

Anticoagulant Capacities of Some Medicinal Mushrooms

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Abstract: Studies with mushrooms have been developed recently and it is figured out that potent properties of secondary metabolites from different mushroom species show great biological activities. There is a growing interest in active metabolites that are obtained from natural sources as an alternative to synthetic drugs. In the review, the potential use of mushroom extract as an anticoagulant agent has been discussed. *Hydnellum peckii*, *Ganoderma lucidum*, *Gaeastrum fimbriatum* and *Auricularia auricula-judae* extracts exhibited a promising anticoagulant activity.

Keywords: Medicinal Mushrooms, Anticoagulant, *Hydnellum peckii*, *Ganoderma lucidum*, *Gaeastrum fimbriatum*, *Auricularia auricula-judae*.

1. INTRODUCTION

Health problems related to heart, blood vessels, and thrombosis (Thromboembolic condition) including ischemic stroke, acute myocardial infarction, unstable angina, pulmonary embolism, and deep vein thrombosis are of the major causes of death in the World [1,2]. Blood coagulation plays serious roles in the incidences of cardiovascular problems. Achieving balance in human body between thrombus formation and destruction of it is very critical. Thanks to a system including platelets, the vascular endothelium, the coagulation cascade, and the fibrinolytic system [3-5]. This complexity in accomplishing the equilibrium in this system made it challenging to be controlled using drugs, and there is always high risk of bleeding due to the narrow therapeutic index of some drugs. This inconvenience prompted researchers to screen for new safe anticoagulants that do not require this strict monitoring. Examples for famous anticoagulant drugs are vitamin K antagonists, such as warfarin; novel anticoagulants (NACs) such as direct thrombin inhibitors (as dabigatran), and factor Xa inhibitors (as rivaroxaban, apixaban) [6].

Mushrooms are tremendous sources for various compounds of therapeutic capacities [7]. Humans knew this from millennia, and hence consumed mushroom all over the world due to their high nutritional values, and some medicinal properties.

A wide variety of compounds isolated from many species of mushrooms, have been identified [8], most of them were fatty acids, terpenoids, proteins, phenols, lectins, steroids, and polysaccharides [9-11].

Mushrooms have been reported to exhibit an assortment of biological activities including but not limited to anticancer, antimicrobial, hypocholesterolemic, antioxidant, antihypertensive, antidiabetic, anti-obesity, hepato-protective, antiaging, anti-allergic, and anti-coagulant activities [7,11].

In this review, the anticoagulant capacities of some mushrooms has been discussed. Out of the thousands of mushroom species already identified, some species were reported as promising sources of anticoagulant compounds. Examples are *Hydnellum peckii* (bleeding tooth mushroom); *Auricularia auricula-judae* (Jelly ear mushroom); *Gaeastrum fimbriatum* (Earthstar mushroom); and the famous *Ganoderma lucidum* (Lingzhi or Reishi).

2. HYDNELLUM PECKII (BLEEDING TOOTH FUNGUS)

Hydnellum peckii belong to the Aphyllophorales order and the Hydnaceae family, commonly called the bleeding tooth fungus. They are widely dispersed in Europe and the Pacific Northwest, commonly in association with conifers and can be found among moss and pine litter. They fruit in the summer months as a solitary or fused fruiting bodies. These fungi are mycorrhiza, living in symbiosis with vascular plant roots. *H. peckii* are non-toxic. *H. peckii* have 2-5mm spines, similar to teeth, on the underside of their cap. As these fungi mature, they become less descript becoming turning grey or brown in color. However, their taste has been described as bitter pepper deeming it inedible. Nitrogen deposition resulting from atmospheric pollution is believed to be a key factor in the observed decline of *H. peckii* populations, particularly in areas of Europe [12].

3. HYDNELLUM PECKII NATURAL PRODUCTS

This fungus does have several beneficial uses. The mushroom of *H. peckii* contains atromentin, which has antibacterial and anticoagulant properties. Additionally, the oozing red “blood” can be used to dye fabrics. [12,13].

4. MEDICINAL EFFECTS OF HYDNELLUM PECKII'S ANTICOAGULANT ACTIVITY

Screening of a 70% ethanolic extract of *Hydnellum peckii* revealed the presence of an effective anticoagulant, named atromentin, similar in activity to the well-known anticoagulant heparin. *In vivo*, 1 mg of the ethanol extract was equivalent to 0.58 units of heparin. *In vitro*, 1 mg of purified atromentin was equivalent to 5.1 units of heparin and 2.3 mg of 70% ethanol extract [14].



Fig1. *Hydnellum peckii*(Photographs taken by dnsolie, Locality United States, Alaska, Southeast Fairbanks County, hosted by <http://mycoportal.org>).

5. AURICULARIA AURICULA-JUDAE (JELLY EAR FUNGUS)

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. 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. Its fruit body is characterized by its high contents of carbohydrates, protein, and minerals such as calcium, phosphorous, potassium, and iron [15,16]. Most *Auricularia* species are edible and are grown commercially in China. *Auricularia auricula-judae* is a popular ingredient in many Chinese dishes; it has been used as a blood tonic and has shown antitumor, hypoglycemic, anticoagulant, and cholesterol-lowering properties [17,18]. *Auricularia auricula-judae* represents a promising source for novel chemical compounds of different biological functions, and there extracts were reported to have anticoagulant activity [19].

Auricularia is a key genus among edible macrofungi, sourced as either wild or cultivated mushrooms. *Auricularia* species are utilized as nutrient-rich foods and medicinal resources, with particular prominence in Traditional Asian Medicine. *Auricularia* species are used predominantly within the food industry, there is strong potential for their use in the production of therapeutic drugs, thus making it necessary to identify relevant bioactive compounds and further our understanding of its pharmacological properties [20].

6. AURICULARIA AURICULA-JUDAE NATURAL PRODUCTS

Carbohydrates are the major nutritional constituent of edible *Auricularia* species in addition to proteins, fat, fiber, ashes vitamins and minerals. Also polysaccharides were the major active compounds found in edible *Auricularia* species in relation to their nutritional value, extraction

methods, 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 [20].

Elkhateeb et al., [19] reported that in *Auricularia auricula-judaen*-hexane extract, seventeen compounds were identified. Tetradecane (1.1%), Pentadecane (1.5%), Hexadecane (0.8%) as hydrocarbon compounds. Hexadecanoic acid, methyl ester (2.25%), cis- 9-hexadecenoic acid (0.8%), hexadecanoic acid (5.7%), 1-(5'-acetoxy-2',4'-dimethoxy-6'-hydroxyphenyl)-2-methylantraquinone (1.35%), 9,12- octadecadienoic acid (z,z)-, methyl ester (2.63%), 9-octadecenoic acid (Z)-, methyl ester (7.05%), 11-octadecenoic acid, methyl ester (1.47%), octadecanoic acid, methyl ester (1.22%) . It was found that oleic acid (62.31%) was represented as the major compound, 6,9,12-octadecatrienoic acid, methyl ester (1.05%), mesoaminoacactaethylporph (1.65%), 2-(2,6-dimethoxy-4-(2,2-bis (ethoxycarbonyl) ethyl]phenyl)-9-(2,6- dimethoxyphenyl)-1,10-phenanthroline (0.89%), 1,2-benzenedicarboxylic acid, bis (2-ethylhexyl) ester (5.20%) and anthraergosta-5,7,9,22-tetren-3-ol (1.36%).

Kadnikova et al., [21] reported that main components of *Auricularia auricula-judae* (ash, protein, fat, total carbohydrate), water-soluble polysaccharide, cellulose, chitin, pectin, uronic acids, amino acid and mineral element contents, as well as neutral sugar composition were determined. This fungus contains 3.6% of ash, 12.5% of protein, 1.7% of fat and a large amount of carbohydrates (66.1%) per dry matter.

7. MEDICINAL EFFECTS OF AURICULARIA AURICULA-JUDAEAS ANTICOAGULANT ACTIVITY

An acidic polysaccharide with anticoagulant activity was isolated from the edible mushroom *Auricularia auricula* using water, alkali or acid extracts. The alkali extract showed the highest anticoagulant activity and was thereby further purified using gel filtration chromatography. Specific anticoagulant activity of the purified polysaccharide was 2 IU/mg and its average mass was f 160 kDa. The polysaccharide from *Auricularia auricula* contains mainly mannose, glucose, glucuronic acid and xylose but no sulfate esters [15].

Auricularia auricula anticoagulant activity was due to catalysis of thrombin inhibition by antithrombin but not by heparin cofactor II. Inhibition of Factor Xa by antithrombin was not catalyzed by the polysaccharide. The glucuronic acid residues were essential for the anticoagulant action of the mushroom polysaccharide since the activity disappeared after reduction of its carboxyl groups. The polysaccharides from these mushrooms may constitute a new source of compounds with action on coagulation, platelet aggregation and, perhaps, on thrombosis [15].

Therefore the edible mushroom *Auricularia auricula* may become a new source of anticoagulant compounds. Evaluation of *Auricularia auricula* polysaccharide as a novel alternative agent in thrombosis therapy requires further studies on characterization of its anticoagulant nature and the possible effect on experimental models of thrombosis [15].



Fig2. *Auricularia auricula-judae*(Photographs taken by Waill A. Elkhateeb, Locality:Hakozaki Higashi-ku Fukuoka-shi Japan).

8. GEASTRUM FIMBRIATUM (EARTHSTAR FUNGUS)

Geastrum fimbriatum is an inedible mushroom belonging to family Geastraceae. It is also named fringed earthstar or sessile earthstar. It gains its name from its morphology. The word fimbriatum means fringed or fibrous referring to the fringed opening of the spore sac [22].

In early stages, it lies in soil like a stone where it is rounded in shape, and when it gets mature it pushed up to the soil surface and its outer peridium splits into several segments or rays (ranging between 5 to 8 segments). These rays are curved downwards exposing the inner peridium (spore sack)

[23]. The outer peridium then start to expand to the outside developing a star-like shape on the ground. Before being expanded these segments outer surfaces are cottony with some soil particles adhered to them, while after expansion these cottony surfaces peel off revealing a grayish brown, smooth surface. The spore sack is about 2 cm in diameter with conical apical pore and buffy to greyish brown smooth surface. The spores are light brown in color with globous surface and range between 4-7 μm , the powdery spores eject from the sac when it is hit by raindrops or blown by a wind. It has a large fruit bodies (up to 5 cm across) with no distinguishing odor or taste. Although it was mentioned that *Geastrum fimbriatum* is an inedible mushroom [22], it was found to be eaten by Madhya Pradesh tribe [23].

9. DISTRIBUTION AND ECOLOGY

Geastrum fimbriatum is a saprobic, hypogeous mushroom that has been reported in broad leaved wood and conifers, they may be single or aggregated in small groups. It is found in several locations including Europe [24], Latin America [25], eastern North America [26] and Asia [27].

10. *GEASTRUM FIMBRIATUM* NATURAL PRODUCTS AND THEIR ANTICOAGULANT ACTIVITY

As it was mentioned before, the blood vessels health problems and thrombosis are considered one of the major reasons leading to death in the World [1]. Due to the restriction to the use of many anticoagulants that show undesirable side effects including hemorrhagic risk, much more interest has been directed towards developing new safer, potent and specific antithrombotic as well as anticoagulant agents that exhibit less risk and are compatible with other drugs [28]. Warfarin is an example of anticoagulant drug that exhibits many undesirable side effects including gum and nasal bleeding, bruising, haemoptysis, dark or bloody vomit or stool as well as many other complications [28]. There could be other better choices that prevent and treat a variety of cardiovascular diseases and that could be obtained from nature with lower toxicity and no side effects [29,30].

The studies showed that *Geastrum fimbriatum* demonstrated a promising anticoagulant activity, where the activated partial thromboplastin time (APTT) assay which is used to estimate the intrinsic coagulation pathway showed that *Geastrum fimbriatum* ethanolic extract prolonged the coagulation time (67 seconds) compared to DMSO which is the negative control (50 seconds), however the prothrombin time (PT) which was employed for the evaluation of the extrinsic coagulation pathway did not show any positive activity. Both assays were conducted using commercial human plasma, where acetylsalicylic acid was used as a positive control and dimethyl sulphoxide (DMSO) used as a negative control [29,30].

These results revealed that *Geastrum fimbriatum* can find potential applications as new anticoagulant as well as antiinflammatory agent from natural source. However, further studies should be conducted to evaluate the safety and the cytotoxicity of that mushroom.



Fig3. *Geastrum fimbriatum* (*Earthstar fungus*) (collected by MBouck, Locality: Australia, Victoria, East Warburton, hosted by <http://mycoportal.org>).

11. GANODERMA LUCIDUMA POLYPORUS MUSHROOM

Ganoderma lucidum is a polypore mushroom belonging genus *Ganoderma* that grows as saprotrophs or parasites [31]. It has been used for many years in Far East countries including China, Japan, and

Korea, as a potent medicinal fungus [32]. It is known by two different names in China and Japan, the Chinese call it “lingzhi” referring to its essence of immortality and spiritual potency, while the Japanese named this mushroom reishi or mannentake which means 10,000 year mushroom [32].

In Latin, the word *lucidus* means brilliant or shiny referring to the mushroom’s fruiting body appearance which is varnished and sculptured [33]. It is a dark large mushroom with a woody texture and glossy external surface, it has a kidney shaped cap giving it a distinct morphology [31]. It is not classified as edible mushrooms, due to their bitter taste also their fruiting bodies are so hard with no fleshy texture making it so hard to be eaten [34]. *G. lucidum* exhibits a great popularity for its pharmaceutical benefits rather than the nutritional ones [33].

12. DISTRIBUTION AND ECOLOGY

Ganoderma lucidum is an annual mushroom that prefer hot and humid climates in the subtropical regions of the Orient [33]. It can grow as saprotrophs or parasites [31] on a diverse range of trees, especially deciduous giant trees such as maple, oak, willow, elm. It grows close to the soil surface at the stump of such trees and sometimes it appears on the soil surface as it arises from buried roots [35]. On the other hand, it is less frequently growing on coniferous trees found in Asia, Europe and America.

The wild lingzhi is very rare since out of each 10,000 deciduous trees only two or three show lingzhi growth. Nevertheless, lingzhi can be artificially cultivated now a day on various substrates including sawdust/woodchips or hardwood logs [36], residues of farm crops or cotton seed husk [37], sunflower seed hull [38], wheat straw [39], corn cobs [40].

Ganoderma species are white rot fungi that show a critical ecological role in nutrient mobilization due to their decomposing effect towards woody plants. They are also effectual for bioremediation and bioenergy production due to their lignocellulose decomposing enzymes [41,42].

13. GANODERMA LUCIDUM NATURAL PRODUCTS

It is well established that about 90% of the mushrooms weight is water and the remaining 10% is formed of other components such as protein, carbohydrates, vitamins and minerals, ash and fiber. It was reported that the nonvolatile components of *G. lucidum* consists of 7–8% crude protein, 26–28% carbohydrate, 1.8% ash, 59% fiber, and 3–5% fat [43].

Polysaccharides, triterpenes and peptidoglycans are considered the major biologically active compounds in *G. lucidum* [44,45]. However, their amounts can be extremely diverse in natural and commercial products, this diversity results from using different species as well as the variation in the production conditions [33].

A variety of polysaccharides that differs in their sugar and peptide compositions as well as differ in their molecular weight (e.g., ganoderans A, B, and C) have been obtained from *G. lucidum* spores, mycelia and fruit bodies. Due to the unique chemical and rheological structure of these polysaccharides, they show a wide range of crucial biological activities such as antitumor, antiinflammatory, immunostimulating and hypoglycemic effects [46-48]. The structural analysis of the produced polysaccharides revealed that the major sugar in their structures is the glucose [33].

Among the other important bioactive compounds isolated from *G. lucidum* are peptidoglycans. These include a proteoglycan that shows a promising antiviral activity, also a fucose-containing glycoprotein fraction was also extracted from *G. lucidum* [49], additionally, another water-soluble glycopeptide was extracted from the fruit bodies [50].

Terpenes are also vital bioactive compounds produced by *G. lucidum*, which are well known to exhibit crucial pharmacological activities including antitumorigenic, hypolipidemic and anti-inflammatory activities [51]. These natural compounds have carbon skeletons formed of one or more isoprene C₅ units, their molecular weights range from 400 to 600 kDa and they are extremely oxidized with complex chemical structure [51]. The extraction of triterpenes is carried out by using solvents such as methanol, ethanol, chloroform, ether, and acetone. This step is followed by a purification process usually by using normal and reverse phase HPLC [52].

Kubota et al. [53] reported the first triterpenes extracted from *G. lucidum* which are the ganoderic acids A and B. After that, hundred or more triterpenes were isolated from *G. lucidum*. The chemical composition of these triterpenes were well identified and it was observed that the majority of the triterpenes are ganoderic and lucidenic acids, while other triterpenes including ganoderiols, ganoderals and ganodermic acids also have been reported [54].

Beside these major compounds, the elemental analysis showed the presence of several vital minerals in *G. lucidum* fruit bodies. These include potassium, calcium and magnesium, phosphorus, sulfur, and silica were detected. Other minerals were also reported but they are found in smaller amounts such as iron, copper, manganese, strontium, sodium. Some heavysuch as mercury, lead and cadmium metals are detected in small amounts as well [55].

14. ANTICOAGULANT ACTIVITY

Ganoderma lucidum has been used as traditional medicinal herb to treat various disease for about two thousand years [56]. It shows a great usefulness for the treatment of various cardiovascular disorders. *Ganoderma lucidum* produces metalloprotease that exhibits both antithrombotic and fibrinolytic activities [57]. The blood clotting and lysis systems are highly regulated by several vital enzymes and any disturbance in these systems will results in life threatening cardiovascular diseases. As it was known that blood clots are formed by thrombin from fibrinogen however they are lyzed by plasmin that is activated from plasminogen by tissue plasminogen activator. A fibrin plate methods assay was employed to test fibrinolytic protease of *G. lucidum* extract. A putative metalloprotease has been isolated from the mycelium of *G. lucidum*. The protease hydrolyzed human fibrin and fibrinogen as well as it showed a promising anticoagulant activity [57]. This enzyme was found to be a Zn^{2+} metalloprotease as each mol of protease contains about 1.07 mol of Zn^{2+} . The purified enzyme was able to hydrolyze the α , and β chain when incubated with human fibrinogen, however it did not affect γ chain of fibrinogen. On the other hand, thrombin, hemoglobin, immunoglobulin and albumin are not affected by the presence of the protease enzyme under similar conditions [57].

An anticoagulant activity using human plasma was also displayed by *G. lucidum* metalloprotease. The activated partial thromboplastin time (APTT) and thrombin time (TT) test in human plasma were used to evaluate the anticoagulant activity of the purified protease enzyme. As mentioned before APTT is employed to detect the coagulation defect in the intrinsic pathway, nevertheless TT assay is more sensitive to estimate the anticoagulant activity of the protease enzyme. The results showed that the prolonged TT could be related to the degradation of fibrin or fibrinogen. It was reported that the TT was prolonged by 2 and 3 times the control time at protease concentrations of 220 and 240 nM respectively. However, the APTT required higher concentrations of the protease enzyme to reach 2 and 3 times the control value, where the protease concentrations were 1.1 and 2.2 μ M respectively [57].

Additionally, *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. The clinical trials proved that two months administration of *G. lucidum* extract improved the blood pressure of hypertensive patients at the primary stage to reach normal blood pressure values [58]. Another study reported that *G. lucidum* extract prevented the development of atherosclerosis in rats as it lowered blood lipid level [59].



Fig4. *Ganoderma lucidum*(Photographs taken by Ahmed I. El-Diwany and Waill A. Elkhateeb, Locality: Cairo, Egypt).

Polysaccharides, one of the major bioactive compounds isolated from *G. lucidum* was found to improve many cardiovascular disorders such as chest pain and palpitation. Also it improves

improvement in ECG in many cases, in addition to their hypotensive, antithrombotic and hypolipidemic activities [60].

As a conclusion, *G. lucidum* is regarded as an effective medicinal herb showing variable biological activities including control of some cardiovascular diseases which is a global leading cause of death. Further clinical trials should be conducted to evaluate and confirm the safety and efficacy of *G. lucidum* natural products.

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