and bacteria are ecologically important as decomposers, as well as being parasites of plants and animals. Often both of these organisms inhabit the same ecosystem and therefore compete for food supplies [1]. From this "compresence" arises the production by both organisms, fungi and bacteria, of secondary metabolites that function as inhibitors of microbial growth or toxins. These compounds constitute a rich library of antimicrobial agents, many of which have been developed as antibiotics in pharmacology (for example, penicillin from Penicillium chrysogenum, nystatin from Streptomyces noursei, amphotericin B from S. niveus). The Lentinan polysaccharide extracted from Lentinus edodes (Shii-take) has also been recognized by the Japanese Ministry of Health since 1985 as a drug for the treatment of stomach cancer [1]. Mushrooms reproduce by means of spores, microscopic cells released in considerable numbers which, by germinating, produce a so-called "primary mycelium". Through the spread of spores, invisible to the naked eye, fungi are present practically everywhere. It has been calculated that we inhale 1 to 10 spores with each

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breath, therefore approximately 300,000 per day. There are fungi that can decompose hydrocarbons and research is being studied for their use in the environmental sector [1]. In the official systematic classification, fungi are divided into four major phyla (new classifications are also possible):

- Ascomycota

They constitute 75% of the mushroom species; the best known are morels, truffles, yeasts and Penicillium. They feed on biological matter, both living and dead; one of the characteristic structures is the ascus, a group of cells in which meiosis takes place.

- Basidiomycota

Includes all those species of mushrooms that have septate mycelium, sexual and asexual reproduction with non-motile spores.

- Chytridiomycota

They are aquatic mushrooms; the name refers to the chytydrium, the structure that contains the spores; the Chytridiomycota are the most primitive of the fungi and are generally saprophytic.

- Zygomycota

They are fungi that reproduce sexually (hence the name) with monoflagellate spores; they can be both saprophytes and parasites (of both animals and plants). The Zygomycetes are almost exclusively terrestrial and are widespread on all continents.

The macro fungi can be visible to the naked eye and belong mostly to the ascomycetes and basidiomycetes groups, what we observe with our eyes sprouting out of the ground, or from the culture substrate, is constituted by the aerial mycelium, the set of hyphae which constitutes the carpophore (or "fruiting body") of the fungus, conceived for reproductive purposes for the diffusion of spores. According to an empirical classification, macrofungi are also divided into:

- Epigeal: with the fruiting body above the ground
- Hypogea: with the fruiting body below the ground [1].

The Ecological Functions of Mushrooms

Many plants (about 90%) have evolved by creating symbiosis (mycorrhizae) with fungi; the latter can act as a parallel "immune system" and in many cases constitute a "parallel digestive system" for plants. Furthermore, mycorrhizae make the waste products of plants and animals bioavailable again. Before feeding on the substrate, in fact, they must inactivate toxins and counteract pathogens of the environment. It is therefore possible to extract enzymes, antibiotics and defensive substances (e.g. triterpenes) from mushrooms to use them in human and veterinary medicine. Therefore, although they are the source of devastating plagues for animals and plants, at the same time mushrooms are one of the best sources of medicines for humans. Furthermore, in frontier fields of recent scientific research, attempts are being made to use mushrooms as real synthesis laboratories for the production of new "organic" molecules, by inserting "inorganic" starting elements into their growth substrate.

Mushrooms as Food

Fresh mushrooms, for food use, are made up of about 90% water. The remaining fraction consists of proteins (from 20 up to 40%), fats (about 2-3%), carbohydrates (about 70%) and minerals, such as P, K, Ca, Fe, Mg, Cu, Zn, Si and others (0.8-1.2%). A high potassium content is a characteristic of mushrooms. Among the carbohydrates we find soluble compounds, such as glucose, xylose, rhamnose, sucrose and trehalose and the "fibers", made up of complex polysaccharides that are not easily absorbed, such as for example glycogen (a molecule used by the mushroom as an energy reserve) and chitin (main constituent of cell walls that partially decomposes with cooking). The metabolites of carbohydrate digestion present in mushrooms are also excellent nutrients for intestinal probiotic bacteria. The content in essential amino acids is very high and this gives both a high biological value (about 80%) to the proteins contained, and a high digestibility (90%) of the same. The fat content consists mainly of linoleic and oleic acids, as well as other fatty acids, sterols and phospholipids. Mushrooms are also a source of vitamins. The main vitamins synthesized by mushrooms are C (7-8 mg/100 g of fresh mushroom), B2 (0.7-0.8 mg/ 100 g f.m.), B6 (1 mg/ 100g f.m.), PP (4.9 mg/100 g f.m.), K (7 mg/100 g f.m.) and D (3.8 mg/100 g f.m.) [5]. Mushrooms are also the only non-animal source of vitamin D [2,3]. Mushrooms, therefore, due to the variability and characteristics of their compounds, represent a food of great nutritional interest [5].

Ganoderma Lucidum

Ganoderma lucidum (Curtis) P. Karst.

Classification

Fungi – Basidiomycota - Basidiomycetes – Polyporales – Ganodermataceae - Ganoderma

Description

It is the best-known mushroom in mycotherapy and probably also the one with the highest number of studies. It is best known by the Japanese name of "Reishi", while the Chinese name is Ling Zhi or Ling chi. It has a semicircular hat, often hunched over and with a hard, leathery, smooth or lumpy surface, concentrically corrugated, of a more or less intense red color with a whitish-yellowish edge. The stem is lateral, of the same color as the cap. The flesh is woody, very leathery, white-ochre in colour. Saprophyte of stumps or hardwoods, especially oak, grows from spring to autumn.

Uses in Mycotherapy

The cap and stem of the mushroom are used. It is mainly used as an immunomodulator. Active constituents include polysaccharides

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(such as beta-glucans) and triterpenes [6] including ganoderic acids. Reishi extracts can stimulate macrophages, alter the levels of TNF- α (Tumor necrosis factor) and interleukins [7-9] and inhibit platelet aggregation [10,11]. Clinical studies indicate that reishi extracts improve Lower Urinary Tract Symptoms (LUTS) in men [12-14], exert mild antidiabetic effects, and may improve dyslipidemia [15]. In vitro and animal studies indicate that Reishi has chemo preventive effects [16], relieves chemotherapy-induced nausea [17], improves the efficacy of radiotherapy [16], and increases the sensitivity of ovarian cancer cells to cisplatin [18]. It was also effective in preventing cisplatin-induced nephrotoxicity [19]. In some clinical studies, Reishi has increased the antioxidant capacity of plasma [20,21], and improved the immune responses in some cancer patients [22]. In some cases, a remission of Hepatocellular Carcinoma (HCC) has been described [23]. An in vitro study showed that Reishi extract has toxic effects on leukocytes [24]. Further research is therefore needed to determine its safety and efficacy, as an adjuvant in the treatment of cancer or even as an anticancer agent [19].

Mechanism of Action

The identified triterpenes have adaptogenic, antihypertensive, and anti-allergic effects. Furthermore, they can inhibit tumor invasion by reducing the expression of metalloproteinases [25] and decreasing tumor metastasis by limiting attachment to endothelial cells [26]. Some polysaccharides present in Reishi, such as beta-glucans, have demonstrated anticancer and immunostimulant activities [27]. They can induce the maturation of normal monocytes and leukemic blasts (immature cells) into dendritic cells [28]. The adenosine in Reishi is considered responsible for the inhibition of platelet aggregation [10]. Reishi extracts have demonstrated the ability to stimulate macrophages and to alter the levels of TNF-α and interleukins [7-10]. Reishi can increase plasma antioxidant capacity [11,12] and improve the immune response in cancer patients [22]. Additionally, Reishi extracts can inhibit 5-alpha-reductase, an important enzyme that converts testosterone to dihydrotestosterone, and is upregulated in benign prostatic hyperplasia [12]. Cardio-protective effects were highlighted in a 2011 study of 26 people with mild hypertension [29]. This mushroom has also shown potential antihypertensive activity as an ACE inhibitor (Angiotensin Converting Enzyme) and a good antioxidant capacity. Studies on the anti-allergic action have shown the inhibition of histamine production and, more generally, a modulation of the immune system, with a rearrangement of a correct balance of Th1/Th2 lymphocytes [30].

In vivo studies have shown efficacy in model cases of allergic rhinitis [31]. Ganoderic acids (mainly C-ganoderic acid) have shown both systemic and topical anti-inflammatory activity in vivo [32,33]. Acids A, B, G and H showed greater activity than acetylsalicylic acid [34]. In vitro and in vivo studies have shown protective activity of the liver against the toxicity induced by various toxic substances. Furthermore, the in vivo protective power against hepatic necrosis induced by noxious substances has been highlighted [35-37]. Positive effects on patients with chronic Hepatitis B has been highlighted by the polysaccharide fraction of the mushroom [38].

Active Constituents

- Polysaccharides: 1,3-1,6 Beta-D-glucan
- Sterols: ergosterol
- Fungal lysozyme
- Triterpenes: ganoderic acids
- Lipids
- Alkaloids
- Glucosides
- Coumarins
- Volatile oil
- Other constituents: riboflavin, ascorbic acid, and amino acids [6].

Agaricus Subrufescens

Classification: Fungi – Basidiomycota - Agaricomycetes – Agaricales – Agaricaceae – Agaricus.

Description

Originally from Brazil, it is one of the most used edible mushrooms in mycotherapy. Saprophytic mushroom with an almond smell, it has a spherical and globular fleshy hair, a short and thick stem of white or whitish color with a ring. Other names by which Agaricus is known are Himematsutake, Agarikusutake, Kawarihiratake in Japan, or Cogumelo do Sol, in Brazil and Ji Song Rong in China or Sun Mushroom in English due to its ability to grow well in full sun. It is available as a freeze-dried mushroom or in liquid extracts such as concentrates, teas, or capsules. The whole mushroom is often added to soups, sauces, or hot herbal teas. It is grown in Japan for medicinal uses. It has been used to treat diabetes, atherosclerosis, hepatitis, hyperlipidemia, dermatitis, and various neoplasms. The polysaccharides and anti-angiogenic molecules present in Agaricus are the compounds believed to be responsible for its anticancer properties. Although there are multiple positive results in vitro and on animals, the available information is still insufficient for a potential use of this mushroom for oncological use, both to define the mechanism of action of its components and its safety and interaction with drugs. Agaricus has also been shown to have antidiabetic effects in vitro and in animal studies [39,40]. Results of a study conducted in human subjects with type 2 diabetes suggest beneficial effects of Agaricus extract in improving insulin resistance [41,42].

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while a pilot study in 31 healthy volunteers, with a well-characterized extract of mushrooms grown outdoors, indicates that Agaricus extract can reduce weight, body fat, blood sugar and cholesterol levels [43]. The anticancer and immunomodulatory effects of Agaricus are due to direct immunopotentiation or inhibition of angiogenesis [44-48]. An extract of Agaricus ameliorated doxorubicin-induced apoptosis against a drug-resistant human hepatocellular carcinoma [49]. Oral administration of an extract improved the activity of natural killer cells and the quality of life of cancer patients undergoing gynecological chemotherapy [50], but such effects were not observed in a study of elderly women [51]. This demonstrates, as already mentioned, the need to carry out in-depth studies on a large scale. A small pilot study reported that Agaricus extract can improve liver function in patients with hepatitis B [52], while liver damage in cancer patients [53] has been reported following the consumption of Agaricus.

Constituents

- Polysaccharides: beta-1, 6-D-glucan
- Sterols: ergosterol
- linoleic acid
- Lipids
- Anti-angiogenic compounds: sodium pyroglutamate (A-1) and A-2 [44,53].

Mechanism of Action

A recent study suggests that Agaricus extract has estrogen-like activity and may help prevent atherosclerosis through a dual role in cell signaling: the suppression of macrophage development and the recovery of endothelial cells from vascular damage [54]. An important component of Agaricus, ergosterol, has been found to be responsible for the inhibition of tumor growth in mice by direct inhibition of tumor-induced angiogenesis [53]. Other studies have shown that the polysaccharides present in the Agaricus extract caused the activation of macrophages [50] and natural killer cells [55] and induced cytotoxic activity of T lymphocytes in tumor-bearing mice. Specifically, natural killer cell activation is mediated through induced IFN-gamma and IL-12 expression [56]. Both aqueous and organic Agaricus extracts showed a protective effect against cells exposed to methyl methanesulphonate, a mutagenic agent. The stimulus produced by linoleic acid on beta-DNA polymerase, an enzyme involved in the DNA repair mechanism after exposure to alkylating agents, is thought to be responsible for this effect [57]. Agaritine, a hydrazine-containing compound, has shown antitumor activity against U937 leukemic cells mediated through apoptosis [58].

Adverse Reactions

In hormone-sensitive dysfunctions, the possible estrogen-like activity of Agaricus must be taken into account [59] Cases of cheilitis have been reported [60].

Herb Drug Interactions

Cytochrome P450 substrates: Agaricus inhibits CYP3A4 and can affect the intracellular concentration of drugs metabolized by this enzyme [61]. It can lower the blood glucose level [62]. It can cause an increase in liver enzymes [63,64].

Conflict of Interest

No potential conflict of interest was reported by the author(s).

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