

***Fomitopsis officinalis* mushroom: ancient gold mine of functional components and biological activities for modern medicine**

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Polypore mushrooms have been used medicinally for thousands of years. 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. This review describes the importance of medicinal mushrooms, with a specific focus on Agarikon as an example of a globally commercialized medicinal mushroom.

Keywords:

Agarikon (*Fomitopsis officinalis*), biological activities, medicinal mushrooms, secondary metabolites, traditional medicine

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Introduction

Nature is considered an important source for the discovery of new medicines. A vast diversity of important biologically active compounds have arisen in the natural world, shaped by evolution and spanning a large diversity of species across different kingdoms [1]. In the fungi kingdom, medicinal (edible) mushrooms have long been used for the treatment of pathogens and disease. Furthermore, fungi show great potential as sources of antibacterial, antifungal, antiviral, anti-inflammatory as well as immunostimulant and antitumor agents [1–4].

Mushrooms have a rich history of use as food and medicine. 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) [5,6]. Nowadays, medicinal mushrooms are regarded as functional foods and exist as over-the-counter health supplements used in complementary and alternative medicines [7,8].

Several compounds are responsible for the therapeutic activities of many fungi genera; the main groups of these compounds are polysaccharides, terpenes, phenolic compounds, and essential amino acids, as well as minerals such as calcium, potassium,

magnesium, iron, and zinc [6,9]. Polysaccharides represent the major compounds existing in medicinal mushrooms, and they exhibit antioxidant, anticancer, antidiabetic, anti-inflammatory, antimicrobial, antiviral, and immunomodulatory activities [6,10–13]. Glucan polysaccharides especially β -glucans have been reported to exhibit antimicrobial activity, are hypoglycemic, and are able to enhance immunity through the activation of macrophages [14–16]. Terpenes are the compounds responsible for the antioxidant, anticancer, and anti-inflammatory activities among many other biological activities exerted by mushrooms [5,17]. 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 [18]. On the contrary, mushrooms produce many bioactive proteins and peptides, such as lectins and laccases [5,6]. There are many genera of medicinal mushrooms known for their use as a source of therapeutic bioactive compounds. In this review, one of these species, Agarikon (*Fomitopsis officinalis*) is discussed in detail as an example of a promising source of therapeutic bioactive compounds.

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Agarikon (*Fomitopsis officinalis*), a polyporus fungi

Polypores are a group of fungi that develop fruiting bodies; they are characterized by the presence of hymenium (surface with a high density of spore-bearing structures), consisting of multiple, small pores. Although their ecological categorization ranges from being pathogens to saprotrophs, they are often entirely dependent on wood as a substrate [19]. Polypores have been of great interest to those looking for novel medicinal compounds, owing to their rich history of medicinal use by various cultures [20]. *F. 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 (including Mongolia) for the treatment of asthma, cough, gastric cancer, and pneumonia [21–23].

A rich literature base has dealt with *F. officinalis* ethnomycological aspects, but isolation and chemical characterization of single compounds has only recently been explored. According to several reports, there is indication of a broad-spectrum antibacterial and antiviral activity by *F. officinalis*, against pathogens like *Mycobacterium tuberculosis* and *Staphylococcus aureus*, as well as Orthopoxvirus [22,24,25]. Other biological activities of *F. officinalis* extracts include anticancer [21] and anti-inflammatory [26] activities.

Fomitopsis officinalis ecology

F. officinalis can grow as a parasite on a coniferous hosts, or as a saprobiont after the trees die where it causes brown rot [27,28]. Its carpophores are perennial and may last for more than 50 years; they are usually cylindrical or hoof shaped, and sometimes they may grow together to form irregular masses [29]. *F. officinalis* can be easily distinguished from other species by its chalky appearance as well as its specific bitter taste and odor in the earlier stage of growth [30]. 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 [28].

F. officinalis fruit body appear at the initial site of infection, usually a few decades after the tree was first colonized [31]. The infection almost always takes place through heartwood that has been exposed through mechanical damage or through any burls found on the tree. After the fungal spores germinate, the mycelium grows into the woody interior, and from there develops a form of brown rot that starts cracks along the annual rings and rays and finally crumbles to develop small cubes [29]. This fungus species is distributed in the temperate zone, and it was reported in North America, Africa (Morocco), Asia (China, Korea, Japan, India, and Mongolia), and western Europe countries [28] (Fig. 1).

Figure 1



Agarikon (*Fomitopsis officinalis*) (photographs taken by Oluna and Adolf Ceska, Canada, hosted by <http://mycoportal.org>).

Agarikon natural products

F. officinalis produces a variety of secondary metabolites such as eburicoic acid, sulfurenic acid, versisponic acid d, dehydroeburicoic acid, 3-ketodehydrosulfurenic acid [32,33], fomeffcinic acid a-e [34], fomeffcinic acid f, g, dehydrosulfurenic acid, fomeffcinol a-b, fomlactone a-c, laricinolic acid [21,35], agaric acid [36], fomitopsin a, officimalonic acids a-h [26], fomitopsin c [33], fomitopsin f, g, h, trypanocidal demalonyl fomitopsin h, and trypanocidal fomitopsin d ethyl ester [37]. The majority of these compounds exert promising biological activities, such as antimicrobial. In previous phytochemical investigations on *F. officinalis*, drimane sesquiterpenoids [38], lanostane triterpenes with a 12,23-epoxy-26,23-lactone moiety [38,39], and chlorinated coumarins [24] have been reported, and the biological activity of the isolated compounds showed antiviral, anticancer, anti-inflammatory, and antituberculosis activities [37].

Agarikon health benefits and medicinal actions

Exploring the miraculous Agarikon mushroom for biological activities has resulted in many promising outcomes. Agarikon contains many pharmacologically active compounds that beneficially affect human health [40–42]. Several studies have reported biological activities of *F. officinalis* such as antibacterial activity, antiviral activity, anti-inflammatory activity, and antitumor activity.

Antibacterial activity

F. officinalis exhibits many vital biological activities. Chlorinated coumarin from mycelia has been used for the treatment of pulmonary diseases, especially tuberculosis and pneumonia, where it showed antibacterial activities toward *M. tuberculosis* and *Bacillus pneumoniae* as well as other microorganisms [25]. Parkash and Sharma [43] observed a variability in the efficiency of the aqueous and the ethanolic extracts when they were testing the effect of *F. officinalis* against some phytopathogenic microfungi (*Curvularia lunata*, *Fusarium oxysporum*, *Alternaria solani*, and *Aspergillus terreus*), as well as some bacteria (*Bacillus subtilis* and *Escherichia coli*). It was found that the pure ethanolic extract of *F. officinalis* inhibited the growth of *A. solani* and *A. terreus* completely, whereas 1 : 4 diluted extract was able to completely inhibit the growth of *C. lunata* and *F. oxysporum*. Moreover, the same results were reported using the aqueous extract where the growth of *C. lunata* and *F. oxysporum* was completely inhibited by 1 : 4 dilution of the aqueous extract. On the contrary, regarding the antibacterial activity. The pure ethanolic extract exhibited maximum inhibition activity toward *E. coli*, whereas 1 : 4 dilution extract showed maximum

activity against *B. subtilis*. Aqueous extract only showed inhibition activity toward *E. coli* when used in the 1 : 4 dilution. Thus the preparation of the extract plays an important role in the potential antimicrobial activity.

Antiviral activity

Medicinal mushrooms also show antiviral properties, which are helpful in preventing, reducing, or curing infection from various viruses [22]. The mycelium extract of *F. officinalis* has been found to have unique antiviral properties, including activity against the Orthopoxvirus, which is responsible for Smallpox [44]. Stamets [45] reported that *F. officinalis* extract (1–2%) reduced the viral-induced cell damage by 50%, whereas the diluted crude extract (1 : 10⁶) reported a great efficacy against several viruses including herpes, influenza A, and influenza B. Moreover, the aqueous extract of *F. officinalis* showed antiviral activities against human influenza (H3N2) and bird influenza (H5N1) [46].

Anti-inflammatory activity

F. officinalis shows another biological application as an anti-inflammatory agent. Its methanolic extract was able to reduce the production of nitric oxide (NO), which is implicated in several inflammatory diseases including asthma. Han *et al.* [26] reported methyl-lanostane triterpenes of diverse structures, which were able to inhibit NO production in lipopolysaccharide-stimulated RAW264.7 cells, hence reducing the inflammation process. Moreover, it was reported that Agarikon treats musculoskeletal pain owing to its anti-inflammatory properties when applied topically as a poultice [44].

Antitumor activity

Full clinical trials are costly in time and resources, and consequently, fungal extracts efficiency in preventing and treating cancer is still largely unproven. More and rigorous investigation is essential to explore this complex topic further. Nevertheless, there is some promising evidence, indicating that the consumption of some fungal extracts helps in protecting against some cancers types, specially breast and gastrointestinal [47,48].

Lanostane-type triterpenoids, which was reported in *F. officinalis* extract, showed anticancer activity [21]. It was found to inhibit eukaryotic DNA polymerase, a feature which allows it to be a cytotoxic agent and helpful as a cancer chemotherapeutic agent [49].

Wu *et al.* [50] reported that the ethanol extracts of *F. officinalis* exhibit stronger anticancer activities than that

Figure 2



Products containing Agarikon (*Fomitopsis officinalis*) extract (a). *F. officinalis* supplement tablets (<http://www.camformulas.co>) (b). *F. officinalis* powder (<http://www.binge.bh>).

of water extracts toward human breast cancer (MDA-MB-231) cells, hepatoma (HepG2), colon cancer (HCT-116), lung cancer (A549), and mouse sarcoma 180 cells (S-180). This was evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays (MTT assay), which is a colorimetric assay used to measure cell viability before and after being treated with the fungal extract. The results showed that the maximum anticancer activity was shown toward HCT-116, where the cell viability using MTT assay was only $15.7 \pm 4.0\%$ at a concentration of 50 $\mu\text{g/ml}$ after 24 h of incubation.

The intense global interest and value assigned to *F. officinalis* has led to commercial products derived from this valuable medicinal mushroom, as shown in Fig. 2.

Global market of Agarikon

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. Figure 2 illustrates some products based on Agarikon extracts.

Conclusion

Globally, there is a rich history of foods being used as medicine. One such kind of traditional therapy that was commonly used consists of mushrooms with medicinal properties. There are several edible mushrooms that have significant medicinal metabolites, whereas there are other species that may

not be used as food but are valued solely for their medicinal properties. *F. officinalis* is one such species and contains various active compounds which makes it of great interest from a biological and pharmacological perspective.

Several studies have presented promising activities of *F. officinalis*. Many of those studies use relatively crude extracts of *F. officinalis*, and some have confirmed the existence of biological activities of *F. officinalis*, such as antiviral, antibacterial, anticancer, and anti-inflammatory. Further research is required to isolate and identify more bioactive compounds responsible for such biological activities. The relative efficiency of *F. officinalis* in comparison to other medicinal species remains to be elucidated and would be a fertile topic for further investigation.

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Conflicts of interest

There are no conflicts of interest.

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