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Review Article

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What Medicinal Mushroom Can Do?

Waill A. Elkhateeb

Chemistry of Natural and Microbial Products Department, Pharmaceutical Industries Researches Division, National Research Centre, El Buhouth St., Dokki, 12311, Giza, Egypt
Email: waill ahmed@yahoo.com

Abstract Among many traditional medicines, mushrooms have been used in Asian countries for over two millennia as a traditional medicine for maintaining life and long life. Research on various metabolic activities of medicinal mushrooms have been performed both in vitro and in vivo studies. Over the past two decades, medicinal mushrooms industry have developed greatly and today offers thousands of products to the markets. This paper describes the current status of some important world medicinal mushrooms, products, and provides suggestions for further research.

Keywords World medicinal mushrooms, biological activities, bioactive compounds, traditional medicine, secondary metabolites

1. Introduction

It is understood that human beings have constantly been in search of new substances that can improve biological functions and make people fitter and healthier. Recently, the society has turned towards plants, herbs, and food as sources of these enhancers. These products have been called variously vitamins, dietary supplements, functional foods, nutraceuticals, and so forward. Mushrooms, in this regard, are now beginning to receive much deserved attention for their very real health giving qualities. Mushrooms grow wild in many parts of the world and are also commercially cultivated. Nutritionally, mushrooms are a valuable health food and have been used medicinally for centuries in many parts of the world [1-3].

As a group of macrofungi categorized as either ascomycetes or basidiomycetes, they may obtain their nutrition through saprotrophism, parasitism, symbiosis, or a combination of approaches. Mushrooms have a reproductive phase (fruiting bodies) and a vegetative phase (mycelia) [4,5]. Nowadays, medicinal mushrooms are regarded as functional foods and exist as over-the-counter health supplements used in complementary and alternative medicines [6, 7].

In the ancient books of traditional medicines, medicinal mushrooms were occupying the headlines, and the main topics were confirming to their miraculous therapeutic powers. The presence of various phenolic compounds, polysaccharides, and terpenoids and other compounds, is the reason for their potent biological activities as anticancer, antioxidant, antimicrobial, antiviral, antiaging, hepatic protective, hypoglycemic, hypocholesterolemic, and much more biological activities are discovered every day [5, 8]. Many mushroom genera are famous for their promising therapeutic capabilities. In ancient China and most Asian countries, it was believed that medicinal mushrooms had the power to enhance long life and liveliness [9,10].

2. Bioactive compounds in medicinal mushrooms

Mushrooms are rich source of assortment of bioactive compounds that offer great therapeutic potential for the prevention and control of several diseases. Hence, isolation and identification of bioactive compounds from mushrooms crude extracts are required in order to specify which compound is responsible of the observed [5]. Various compounds are responsible for the therapeutic activities of many mushrooms genera. The main group of compounds will be highlighted as follows. Polysaccharides represent the major compounds existing in medicinal mushrooms, and they exhibit antioxidant, anticancer, antidiabetic, antiinflammatory, antimicrobial, and immunomodulatory activities [11-13]. Glucan polysaccharides especially β-glucans have been reported to exhibit antimicrobial activity, hypoglycemic, and enhance immunity through the activating macrophages [14,15]. Terpenes are the compounds responsible for the antioxidant, anticancer, and anti-inflammatory activities among many other biological activities exerted by mushrooms [16]. Phenolic compounds are responsible for antioxidant activities in mushroom extracts through acting as decomposers of peroxidase, inactivators of metals, oxygen scavengers, or inhibitors of free radicals. A long list of phenolic compounds were isolated from mushrooms [17]. On the other hand, mushrooms produce many bioactive proteins and peptides, such as lectins, fungal immunomodulatory proteins, ribosome-inactivating proteins, and laccases [18].

There are many genera of medicinal mushrooms known for their use as a source of therapeutic bioactive compounds. This review describes the importance of medicinal mushrooms with focus on *Cordyceps, C. militaris, C. sinensis, Metacordyceps neogunnii, Ganoderma, G. applanatum,G. lucidum, Auricularia auricula-judae, Fomitopsis officinalis, Inonotus obliquus* and some others as an examples of worldwide medicinal mushrooms.

3. *Cordyceps*

One of the mushrooms genera attracting attention is *Cordyceps* which has long been used in Asian countries for maintaining long and healthy life. Numerous studies on different metabolic activities of *Cordyceps* have been performed both in vitro and in vivo [5]. The fruiting bodies of *Cordyceps* fungi often erupts from the head of the larva and adult stages of many different species of insects [19]. *Cordyceps* are entomophagous fungi from the phylum Ascomycota, family Ophiocordycipitaceae, order Hypocreales, and they are known to parasitize many orders of insects at different life stages from larva to adult stages [20,21]. *Cordyceps* have a wide range of various compounds, some are characterized as nutritional compounds, since they possess all the important amino acids, vitamins such as K and E, besides B vitamins. In addition, they contain many sugars, including monosaccharides, disaccharides, and oligosaccharides, and many complex polysaccharides, proteins, sterols, nucleosides, and trace elements. *Cordyceps* contains abundance of polysaccharides. *Cordyceps* polysaccharide is one of the main bioactive components [19]. There are several species known to have medical value, only a few are cultivated and the most popular and well known are *Cordyceps sinensis* and *Cordyceps militaris* [5, 22].

3.1. Uses and health benefits of *Cordyceps*

Cordyceps Species are widely researched due to the endless list of medicinal biological activities exerted by their extracted compounds. The main uses of *Cordyceps* have been known in old medicine for curing respiratory diseases such as asthma and bronchial cases, as well as for providing body with energy and for boosting sexual power. Modern research now confirms the efficiency of *Cordyceps* in many other fields. Cordycepin produced by *Cordyceps* has a strong antimicrobial activity against almost all species of bacteria. *Cordyceps* showed strong activity against tuberculosis and human leukaemia. *Cordyceps* was shown to be potent in increasing the maximum amount of oxygen and to improve respiratory function. The *Cordyceps* industry is strong and growing, Fig. (1). Various products were commercialized for compounds originated from *Cordyceps* species [5, 23].

Figure 1: Cordyceps products (a) Cordyceps sinensis capsule (www.dutch-headshop.eu), (b) Cordyceps militaris capsule (https://www.shophealthy.in)

4. *Metacordyceps neogunnii*

Metacordyceps neogunnii (*M. neogunnii*) T.C. Wen & K.D. Hyde, namely, *Cordyceps gunnii* (Berk.) Berk. early reported in China which is widely present in Guizhou, Hunan and Anhui provinces [24], has various effects such as analgesia, sedation, improvement of human immunity, anti-tumor, anti-aging, promoting sleep and enhancing memory [25,26]. It has chemical composition and medicinal value similar to those of *Cordyceps sinensis*. Furthermore, it is characterized with such merits as wide ecological amplitude and short cultivation period [27], thus more suitable for large-scale cultivation through modern submerged fermentation. Secondary metabolites of *Cordyceps sinensis* are considered to be major compounds with various effects, from which it is highly likely to find new bioactive substances or lead compounds for drugs [28]. However, at present, the research on *M. neogunnii* mainly focuses on strain identification, genomics analysis and preliminary pharmacological effects, with little on secondary metabolites [29].

5. *Ganoderma*

In Traditional Chinese Medicine (TCM), *Ganoderma* is claimed "to replenish the energy, ease the mind, and relieve cough and asthma" [30]. In herbal medicine, *Ganoderma* is used to increase energy, resist stress, or as a liver tonic [30]. *Ganoderma* is a genus belongs to the family Ganodermataceae. *Ganoderma* has been used from centuries in traditional medicine and specifically in Asia. Currently, *Ganoderma* is existing worldwide as a food supplement. Whole *Ganoderma* or their crude extracts have been intensively investigated for their anti-inflammatory effect [31, 32]. Modern studies associated with animal models and molecular-based research techniques have demonstrated numerous pharmacological effects of *Ganoderma* spp. crude extract [33, 34]. There are nearly 200 medicines and compounded medicines containing *Ganoderma* available within China [35, 36]. Modern research revealed that triterpenoids and polysaccharides were responsible for the pharmacological effect. Elkhateeb et al., [37] studied the gas chromatography–mass spectrometry analysis of *Ganoderma* spp. crude extract resulted in the detection of 39 compounds, which were generally saturated and unsaturated fatty acids, and alkenes. The crude extract exhibited a promising in-vitro cholesterol-lowering activity (100±0%) after 96 h of incubation at room temperature. The same crude extract showed a moderate anti-rotavirus SA-11 strain effect with a therapeutic index of 9.3. Moreover, *Ganoderma* spp. extract displayed a strong activity toward HCT116 human colon carcinoma cell line, resulting in a cytotoxicity of 84.03±0.93% on HCT116 cell line monolayers. *Ganoderma* spp. crude extract represents a promising source of biologically active compounds that could by further investigations represent support and/or alternative to the currently used drugs. There are several species known to have medical value, and the most popular and well known are *Ganoderma applanatum* and *Ganoderma lucidum.*

Ganoderma applanatum is a widely distributed saprobic or parasitic mushroom. Studies proved this genus to have a potent antimicrobial, anti-fibrotic and anti-tumor properties [38]. Other effects are attributed to a wide variety of bioactive components, such as polysaccharides, triterpenes, sterols, lectins and other proteins [39, 40]. Elkhateeb *et* al., [41] collected and identified *Ganoderma applanatum* at the bases of decaying logs in Hakozaki Higashi-ku Fukuoka-shi. Japan. The mushroom was extracted with 80% methanol, and LC-HRMS analysis was conducted to illustrate the bioactive ingredients. The cytotoxicity of the total metabolite extract was evaluated against human colon cancer cell line (Caco-2) which showed IC_{50} value of 160 ± 4.08 µg/ml. The in vivo study on solid Ehrlich tumor (SEC) revealed a decrease in the volume of the developed tumor mass after five days of *G. applanatum* (200 µg/ml) treatment. Elkhateeb *et al*., [41] proved that *G. applanatum* can be a promising candidate as alternative or co-anticancer medications.

LC-HRMS analysis of *Ganoderma applanatum* methanolic extract revealed the presence of 47 metabolites. The identified compounds represent different chemical classes of natural products such as terpenes and polyketides, which represented the majority of the identified compounds, alkaloids, xanthones, isocoumarins, dibenzofurans, and peptides. 11 of the identified metabolites reported to have strong anticancer effect, some with antibacterial, antifungal, antiviral, anti-inflammatory, and antioxidant effects [41].

Ganoderma lucidum (Curtis) P. Karst., known as "Lingzhi" in China or "Reishi" in Japan, is a well-known medicinal mushroom and traditional Chinese medicine, which has been used for the prevention and treatment of bronchitis, allergies, hepatitis, immunological disorders and cancer. *G. lucidum* is rarely collected from nature and mostly cultivated on wood logs and sawdust in plastic bags to meet the needs of international markets. *G. lucidum* also known as Ling Zhi, Reishi, Mannentake is a medicinal, wood degrading basidiomycete with numerous pharmacological effects in addition to its key role in the environment as decomposer in nutrient cycle. *G. lucidum* is considered as "the king of herbs" which grows on the decaying and dead logs of deciduous trees like willow, oak, sweet gum, maple, elm and coniferous trees. The most important pharmacologically active constituents of *G. lucidum* are triterpenoids and polysaccharides, flavonoids, and alkaloids, amino acids, steroids, oligosaccharides, proteins, mannitol, vitamins B1, B2, B6, choline, and inositol [42-46]. Beside these major compounds, the elemental analysis showed the presence of several vital minerals in *G. lucidum* fruit bodies. *G. lucidum* has been considered to be a therapeutic fungal biofactory for bioactive compounds which can reduce the lethal effects of cancer.

5.1. Uses and health benefits of *Ganoderma*

Species of *Ganoderma* are widely researched due to the endless list of medicinal biological activities exerted by their extracted compounds, Fig. (2).

Figure 2: Ganoderma products (a) Ganoderma Reishi capsule (httpswww.amanvida.eu), (b) Ganoderma Reishi capsule (www.HerbHealthPlus.com)

Ganoderma lucidum shows a great usefulness for the treatment of various cardiovascular disorders. *G. lucidum* produces metalloprotease that exhibits both antithrombotic and fibrinolytic activities. Furthermore, *G. lucidum* has a profound protective effect on the cardiovascular system since it is able to lower the blood cholesterol and triglyceride level as well as reduce the blood pressure. Polysaccharides, one of the major bioactive compounds isolated from *G. lucidum* was found to improve many cardiovascular disorders, in addition to their hypotensive, antithrombotic and hypolipidemic activities [46-49]. The *Ganoderma* industry is strong and growing. Various products were commercialized for compounds originated from *Ganoderma* species [50].

6. *Auricularia auricula-judae*

Most *Auricularia* species are edible and are grown commercially in China and Japan. *Auricularia auricula-judae* or as commonly known Judas's ear or the jelly ear fungus, is an edible mushroom characterized by its brownish, ear-like jelly shape [51]. *Auricularia auricula-judae* is a popular ingredient in many Chinese dishes.*Auricularia auricula-judae*has been used as a blood tonic and has shown antitumor, hypoglycemic, anticoagulant, and cholesterol-lowering properties [52, 53]. *Auricularia auricula-judae* represents a promising source for novel chemical compounds of different biological functions, and there extracts were reported to have anticoagulant activity [51]. *Auricularia* species are utilized as nutrient-rich foods and medicinal resources, with particular prominence in Traditional Asian Medicine. *Auricularia* species are used mainly within the food industry, there is strong potential for their use in the production of therapeutic drugs, thus making it necessary to identify responsible bioactive compounds and promote our understanding of its pharmacological properties [54]. Carbohydrates are the major nutritional constituent of edible *Auricularia* species in addition to proteins, fat, fiber, vitamins and minerals. Also polysaccharides were the major active compounds found in edible *Auricularia* species in relation to their nutritional value and pharmacological properties. Potential medical applications for these compounds include the production of novel therapeutic drugs for treating diseases such as cancer, diabetes, and cardiovascular disorders [54].

6.1. Uses and health benefits of *Auricularia auricula-judae*

The fruit bodies of *Auricularia auricula-judae* grow on wood and have been commonly used as a food and as antidiabetic, antihypertensive, antiinflammatory, immunomodulatory, anticancer, and antimicrobial medications in many Asian countries. *Auricularia auricula-judae* fruit body is characterized by its high contents of carbohydrates, protein, and minerals such as calcium, phosphorous, potassium, and iron. Species of *Auricularia* are widely researched due to medicinal biological activities exerted by their extracted compounds, Fig. (3). In industry various products were commercialized for compounds originated from *Auricularia auricula-judae* [5].

Figure 3: Auricularia auricula-judae products (a) Auricularia auricula-judae powder capsule (httpswww.vitalabo.com), (b) Auricularia auricula-judae powder capsule (www.fairvital.com).

7. Agarikon (*Fomitopsis officinalis*)

Polypore mushrooms have been used medicinally for thousands of years. Polypores are a group of fungi that develop fruiting bodies; they are characterized by the presence of hymenium (surface with a high density of sporebearing structures), consisting of multiple, small pores. *Fomitopsis officinalis* (also known as *Fomes officinalis*, *Agaricum officinalis*, and *Laricifomes officinalis*) is a wood decaying fungus in the family Polyporaceae and is commonly known as 'Agarikon.' The fruiting bodies are used as a popular source of medicine in North America, Western Europe, and Asia for the treatment of asthma, cough, gastric cancer, and pneumonia. *F. officinalis* can grows as a parasite on a coniferous hosts, or as a saprobiont after the trees die where it causes brown rot. The upper surface of the fruit body is rough and cracked, with a thin layer that is chalky white, creamy, or nut colored. As they age, the carpophores become darker in color and strongly cracked, its length can reach up to 50 cm or more. *F. officinalis* fruit body appear at the initial site of infection, usually a few decades after the tree was first colonized [55-57].

7.1. Uses and health benefits of Agarikon (*Fomitopsis officinalis*)

Waill Elkhateeb *et al*., [57] describes the importance of medicinal mushrooms, with a specific focus on Agarikon as an example of a worldwide commercialized medicinal mushroom. Medicinal mushrooms, Agarikon (*Fomitopsis officinalis*) is a medicinal polypore mushroom containing a host of pharmacologically active compounds that beneficially affect human health. Agarikon is known for its capability of producing various biologically active compounds with medical applications such as antiviral, antibacterial, anticancer, and anti-inflammatory agents [57].

F. officinalis produces a variety of secondary metabolites such as eburicoic acid, sulfurenic acid, versisponic acid d, dehydroeburicoic acid, 3- ketodehydrosulfurenic acid, fomefficinic acid a-e, fomefficinic acid f, g, dehydrosulfurenic acid, fomefficinol a-b, fomlactone a-c, laricinolic acid, agaric acid, fomitopsin a, officimalonic acids a-h, fomitopsin c, fomitopsin f, g, h, trypanocidal demalonyl fomitopsin h, and trypanocidal fomitopsin d ethyl ester. The majority of these compounds exert promising biological activities, such as antimicrobial [58-63]. Agarikon contains many pharmacologically active compounds that beneficially affect human health, Fig. (4). Several studies have reported biological activities of *F. officinalis* such as antibacterial activity, antiviral activity, anti-inflammatory activity, and antitumor activity [64-69]. Unfortunately, Agarikon grows very slowly and is rarely found, which made its use as a supplement very challenging. This problem encourages culturing of Agarikon using submerged techniques or cultivation in the boreal nature to cover demands of this marvel mushroom [57].

Figure 4: Agarikon (Fomitopsis officinalis) product (a) Agarikonpowder capsule (www.Hostdefense.com)

8. Chaga mushroom (*Inonotus obliquus*)

Chaga mushroom (*Inonotus obliquus*; Family Hymenochaetaceae) is a parasitic fungus growing on birches and used in traditional medicine to treat various human health problems. Chaga is the common name of the black mass of the tree disease fungus *Inonotus obliquus* (Fr.) Pilát. The fungus is the pathogenic agent of canker rot of birch, causing a

heart rot that eventually kills the tree, infection is characterized by black sterile sclerotium, or conks, on trunks of infected trees [70]. *Inonotus obliquus* enters through wounds within the tree and from there causing decay and forming a sterile mycelial mass [71-73].

8.1. Uses and health benefits of Chaga mushroom (*Inonotus obliquus*)

There has been increased interest in investigating additional benefits and uses of 'medicinal mushrooms' or traditionally used fungi in recent decades. One of the potential applications of fungi and fungal extracts is as a wood preservative [74, 75]. Chaga mushroom is another promising medicinal mushroom, chaga and other polypore fungi have been used medicinally for many years due to the presence of a variety of biologically active compounds that occur in their fruiting bodies [67, 68]. Chaga is also reported to contain betulin and betulinic acid. The sterile conk of *I. obliquus* (sometimes referred to as a sclerotium, as it is a solid mass of sterile mycelium) contains other compounds that are active against animal cells and viruses. *I. obliquus* are also known to produce biologically active metabolites such as sterols and related compounds [76, 77].

Numerous, independent studies document its valuable role in preventing and healing cancer, beneficially activating the immune system, inhibiting cellular degeneration due to oxidation, suppressing inflammation, killing and/or inhibiting the growth of viruses, supporting diabetes treatment. Remarkably, this fungus demonstrates virtually no side effects during use in disease treatment [5, 73, 78].

Chaga have traditionally been boiled to make a tea, which is drunk to treat a range of conditions, including cancers, viral and bacterial infections, and gastro-intestinal disorders. *Inonotus obliquus* presented protective effects against the oxidative stress in liver. The high total phenolic contents maybe the reason for its strong antioxidant activity. Like several other mushrooms, *I. obliquus* also possesses anticancer activity. The Ergosterol peroxide from *I. obliquus* exhibits anticancer activity by down-regulation of the β-catenin pathway in colorectal cancer, this proves that *I. obliquus* can be developed as promising medicine to treat colon cancer [79]. The biological activity of the *Inonotus obliquus* is mainly due to the presence of several polysaccharides, the polysaccharides of *Inonotus obliquus* mainly constitutes the following sugars: rhamnose, arabinose, xylose, mannose, glucose, and galactose. Chaga can certainly be regarded as a gift to humankind, it both generates and helps maintain health. Chaga fungus contains a host of pharmacologically active compounds that beneficially affect human health Fig. (5). Several studies have reported biological activities of *Inonotus obliquus* such as anticancer, antioxidation, antiinflammatory, Antidiabetic and enhancement of immunity.Chaga (*Inonotus obliquus*) considered as an important issue in medicinal mushroom science. The prevalence of polyphenolic composites in Chaga indicates its clear antioxidant and anti-cancer, anti-microbial, and anti-hyperglycemic activities and other activities. The glucan and triterpenoid profile of the mushroom allows the use of *I. obliquus* in some cases as a direct antitumor agent [67, 68, 73, 78].

Figure 5: Chaga (Inonotus obliquus) products (a) Chaga powder capsule (httpswww.dutch-headshop.eu). (b) Chaga powder capsule (www.byclue.com)

9. Other genera of medicinal mushrooms

There are many genera of medicinal mushrooms known for their use as a source of therapeutic bioactive compounds, Fig. (6), such as *Geastrum fimbriatum* and *Hydnellum peckii* exhibited a promising anticoagulant activity [46]. *Handkea utriformis*, *Hericium erinaceus*, *Morchella esculenta*, *Sparassis crispa* and *Agaricus blazei* have wound healing effect [80], *Trametes Versicolor* and *Dictyophora Indusiata* exhibited a promising Antioxidant, Antimicrobial, Antihyperlipidemia and Antitumor and Immunity Enhancement effects [81], *Fomes fomentarius* and *Polyporus squamosus* have significant effects as antifungal activity, antibacterial activity, anti-inflammatory effect, antioxidant activity, Antitumor, Antiviral activity [82]. All these activities are exhibited by extracts or isolated compounds from their Fruiting bodies.

Figure 6: Some other medicinal mushrooms products (a) Hericium erinaceus capsule (httpswww.purehealthonline.co.uk). (b) Agaricus blazei capsule (www.ssavemoney.es). (c) Trametes Versicolor capsule (www.sgenewei.com). (d) Sparassis crispa tablets (www.zenmony.com)

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